STATISTICAL ANALYSIS PLAN

PROTOCOL MGB244-001

A Prospective, Randomized, Vehicle Controlled, Double Blinded, Multicenter, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of B244 Delivered as an Intranasal Spray for Preventive Treatment in Subjects with Episodic Migraine

Protocol Number:	MGB244-001
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Name of Test Drug:	B244
Indication:	Episodic Migraine
Phase:	Phase 2
Methodology:	Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, 3-Arm
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Analysis Plan Date:	18 March 2019
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APPROVAL SIGNATURE PAGE

Protocol Title:	A Prospective, Randomized, Vehicle Controlled, Double Blinded, Multicenter, Phase II Study to Assess the Safety, Tolerability, and Efficacy of B244 Delivered as an Intranasal Spray for Preventive Treatment in Subjects with Episodic Migraine
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Date: 18th March 2019

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Spiros Jamas, ScD
Head of Therapeutics,
Co-Founder

Signature: S Jamas

Date: March 18th, 2019

REVISION HISTORY

Version Number	Version Date	Summary and Rational of Revision(s)
1.0	18 March 2019	This is the first final version.

TABLE OF CONTENTS

TABLES AND FIGURES INCLUDED IN THE TEXT

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of Covariance
AOB	Ammonia oxidizing bacteria
ATC	Anatomic therapeutic class
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CGI	Clinical Global Impression
CGI-E	Clinical Global Impression - Efficacy Index
CGI-I	Clinical Global Impression - Global Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CRF	Case report form
CSR	Clinical study report
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic case report form
ePRO	Electronic patient reported outcome
HIT-6	Headache Impact Test-6
ICH	International Conference on Harmonisation
IHS	International Headache Society
IP	Investigational product
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MSQL	Migraine Specific Quality of Life questionnaire
NO/NO_x	Nitric oxide
PP	Per protocol
PT	Preferred Term
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOA	Schedule of Assessments
SOC	System organ class
TEAE	Treatment-emergent adverse event
VRS	Verbal Rating Scale
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

B244 is a purified a strain of *Nitrosomonas eutropha* originally isolated from soil samples. B244 oxidizes ammonia and produces nitric oxide (NO) and nitrite (NO_2-), which are known to be anti-inflammatory and anti-infective. B244 is being developed as topical and intranasal applications of a natural source of ammonia oxidizing bacteria (AOB) and nitric oxide (NO/NO_x) to the human skin and nasal cavity.

Migraine is a chronic, recurrent disorder affecting an estimated 37 million Americans. Migraine is marked by recurring moderate to severe headache with throbbing pain that usually lasts from 4-72 hours, typically unilateral in location, is often accompanied by nausea, vomiting, and sensitivity to light or sound, and is sometimes preceded by an aura and is often followed by fatigue. Around 12% of adults have episodic migraine (headaches on less than 15 days per month) [1], while around 1% of the adult population suffers from migraine and headaches on more days than not [2], a condition termed chronic migraine. In addition, during a migraine attack, individuals experience impaired health-related quality of life and considerable disability [3, 4].

The purpose of this study is to evaluate the safety and efficacy of intranasal B244 as preventive treatment in patients with Episodic Migraine.

1.1.2. Study Objectives

1.1.2.1. Primary Objectives

- To evaluate the safety and tolerability of B244 for preventive treatment in subjects with episodic migraine.

1.1.2.2. Secondary Objectives

- To assess the efficacy of B244 versus vehicle for migraine prevention in subjects with episodic migraine.
- To continue to assess safety during the 28-day follow-up period.

1.1.2.3. Exploratory Objectives

- To evaluate the effect of B244 on changes in cytokine concentration in nasal fluid and blood.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a prospective, randomized, vehicle-controlled, double-blind, 3-arm parallel assignment study assessing the safety, tolerability, and efficacy of B244 delivered as an intranasal spray for preventive treatment in subjects with episodic migraine. This study will enroll approximately 303 subjects.

Enrolled subjects will undergo a 28-day baseline period to establish baseline headache frequency and characteristics.

Subjects will be randomized at the end of the baseline period if the eligibility criteria are met. Randomization will be 1:1:1 so that equal number of subjects will be treated in each Arm of the study.

Subjects will be trained for in-home treatment/assessment on the use of the nasal spray and will apply their first dose of treatment under the supervision of study personnel on site. Subjects will remain under observation at the study site for 1 hour post dosing. Subjects will then be dispensed study medication for 12 weeks of at home dosing (either $1x10^9$ cell/ml; $4x10^9$ cells/ml; or vehicle). While at home, subjects will dose twice daily (am and pm) for 12 weeks during the prevention treatment phase. Subjects will be asked to visit the site every 4 weeks during the 12-week treatment period and 4-week follow-up.

Daily assessments will be made during the 12-week double-blind treatment period for safety, tolerability and efficacy. Additional safety assessments will be made during the follow-up period 28 days after last treatment. Subjects will record their dosing, migraine incidence/severity/ duration, and rescue (acute migraine specific) medications using a study diary.

1.2.1.1. Randomization Methodology

Randomization will be evenly allocated across 3 treatments (B244 – $1x10^9$, B244-$4X10^9$ or vehicle), so that equal numbers of subjects will be treated in each of the 3 treatment groups of the study. Randomization will occur after the 4-week baseline period for the study. Details of the randomization scheme are provided in a separate document – "Randomization Plan."

1.2.2. Stopping Rules and Unblinding

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator. Reasons for withdrawal (subjects who refuse to complete any remaining study visits) or discontinuation (subjects who prematurely stop the application) at any time during the study may include, but are not limited, to the following:

- For safety reasons, either at the discretion of the Investigator or at the subject's request.
- For protocol violations at the discretion of AOBiome.
- Due to concomitant therapy that could interfere with the results of the study (the Investigator will report all such information on the CRFs and decide, in accordance with AOBiome, whether the subject is to be withdrawn).

The reason for subject study withdrawal will be recorded in the electronic Case Report Form (eCRF). Data from subjects withdrawing from the study will be considered evaluable up to the point at which they are withdrawn using the same criteria for evaluability as for subjects who complete the study.

The Investigator may unblind a subject's treatment assignment only in the case of emergency or in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as determined by the Investigator. It is preferred (but not required) that the Investigator first contact the Medical Monitor to discuss options before unblinding the part subject's treatment assignment. The Investigator must notify the Sponsor as soon as possible when a subject's treatment assignment is unblinded without revealing the treatment assignment of the unblinded subject unless that information is deemed important for the safety of subjects currently in the study. The date and reason for the unblinding must be documented in the subject's study record.

The Medical Monitor may unblind the treatment assignment for any subject with a serious adverse event (SAE). If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report identifying the subject's treatment assignment may be sent to clinical investigators in accordance with local regulations and/or sponsor policy.

1.2.3. Study Procedures

The schedule of assessments, as outlined in the study protocol, is presented in Table 1.

The study flow is presented in Figure 1.

Table 1: Schedule of Assessments

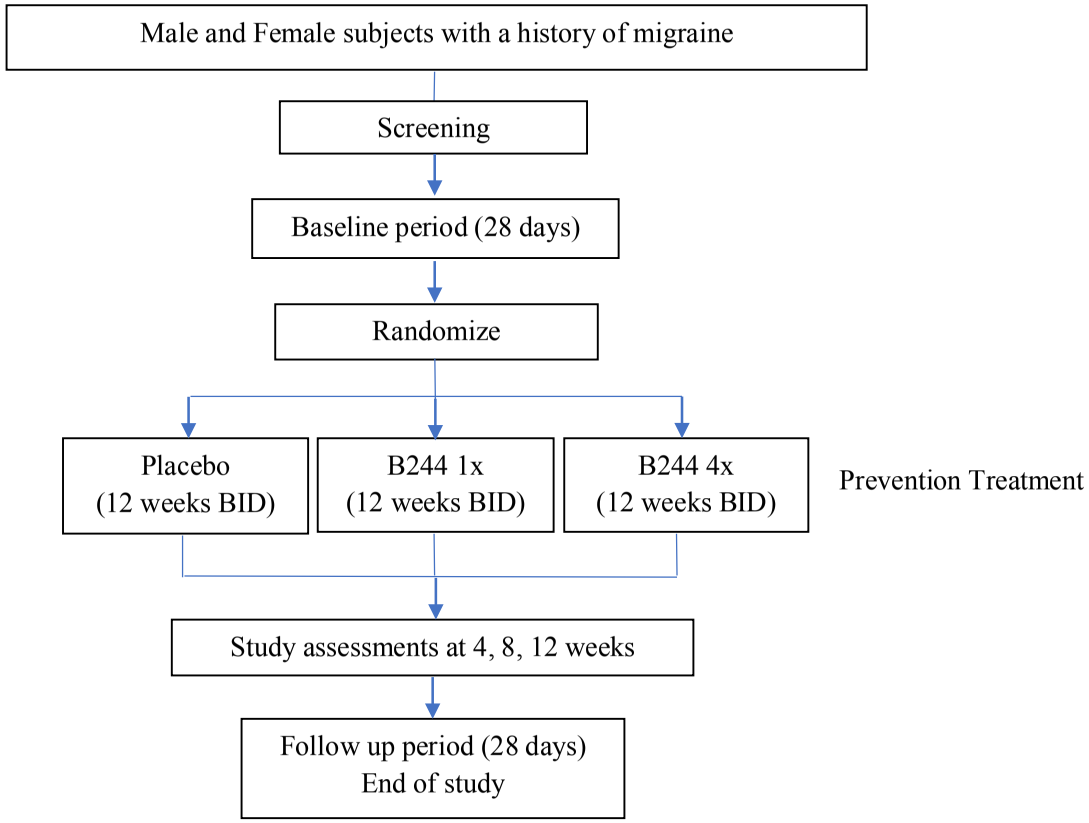
Visit Name (Day)	Screening	Baseline (Beginning of 4-week baseline period)	Randomization (End of 4-week baseline period)	Prevention Treatment Week 4	Prevention Treatment Week 8	Prevention Treatment Week 12	Follow-Up (End of Study) Week 16	Unanticipated/ Early Termination Visit
Visit	V1 (Day -29)	V2 (Day -28)	V3 (Day 0)	V4 (Day 28)	V5 (Day 56)	V6 (Day 84)	V7 (Day 112)	
Visit Window, in Days	-42 to -28	-31 to -27	±3	±3	±3	±3	±3	
Informed Consent[1]	X							
Inclusion/Exclusion Criteria[2]	X	X	X[17]					
Demographics	X							
Medical History	X							
Smoking Status	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Vital Signs (HR, BP, Respiratory Rate)	X	X	X	X	X	X	X	X
Brief Physical Exam	X	X	X	X	X	X	X	X
Neurological Exam	X	X	X	X	X	X	X	X

Visit Name (Day)	Screening	Baseline (Beginning of 4-week baseline period)	Randomization (End of 4-week baseline period)	Prevention Treatment Week 4	Prevention Treatment Week 8	Prevention Treatment Week 12	Follow-Up (End of Study) Week 16	Unanticipated/ Early Termination Visit
Visit	V1 (Day -29)	V2 (Day -28)	V3 (Day 0)	V4 (Day 28)	V5 (Day 56)	V6 (Day 84)	V7 (Day 112)	
Body Weight	X	X	X	X	X	X	X	X
Height	X							
Blood Collection[3]			X	X	X	X	X	X
12-Lead ECG	X		X			X		
Randomization[4]			X					
Nasal Insepction[5]	X	X	X	X	X	X	X	X
Delivery of Investigational Product[6]			X					
Investigational Product Compliance[7]			X	X	X	X		
Counseling[8]			X	X	X	X		X
Laboratory Testing[9]	X		X			X		X
Urinary Pregnancy Test[10]	X							

Visit Name (Day)	Screening	Baseline (Beginning of 4-week baseline period)	Randomization (End of 4-week baseline period)	Prevention Treatment Week 4	Prevention Treatment Week 8	Prevention Treatment Week 12	Follow-Up (End of Study) Week 16	Unanticipated/ Early Termination Visit
Visit	V1 (Day -29)	V2 (Day -28)	V3 (Day 0)	V4 (Day 28)	V5 (Day 56)	V6 (Day 84)	V7 (Day 112)	
Nasal Fluid[11]			X	X	X	X	X	X
Safety AEs	X	X	X	X	X	X	X	X
Study Diary[12]	X	X	X	X	X	X	X	X
Migraine Pain Intensity Score	X	X	X	X	X	X	X	X
MIDAS[13]		X	X			X		X
HIT-6[14]		X	X	X	X	X	X	X
MSQL[15]		X	X	X	X	X	X	X
CGI[16]		X	X	X	X	X	X	X
Subject Satisfactory Survey							X	X[18]

1. Informed consent can be obtained up to 14 days prior to the baseline visit (V2).
2. Inclusion and exclusion criteria will be reviewed at Screening (V1), Baseline (V2), and Randomization (V3) visits to make sure nothing changed.
3. Blood samples for biomarkers will be collected and processed on site. Serum/plasma samples will be frozen onsite and shipped to the Central lab for storage.
4. Subject's demographic data and medical history are blinded to the statistician for randomization and treatment assignment. Only subjects with 4-14 migraine headache days per month during baseline period (28 days between V2 and V3) will be randomized.
5. Nasal inspection will include clinical examination of the nasal mucosa, sinuses, and upper airway using an otoscope.
6. Subjects will be trained for in-home treatment/assessment on the use of the nasal spray, and have their first dose of treatment on site (V3). Subjects will remain onsite for observation for 1 hour post dosing. Subjects will then be dispensed study medication for 12 weeks of at home dosing.
7. Weight of individual IP bottles will be obtained at visits V3 (before and after first dose), V4, V5, V6, and unanticipated/early termination visit.
8. Subjects will be counseled on the application of the nasal spray, study diary, and answer any questions.
9. Fasting blood sample for a comprehensive metabolic panel, complete blood count, chemistry, lipid panel, and liver function test-15 ml. Also includes urinalysis. Patients should fast for at least 8 hours before the test. Blood will be shipped to the central lab for processing.
10. Urine pregnancy test to be done on WOCBP.
11. Intranasal strip will be used to collect nasal fluid for inflammatory cytokines. Optionally, nasal fluid may be evaluated for nasal microbiome (e.g., PCR) to confirm presence of B244.
12. Subjects will be asked to fill out a daily migraine-history diary from screening to treatment with study drug and a migraine-treatment diary from treatment through the remainder of the follow-up period. Baseline period, prevention treatment, and follow up observation period for study assessments will be daily and will include dosing, migraine days, headache days, migraine intensity, headache intensity, rescue meds (acute migraine specific meds), nausea, vomiting, photophobia, and sonophobia. Collect sufficient information about the headache in the trial (i.e., headache intensity, presence/absence of associated symptoms, unilateral/bilateral location, aggravation by exercise, throbbing/non-throbbing) to verify the headache is a migraine.
13. Migraine Disability Assessment questionnaire.
14. Headache Impact Test-6 questionnaire.
15. Migraine Specific Quality of Life questionnaire.
16. Clinical Global Impression scale
17. Subjects are randomized upon confirming the inclusion/exclusion criteria and the entry criteria of 4-14 migraine headache days during the baseline period.
18. Only for Early Termination Visit due to study discontinuation or withdrawal.

Figure 1: Study Flow



1.2.4. Efficacy, Safety and Exploratory Parameters

1.2.4.1. Safety Parameters

The primary endpoint is to assess safety and tolerability of the drug. Safety and tolerability will be assessed by reporting of adverse events, physical examination, vital signs (blood pressure, heart rate, respiratory rate), ECG, Laboratory test values, concomitant medications and rescue medications.

1.2.4.2. Efficacy Parameters

The efficacy endpoints will be assessed by:

- Mean change in monthly migraine days from baseline (Day -28 to-1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Proportion of subjects experiencing at least 50% reduction in monthly migraine days from baseline (Day -28 to -1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly migraine attacks from baseline (Day-28 to -1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly acute migraine specific medication days from baseline (Day -28 to -1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly moderate and severe headache days (migraine pain-intensity score) from baseline (Day -28 to -1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly headache days (migraine and non-migraine headache) from baseline (Day -28 to -1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly headache hours (migraine and non-migraine headache hours) from baseline (Day -28 to -1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change from end of baseline assessment (V3) to assessment after 12 weeks of treatment (V6) in disability, as measured by the Migraine Disability Assessment (MIDAS) questionnaire.
- Mean change from baseline (V3) to 12 weeks of treatment and to 4 weeks of follow-up period in monthly Headache Impact Test-6 (HIT-6) questionnaire (i.e., V4, V5, V6 and V7).
- Mean change from baseline (V3) to 12 weeks of treatment and to 4 weeks of follow-up period in monthly Migraine Specific Quality of Life questionnaire (MSQL) questionnaire (i.e., V4, V5, V6 and V7)
- Difference in Clinical Global Impression (CGI) score between treatment groups after every 4 weeks of treatment and after 4 weeks of follow-up period (i.e., V4, V5, V6 and V7).

1.2.4.3. Exploratory Parameters

- Mean change in migraine days from end of treatment (Day 57 to 84) to follow-up (Day 1P to 28P).
- Mean change in migraine associated symptoms: nausea/vomiting, photophobia and sonophobia from baseline (Day -28 to -1) to 12 weeks of treatment and to 4 weeks of follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).

1.3. Subject Population

Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: Includes all randomized subjects who received at least 1 dose of drug and have 80% electronic patient reported outcome (ePRO) diary compliance. Subjects will be analyzed according to the treatment assigned by the randomization schedule.
- Safety Population: Includes all subjects who received at least 1 dose of study medication. Subjects will be analyzed according to the study drug received.
- Per Protocol (PP) Population: Includes subjects who administered at least 50% of Investigational Product (IP) (based on the weight of IP used over 84 days calculated using the algorithm: unused bottle weight – used bottle weight – priming volume weight) must be at least 50% of the initial theoretical product weight i.e.(0.14 g per spray × 4 sprays per day × 42 days = 23.52 g)), have completed their Week 12 visit and did not have any major protocol violations.

The ITT population is the primary population for the analysis of efficacy parameters. A subset of efficacy parameters will be evaluated for the PP population (see Section 3.3). The Safety population is the primary population for the analysis of safety endpoints.

1.4. Migraine and Headache Endpoint Definitions

Migraine data will be based on the daily migraine diary which is captured using an ePRO device.

Migraine: Migraine is defined in accordance with the International Headache Society (IHS). For the purpose of migraine endpoints, a headache will be considered a migraine if it meets the IHS definition for migraine without aura, migraine with aura, or probable migraine. Requirements for the IHS criteria are described below.

Migraine without aura (per IHS 1.1 criteria):

- Headache attacks lasting 4-72 hours
- At least 2 of the following:
    - unilateral location
    - pulsating quality
    - moderate or severe pain intensity
    - aggravation by or causing avoidance of routine physical activity

- At least one of the following
    - nausea and/or vomiting
    - photophobia and sonophobia

Migraine with aura (per IHS 1.2 criteria):

- Migraine associated with one or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, retinal.
- At least 3 of the following:
    - At least one aura symptoms spreads gradually over >5 min
    - 2 or more aura symptoms occur in succession
    - Each individual aura symptoms lasts 5-60 min
    - At least one aura symptom is unilateral
    - At least one aura symptom is positive
    - The aura is accompanied or followed within 60 min by Headache

Probable Migraine:

A probable migraine is defined as a headache that meets only 2 of the 3 criteria listed in the migraine without aura definition

Migraine Day:

Migraine day is defined as any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). It is a self-reported headache which meets the IHS criteria for migraine with or without aura or probable migraine. A headache reported with aura qualifies as a migraine day.

- If the patient uses a migraine specific medication such as a triptan, any headache attack at least 30 minutes in length will be counted as a migraine day.
- Migraine day will be determined from a 24-hour period from 12 am to 11:59 pm each day.

Migraine attack:

A migraine attack is defined as an episode of any qualified migraine headache. To distinguish an attack of long duration from two attacks or to distinguish between attacks and relapses:

- A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (i.e., <48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack and not two.
- An attack treated successfully with medication but with relapse within 48 hours (i.e., <48 hours between the start of the migraine attack to the time of recurrence) will be considered as one attack.

Headache Day:

A calendar day on which a headache occurred (migraine and non-migraine headache).

1.5. Protocol Deviations

All the following deviations will be summarized on the ITT patient population and may include:

- Inclusion or exclusion criteria not satisfied.
- Deviations related to the Investigational Product administration
- Not permitted concomitant medications.
- Less than 80% of the ePRO migraine diary is completed.

At the discretion of the Sponsor, major protocol deviations, as determined by a review of the data prior to unblinding of the study results and the conduct of statistical analyses, may result in the removal of a subject's data from the PP population. The Sponsor or designee will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable; this file will include a description of the protocol deviation and clearly identify whether or not this violation warrants exclusion from the PP population. This file will be finalized prior to hard database lock.

All protocol deviations will be presented in a data listing.

2. GENERAL STATISTICAL METHODS

2.1. Sample Size Justification

Approximately 303 subjects will be enrolled in order to achieve a target sample size of 264 (i.e., 88 subjects per arm), allowing for a 10-15% drop-out rate.

Group sample sizes of 88 per arm achieve 80% power to reject the null hypothesis of equal means when the population mean difference is $\mu_1 - \mu_2 = -3.8 - -2.3 = -1.5$, where μ_1 is the mean reduction in migraine headache days for an active treatment arm and μ_2 is the mean reduction in migraine headache days for placebo. The sample size calculation assumes a standard deviation for both groups of 4.0 and a Bonferroni adjusted significance level (alpha) of 0.05 using a one-sided two-sample equal-variance z-test. Testing each active treatment arm versus vehicle at an adjusted significance level of 0.05 maintains an overall error rate of 0.10.

2.2. General Methods

The analyses will be conducted on all subject data when the trial ends. Data will be presented by treatment group and pooled B244 group except where noted. Listings will be sorted by treatment group and subject.

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc.

All outputs will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

Assuming raw or derived variables are to 'x' decimal places, the data will be presented as follows:

- Range to x decimal places
- Mean and median to (x+1) decimal places
- SD to (x+2) decimal places
- (x+2) should not be greater than 4 decimal places
- Percentages may be calculated without a decimal place or with (x+1) decimal place

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints with all tests conducted at the one-sided, 0.05 level of significance. Summary statistics will be presented, as well as a one sided 95% confidence intervals for the difference in treatment groups means, and the p-value from the hypothesis test of no difference in treatment

group means. P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as <0.001, and p-values that round to 1.00 will be presented as >0.999.

Monthly total:

The monthly totals for the various parameters will be based on a 4-week period as follows:

Monthly totals for Baseline: Total between study day -1 to -28

Monthly totals for Week 4: Total between study day 1 - 28

Monthly totals for Week 8: Total between study day 29 - 56

Monthly totals for Week 12: Total between study day 57 – 84

Monthly totals for Week 16 (follow up period): Total between 1P – 28P

2.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software v9.4 or later unless otherwise noted. Medical history and AEs will be coded using MedDRA v21.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary March 2018.

2.4. Baseline Definitions

For all safety analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug. For all efficacy analysis, baseline period is defined as the 4-week period before randomization where the subject is observed for their medical condition – Migraine. Specifically, baseline period is the 4-week period starting from the day prior to the randomization date and going back 28 days to the baseline date. The baseline date (regardless of the baseline visit V2 date) is the first day of the 28-day period that ends on the day before the randomization date. The day of first dose of study medication is Day 0 in the Schedule of Assessments (SOA) and will be considered Relative Study Day 1 in order to construct Clinical Data Interchange Standards Consortium (CDISC) compliant datasets.

2.5. Methods of Pooling Data

Subjects will be pooled across all sites. Data will be presented by treatment group and by pooled B244 group.

2.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

2.7. Multiple Comparisons/Multiplicity

The secondary efficacy endpoints are considered descriptive or exploratory and, therefore, the analyses will not be adjusted for multiple endpoints.

2.8. Subpopulations

Exploratory subgroup analysis by race, gender, and age will be analyzed. In addition, subjects with and without medical history of depression will be analyzed. Furthermore, subjects with systolic blood pressure of <120 mmHg, 120-139 mmHg, and ≥140 mmHg will be analyzed for the primary and secondary efficacy endpoints.

2.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects who dropout after enrollment but prior to randomization will be replaced.

2.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the case report form will be included in data listings that will accompany the clinical study report.

2.10.1. Efficacy Data

When analyzing the ePRO migraine diary entries and the start and stop dates and times of migraine/ headache, the following imputation rules will be followed:

If the start date and/or time of the migraine/headache is missing for a headache that is not a continuation since the last diary entry (i.e., a new headache), then the beginning of the calendar day for the current diary entry (i.e., 00:00) will be used as the start date and/or time.

If the stop date and/or time of the migraine/headache is missing for a headache that is not ongoing at the time of diary entry (i.e., headache ended), then the ePRO date and time stamp of the current diary entry will be used as the stop date and/or time.

If both the start date and/or time and the stop date and/or time of the migraine/headache are missing, then both imputation rules above will apply.

If a migraine/headache is reported as a continuation of the headache from the last diary entry in error (i.e., reporting that a migraine/headache is continuing from the last diary entry even though there was no migraine/headache reported or it was closed out in the previous entry) and as a result the start date and/or time of the migraine/headache is unknown, then the last diary entry date and time stamp will be considered as the start date and time.

If there is a diary entry (regardless of whether it is a new migraine/headache or a continuation since the last entry) and the migraine/headache is currently ongoing at the time of diary entry that is continuing into the next diary day but is reported as a no headache day in the next diary entry, then the headache end date and time will be 23:59 the previous diary entry.

If there are any missing diary entry or entries after a diary entry with a migraine/headache reported as ongoing at the time of that diary entry, then the end date and time of the migraine/headache will be 23:59 the day of the diary entry.

If there is a diary entry that is not a continuation of the migraine/headache from the last entry (i.e., a new headache) and is ongoing at the time of entry (i.e., headache is not closed out) but a new migraine/headache is reported in the next diary entry that is not a continuation from the last entry (i.e., another new headache), then the headache end date and time of the original headache will be 23:59 the previous day and the headache start time will be as reported.

Migraine duration will be truncated at a maximum of 72-hour duration, regardless of reported or imputed dates and times.

Migraine/headache start date and times that are reported to have begun more than 48 hours before the ePRO date and time stamp for the same entry will not be considered for analysis.

Migraine/headache start date and times that are after the ePRO date and time stamp for the same entry will also not be considered for analysis.

Migraine/headache start and/or end times that are inadvertently entered in 12-hour clock will be converted to 24-hour clock for analysis.

Migraine/headache dates that are inadvertently entered with the wrong month will be converted to the current month of diary entry.

For multiple distinct diary entries on the same date without a missing diary entry the previous day, entries for continued and/or ongoing migraine/headache will be selected first. If none occur, entries with reported migraine/headache occurrence will be selected over entries without migraine/headache occurrence. If there are multiple migraine/headache entries that overlap in time of occurrence, migraine entries will be taken over headache entries. For multiple migraine or multiple headache entries that overlap in time of occurrence, respectively, the start and stop date and time of the longest migraine/headache duration will be included.

For multiple distinct diary entries on the same date without a missing diary entry the previous day, multiple entries will be considered if the multiple migraine/headache entries do not overlap in time. For example, if there are 2 entries, both entries will be considered if the first entry is closing out a headache (with an end date and time) that is a continuation from the last entry but not ongoing at the time of entry, and the second entry is a second migraine/headache attack that started after the first migraine/headache is closed out.

For duplicate identical diary entries on the same date without a missing diary entry the previous day, then only the last entry will be considered.

If there is a missing diary entry on a given date, two diary entries will be allowed for analysis the next day, one for the missing day (between 24- and 48-hour recall) and the other for the usual diary entry (up to 24-hour recall).

If there is a diary entry that is a continuation of the migraine/headache from the last entry and is not ongoing at the time of entry (i.e., headache is closed out) but another migraine/headache is reported in the next diary entry as a continuation from the last entry, then the headache start date and time of the new headache will be 00:00 in the next diary entry.

For distinct diary entries on different dates that cover the same headache event, only the latest diary entry covering the same headache event will be included.

2.10.2. Adverse Event Data

When tabulating adverse event data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment.

In all cases, the resulting date will be compared to the AE end date, if present. If the imputed start date is later than the AE end date, then the start date will be set equal to the end date. The imputed start date is used only for determining treatment emergence; data listings will present the partial date as recorded on the CRF.

Missing AE severities will not be computed and will be considered missing in any tabulations of AE severity. When relation of AEs to the study drug is missing, the AE will be considered "related" to study drug.

2.10.3. Prior and Concomitant / Rescue Medication

When tabulating prior/concomitant medication data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the start date to the date of first dose.
- If the month and day are missing and the year is earlier than the year of the first dose, then set the start date to December 31. Otherwise, set the start date to January 1.
- If only the day is missing, if the month/year is earlier than the month/year of the first dose then set the start date to the first day of the month. Otherwise, set the start date to the last day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing, then set the end date to December 31.
- If only the day is missing, then set the end day as the last day of the month.

If the imputed start date is later than the imputed end date, then set the imputed start date to the imputed end date.

When tabulating rescue medication data, missing dates and/or times of rescue medications taken will be handled as follows:

- If the date and/or time of the rescue medication taken is missing, then the headache start date and time for that day will be used; if there is no headache or if no sufficient information is available, then the ePRO date and time stamp (converted to local date and time) will be used.
- If the date and/or time of the rescue medication taken is wrongly entered (i.e., the date and/or time is not within 48 hours of the ePRO date and time stamp OR is entered using a 12 hour clock instead of a 24 hour clock), then the headache start date and time for that day will be used; if there is no headache or if no sufficient information is available, then the ePRO date and time stamp (converted to local date and time) will be used.
- Multiple entries of rescue medication taken in a given calendar day with the same medication or different medications will be counted as one rescue medication day.

2.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

2.12. Rebaselining

During the baseline period of 4 weeks if the subject meets the eligibility criteria of 4-14 migraine days but is short on diary compliance of 80%, then:

1. Any missed entries that were entered the next day, allowing for up to 48-hour recall would be counted to make up the compliance to 80%.

2. If the criterion is still not met, then additional 4 days (over the ± 3-day window) would be added to the screening period and the last 28 days before randomization would be considered as the baseline period.
3. If the criterion is still not met, then the baseline period could be shifted (i.e., reset) to allow subjects to enter additional diary days as needed to make up the compliance to 80% and the last 28 days before randomization would be considered as the baseline period.

2.13. Diary Compliance

For calculating diary compliance, one migraine diary entry per day will be considered. If there is no entry for a particular day, the subject will be considered noncompliant for that day. If there are more than one entry for a particular day to cover the entry for the previous day (allowing 48-hour recall), then the subject will be compliant for that day and the day before. Each completed subject's total diary compliance will be calculated from the baseline visit (V2) to the follow-up visit (V7).

In December 2018, IBM ePRO diary was down for a period of 10 days and around 10 subjects were not able to enter in data during that period. Those days will not be counted for calculating compliance for that month for that subject. Subject details and dates will be specified in a 'Note to file' as it will need to be hard coded while programming.

2.14. Normalizing Data

If the number of days the subject has entered the ePRO diary is less than 28 days per month (i.e., the subject has missed entries and have less than 100% diary compliance) or if there are less than 28 days available during an evaluation period (e.g., the last 4 weeks of treatment duration may be shortened due to end of treatment visit scheduling or the 4 week follow-up period is less than 28 days due to visit window scheduling), then the data will be normalized to calculate some of the efficacy parameters. It will be normalized by multiplying it by (28/x) where x is the actual number of days in the period or the days the subject had a diary entry.

The parameters where data will be normalized are: monthly migraine days, monthly migraine attacks, monthly acute migraine specific medication days, monthly moderate and severe headache days, monthly headache days, monthly headache hours.

2.15. Interim Analyses

No interim analyses are planned for this study.

3. STUDY ANALYSES

3.1. Subject Disposition

A tabulation of the disposition of subjects will be presented by treatment assignment and pooled B244 group. The number screened, enrolled and the number randomized, the number treated in each arm and the reasons for study discontinuation will be reported. Summaries of the number in each analysis set will be presented.

Entry criteria and protocol deviations will be listed. Screen failures will be listed.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

3.2. Demographics and Baseline Characteristics

Demographic and baseline characteristic data summarization will be performed in order to descriptively assess the comparability of strata and treatments. Summaries will be performed on the ITT, Safety and PP populations. Data to be tabulated will include age, sex, child-bearing potential (for females only), race, ethnicity, weight, height, body mass index (BMI), and smoking history as well as baseline characteristics.

Medical history will be coded using MedDRA v21.0, and the number and percentage of patients experiencing at least 1 such diagnosis by MedDRA System Organ Class (SOC) and preferred term (PT) will be reported. BMI and age will be analyzed as a continuous variable using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Sex, race, ethnicity and smoking status will be summarized by frequency (count and percent). Summary statistics for migraine data collected during the 4 week baseline period prior to the randomization period will be presented in a table by treatment group and pooled B244 group and will include the following parameters: Number of Migraine days, Number of Migraine attacks, Number of Acute Migraine Specific Medication days, Number of Moderate and Severe Headache Days, Number of Headache Days, Number of Headache hours, MIDAS score, HIT-6 score and MSQL score– all calculated at the end of the baseline period before randomization.

Demography, general medical history, and smoking history will be presented in data listings. Medical history will also be presented in a data listing.

3.3. Efficacy Evaluation

Efficacy analyses will be conducted using the ITT and PP population. In the event that these two populations are the same, only the ITT tables will be produced.

3.3.1. Continuous Outcomes

3.3.1.1. Monthly Migraine Days

Monthly migraine days is defined as the sum of migraine days calculated at the end of a 4-week period. It will be calculated at the end of 4-week baseline period and at the end of weeks 4, 8, 12 and 16.

Mean migraine days per month will also be calculated for the 12-week treatment period.

A sensitivity analysis will also be performed where all subjects with greater than or equal to 50% diary compliance will be considered.

3.3.1.2. Monthly Migraine Attacks

Monthly migraine attacks are defined as the sum of migraine attacks calculated at the end of each 4-week period. It will be calculated at the end of 4-week baseline period and at the end of weeks 4, 8, 12 and 16.

3.3.1.3. Monthly Acute Migraine Specific Medication Days

It is defined as the sum of the days on which the subject took a rescue medication for alleviating the Migraine/Headache pain. It will be calculated at the end of 4-week baseline period and at the end of weeks 4, 8, 12 and 16. If the patient took more than one medication during that day or multiple doses in a given day, this counts as one acute migraine specific medication day.

The list of rescue medications is as follows:

- All acute/abortive migraine medications (via mouth or injection only) such as triptans and ergot containing preparations (ergotamine tartrate, DHE 45).
- NSAIDs and analgesics (for example, acetaminophen, acetylsalicylic acid, combination analgesics) for migraine and non-migraine headaches.
- Opioid/barbiturate containing medications.

3.3.1.4. Monthly Moderate and Severe Headache Days

It is defined as the sum of the Migraine/Headache days that were rated 2 (moderate pain) or 3 (severe pain) by the subject on Migraine Pain Intensity Scoring scale calculated at the end of a 4-week period. It will be calculated at the end of 4-week baseline period and at the end of weeks 4, 8, 12 and 16.

Migraine Pain Intensity Score

International Headache Society guidelines for the conduct of controlled trials of headache treatments recommend the use of the 4-point verbal rating scale (VRS) to measure pain intensity.

The 4-point VRS scale for pain intensity is as follows:

0 = no pain

1 = mild pain (bothersome but not interfering with normal function)

2 = moderate pain (interfering with normal function)

3 = severe pain (requiring bedrest and unable to function)

3.3.1.5. Monthly Headache Days

It is defined as the sum of the headache (migraine and non-migraine headache) days calculated at the end of a 4-week period. It will be calculated at the end of the 4-week baseline period and at the end of weeks 4, 8 and 12.

3.3.1.6. Monthly Headache Hours

It is defined as the sum of the headache (migraine and non-migraine headache) hours calculated at the end of a 4-week period. It will be calculated at the end of the 4-week baseline period and at the end of weeks 4, 8 and 12.

3.3.1.7. MIDAS

Migraine Disability Assessment questionnaire examines the relationship between impact of migraine and quality of life. It is a set of 5 questions that need to be answered by the subject and the total number of days from those 5 questions gives the MIDAS score. A lower score represents a lower impact of migraine on the quality of life. It will be assessed at the beginning and end of the baseline period and at week 12.

MIDAS Grade	**Definition**	**MIDAS Score**
I	Little or No Disability	0-5
II	Mild Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

3.3.1.8. HIT-6

Headache Impact Test - 6 questionnaire examines the relationship between impact of migraine and quality of life. It is a set of 6 questions that need to be answered by the subject. Each question can get 6 to 13 points depending on the answer and the total of the points for each answer would give a total score. A lower score represents a lower impact of migraine on the quality of life. It will be assessed at the beginning and end of the 4-week baseline period and at the end of weeks 4, 8, 12, and 16. The results for each question of the HIT-6 will be assigned a score as follows:

Answer	**Points for Each Question**
Never	6
Rarely	8
Sometimes	10
Very Often	11
Always	13

Class	Total Score
I	36-49
II	50-55
III	56-59
IV	60 and more

3.3.1.9. MSQL

Migraine Specific Quality of Life questionnaire also examines the relationship between impact of migraine and quality of life. It is a set of 14 questions that need to be answered by the subject. It will be assessed at the beginning and end of the 4-week baseline period and at the end of weeks 4, 8, 12, and 16.

The questions measure the impact of migraine on health-related quality of life across three domains: 1) Role Function-Restrictive (seven questions) examines the degree to which performance of daily activities is limited by migraine; 2) Role Function-Preventive (four questions) examines the degree to which performance of daily activities is prevented by migraine; 3) Emotional Function (three questions) examines feelings of frustration and helplessness due to migraine. The questionnaire results will be recorded in the eCRF.

The results (precoded item value) for each question of the MSQL v2.1 will be recoded to a final item value as follows:

Answer	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

A raw domain score (algebraic sum of the final item value for all items in that domain, using imputed scores where applicable) will be calculated and transformed to a 0 to 100 scale as follows:

MSQL Domain	Raw Score Range	Transformation Formula
Role Function-Restrictive	7 to 42	(Raw Score – 7)*100/35
Role Function-Preventive	4 to 24	(Raw Score – 4)*100/20
Emotional Function	3 to 18	(Raw Score – 3)*100/15

Questions 1 to 7 of the questionnaire will be grouped together as Role Function-Restrictive domain, questions 8 to 11 as Role Function-Preventive domain and questions 12 to 14 as the Emotional Function domain. A higher raw score (algebraic sum of the final item value for all items in that dimension) represents a lower impact of migraine on the quality of life and a better health status. The transformation process allows each domain score to reflect the percentage of the total possible score achieved (since 100 equals the highest score).

In the event that responses on one or more items within a dimension are missing, a missing item value will be estimated using the average of the other items within the same dimension. This will only be done if at least half of the items within a dimension have been answered. When the number of missing responses exceeds the limits as noted above (i.e., the number of missing responses were more than half the questions in that dimension, meaning that imputation of missing scores will not be done), a domain score may not be estimated and should be considered as missing.

3.3.1.10. CGI

Clinical Global Impression: The clinician will assess the measures improvement and efficacy of treatments in patients. There are 3 subscores – CGI-S (Severity of Illness – a 7 pointer scale), CGI-I (Global Improvement – a 7 pointer scale) and CGI-E (Efficacy index – a 16 pointer scale). Severity of illness will not be assessed due to the mental health nature of the question. There is no total score or global score for this questionnaire just subscores. It will be assessed at the at the end of weeks 4, 8, 12, and 16. CGI-I will be the primary efficacy assessment for CGI. CGI-S will not be analyzed as it is not being captured.

Analysis Methods for Continuous Outcomes:

Summary statistics for actual and change from end of baseline (randomization) to Weeks 4, 8, 12 and 16 (as applicable) by treatment group and pooled B244 group will be presented for the following parameters.

- Monthly Migraine Days
- Monthly Migraine Attacks
- Monthly Acute Migraine Specific Medication Days
- Monthly Moderate and Severe Headache Days (based on the migraine pain intensity score)
- Monthly Headache Days
- Monthly Headache Hours
- MIDAS score (Baseline and Week 12 only)

- Monthly HIT-6 score
- Monthly MSQL domain scores
- Monthly CGI sub scores (only actual at each timepoint)

To assess treatment effect, change from baseline in parameter values will be analyzed using a mixed effect model including fixed effects for baseline value, treatment (B244 1x, B244 4x, or placebo), and time (Month 1, 2, 3, 4), and a repeated effect for subject. An interaction term between treatment and time may be included.

Estimates of the adjusted LS mean, difference in LS means, and corresponding 95% CIs will be obtained from the model. Linear contracts of the differences between the dose groups (B244 1x or B244 4x) and placebo at each month will be used to compare the results between treatments using LS means between each active treatment group and placebo. Nominal 1-sided p-values and 95% CIs will be reported at Month 1, 2, 3 and 4.

- Mean change in monthly migraine days from end of baseline (randomization) (Day -28 to -1) to 12 weeks of treatment and to follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly migraine attacks from end of baseline (randomization) (Day -28 to -1) to 12 weeks of treatment and to follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly acute migraine specific medication days from end of baseline (randomization) (Day -28 to -1) to 12 weeks of treatment and to follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly moderate and severe headache days (migraine pain-intensity score) from end of baseline (randomization) (Day -28 to -1) to 12 weeks of treatment and to follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly headache days from end of baseline (randomization) (Day -28 to -1) to 12 weeks of treatment and to follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change in monthly headache hours from end of baseline (randomization) (Day -28 to -1) to 12 weeks of treatment and to follow-up period (i.e., Day 1-28, 29-56, 57-84, 1P-28P).
- Mean change from end of baseline (V3) to 12 weeks of treatment (V6) in disability, as measured by the Migraine Disability Assessment (MIDAS) questionnaire.
- Mean change from end of baseline (V3) to 12 weeks of treatment and to 4 weeks follow-up period in monthly Headache Impact Test-6 (HIT-6) questionnaire score. (i.e.,V4, V5, V6 and V7).
- Mean change from end of baseline (V3) to 12 weeks of treatment and to 4 weeks of follow-up period in monthly Migraine Specific Quality of Life (MSQL) questionnaire dimensional scores. (i.e., V4, V5, V6 and V7).
- Difference in Clinical Global Impression (CGI) score between treatment groups after every 4 weeks of treatment and after 4 weeks of follow-up period (i.e., V4, V5, V6 and V7).

A shift table from end of baseline (V3) to week 12 (V6) will be presented for the MIDAS, and HIT-6.

By subject listings will be provided presenting the migraine days, headache days and severity, Rescue medications used for headaches and migraines, Migraine Disability Assessment Questionnaire, Headache Impact Test-6 (HIT-6) questionnaire, Migraine Specific Quality of Life questionnaire, and Clinical Global Impression (CGI) sub scores.

3.3.2. Binary Outcomes

Fisher's Exact test will be used to make treatment group comparisons for the following binary outcome:

- Proportion of subjects experiencing a ≥ 50%, ≥ 75% reduction in monthly migraine days from end of baseline to 12 weeks of treatment.

3.4. Pharmacokinetic Evaluation

No pharmacokinetic analyses will be conducted.

3.5. Safety Analyses

Safety analyses will be conducted using the Safety population.

3.5.1. Study Drug Exposure

The cumulative amount of study drug exposure will be estimated by calculating the difference between the weight of the 3 bottles of drug at the time the drug was dispensed and the weight of each of the 3 bottles after 4 weeks of use. If for some reason, the kit was replaced during the study, then the total weight of all the bottles of all the kits will be considered for calculating the weight of the product used. These weights will be compared to the weight of the product that would be used if the subject was compliant with the protocol and used the spray 4 times per day (1 spray per nostril BID) for 12 weeks.

Percent compliance will be summarized for each subject from date of first dose through the treatment period based on the net weight of the product administered. Net weight is calculated as the sum of weights collected after priming of each of the three bottles minus the weights collected after 4 weeks of use. Weight difference of the first bottle before and after priming will be used as the priming weight for the second and third bottles. Based on information provided by AOBiome, the expected amount of study drug used over 12 weeks is approximately 0.14 g per spray times 4 sprays per day times 84 days = 47.04 g.

$$Percentage\ Compliance = \frac{(NetWeightOfStudyDrug)*100}{(0.56g/day*84DaysOnStudy)}$$

The number of days the subject administered study drug, the amount of product used, and the percent compliance will be summarized by treatment group and presented in a by-subject data listing. The subject listing will also include by-visit IP weights. Percent compliance will be calculated only for subjects who returned the study drug at the end of Week 12. In the listing, subjects who withdrew from the study early will be flagged.

Dose compliance for each subject will also be calculated based on the number of doses out of the total doses that were administered from the dose administration diary.

When tabulating dose administration data, missing or wrongly entered dates and/or times of dose administration will be handled as follows:

- If the date and/or time of the dose administration is missing, then the ePRO date (converted to local date) and 06:00 will be used for the morning dose and ePRO date and time stamp (converted to local date and time) will be used for the night time dose for that day.
- If the date and/or time of the dose administration is wrongly entered (i.e., the date and/or time is not within 48 hours of the ePRO date and time stamp OR is entered using a 12 hour clock instead of a 24 hour clock), then the ePRO date (converted to local date) and 06:00 will be used for the morning dose and ePRO date and time stamp (converted to local date and time) will be used for the night time dose for that day.
- Two dose administration entries will be allowed in a given day if there was a missed entry the day before; one would be the normal entry for that day and the other would be for the day before.

3.5.2. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as any AEs that begin or worsen on or after the start of study drug through 28 days after the last dose of study drug. If the start date of the adverse event is missing then the date will be imputed such that the AE is treatment emergent.

Serious Adverse Event (SAE): An AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Associated with Use of the Study Drug: There is a reasonable possibility that the experience may have been caused by the study drug. If the Investigator does not know whether or not study drug caused the event, then the event will be handled as "related to study drug" for reporting purposes. The determination of whether an AE is related to study drug is as follows:

- Related: The AE has a missing, unknown, possible, probable or definite relationship to the study medication.
- Not related: The AE is unlikely or definitely unrelated to the study drug.

A treatment-related TEAE is defined as a TEAE that was considered by the Investigator to be at least possibly related to the study drugs. If the 'Relationship to study drug' is missing, then it will be imputed as 'Related to study drug.'

If a subject experiences the same AE more than once with different toxicity grades, the event with the highest grade will be tabulated in the "by grade" tables. If a subject experiences multiple AEs under the same preferred term (SOC), the subject will be counted only once for that preferred term (SOC). In addition, AEs with a missing severity will be presented in the summary table as an intensity category of "Missing."

An overall summary table presenting the number of subjects who experienced the following will be presented by treatment arm and pooled B244 group: any TEAE, any related TEAE, any severe (or Grade 3 or 4) TEAE, any severe related TEAE, any serious TEAE, any serious

related TEAE, any TEAE leading to discontinuation of study drug, any TEAE leading to study discontinuation, and any TEAE leading to death.

The incidence of TEAEs will be summarized by MedDRA SOC and preferred term. Tables summarizing the incidence of TEAEs will be generated for each of the following:

- All TEAEs
- TEAEs reported as treatment-related
- Severe or Grade 3 or 4 TEAEs
- Severe or Grade 3 or 4 TEAEs as treatment-related
- Serious TEAEs
- Serious TEAEs as treatment-related

If no subjects experience any of the events in the overall summary table, the corresponding table by SOC and preferred term will not be produced.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on-study will be listed in subject data listings.

By-subject listings also will be provided for the following: serious AEs, subject deaths, and AEs leading to withdrawal.

3.5.3. Laboratory Data

Clinical laboratory values will be expressed in SI units reported by the central laboratory.

The actual value and change from end of baseline (randomization) to Week 12 will be summarized for each hematology, chemistry and urinalysis parameter by treatment group and pooled B244 group. In the event of repeat values, the last non-missing value per visit will be used.

All laboratory data will be provided in data listings. Values outside of the lab parameter's normal range will be flagged as high, low, or abnormal based on the range of the test.

Urine pregnancy test results will also be provided in a data listing.

3.5.4. Vital Signs and Physical Examination

Vital sign measurements will be presented for each subject in a data listing. Systolic blood pressure, diastolic blood pressure, heart rate, and weight will be summarized using descriptive statistics as actual value and change from end of baseline (randomization) by each visit and by treatment group and pooled B244 group.

Responders are defined as subjects with ≥10 mmHg systolic blood pressure reduction from baseline or ≥5 mmHg diastolic blood pressure reduction from baseline in the clinic setting. Responder subjects whose systolic blood pressure is ≥120 mmHg at baseline (Visit 3). Responder analysis will be performed for in-clinic blood pressure reduction after 4, 8, and 12 weeks of treatment and 4 weeks of follow-up against baseline. The number and percentage of subjects as responders will be calculated by treatment group and pooled B244 group. In addition, the number and percentage of all subjects whose blood pressure recorded either ≥130 mmHg systolic blood pressure or ≥80 mmHg diastolic blood pressure at each visit will be reported.

All physical examination (including neurological examination), vital signs, and nasal inspection findings will be presented in separate by subject data listings. Systolic and diastolic blood pressure by subject by visit for responders will also be presented in a listing.

3.5.5. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Concomitant medications will be tabulated by treatment group and pooled B244 group, where any medications that did not end prior to first dose will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The use of concomitant medications will be included in a by-subject data listing. A separate listing for rescue medications will also be presented.

3.5.6. Electrocardiogram

Electrocardiogram results will be summarized descriptively, including the number and percentage of subjects with normal, abnormal, and clinically significant abnormal results at Screening, End of Baseline (randomization) and at Week 12 by treatment group and pooled B244 group.

Electrocardiogram data for each subject will be provided in a data listing.

3.6. Exploratory Analyses

3.6.1. Migraine Days After Treatment

Mean change in migraine days from the last 4 weeks of treatment (Day 57 - 84) to the 4-week follow-up period (Day 1p -28P) will be evaluated and presented by treatment group and pooled B244 group.

3.6.2. Migraine Associated Symptoms

Mean change in the number of days with Migraine associated symptoms:

a) Nausea / vomiting

b) Photophobia and sonophobia

will be evaluated. Number of days with nausea / vomiting or photophobia and sonophobia during the baseline period of 4 weeks will be compared against the number of days with symptom during weeks 1 to 4, 5 to 8, 9 to 12 and 13 to 16 and will be presented by treatment group and pooled B244 group.

3.6.3. Anchor Identification

A minimally clinically important difference in migraine headache days may be determined by assessing associations between patient reported MIDAS and/or clinician reported CGI measures with change from baseline in migraine headache days.

4. CHANGES TO PLANNED ANALYSES

1. Cytokine concentration Analysis specified in the Protocol as exploratory analysis will not be analyzed at this point as we won't receive any data for the same.
2. The ITT population definition is modified to include only subjects with 80% ePRO diary compliance in addition to the conditions already mentioned in the protocol.
3. All efficacy analysis will be based on mixed model analysis instead of the z test as specified in the protocol.
4. The 'headache day' definition is modified and is defined as a calendar day on which a headache occurred (migraine and non-migraine headache), as clarified from the protocol which defines a headache day as a non-migraine headache day.

5. REFERENCES

1 Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. Neurology 2002; 58: 885–94.

2 Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology 2008; 71: 559–66.

3 Terwindt GM, Ferrari MD, Tijhuis M, Groenen SMA, Picavet HSJ, Launer LJ. The impact of migraine on quality of life in the general population. The GEM Study. Neurology 2000; 55: 624-9.

4 Lipton RB, Hemelsky SW, Kolodner KN, Steiner TJ, Stewart WF. Migraine, quality of life and depression. A population- based case-control study. Neurology 2000; 55: 629–35.

6. STATISTICAL OUTPUT

6.1. List of Statistical Output

6.2. Statistical Output Shells

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.1.1

Subject Enrollment and Disposition
(All Enrolled Subjects)

Disposition	Statistics	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Total Number of Subjects					
Screened	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Screened Failures [1]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Enrolled	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomized [1]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treated [2]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed the Study [3]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study Population [4]					
Intent-to-Treat (ITT)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Per Protocol (PP)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Early Study Discontinuation					
Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of consent by subject	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator's decision	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Percentage based on number screened.
[2] Percentage based on the number randomized.
[3] Percentage and all subsequent percentages based on the number treated.
[4] Intent-to-Treat Population: includes all randomized subjects who receive at least 1 dose of study medication and have 80% epro diary compliance, analyzed according to the treatment assigned by the randomization schedule.
Safety Population: Includes all subjects who receive at least 1 dose of study medication. Subjects will be analyzed according to the study drug received.
Per Protocol Population: Includes subjects who administered at least 50% of IP (based on the weight of IP used calculated using the algorithm: unused bottle weight – used bottle weight – priming volume weight) must be at least 50% of the initial theoretical product weight i.e.(0.14 g per spray x 4 sprays per day x 42 days = 23.52 g)), have completed their Week 12 visit and did not have any major protocol violations.
Source: Listing 16.2.1.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB224-001

Table 14.1.2.1A

Demographics and Baseline Characteristics
(ITT Population)

Parameter	Statistics	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Age (years)	n	xx	xx	xx	Xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Sex					
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Child-bearing potential (for females only)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No					
Race					
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity					
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Listing 16.2.4.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics Confidential Page 2 of x
Protocol MGB224-001

Table 14.1.2.1A

Demographics and Baseline Characteristics
(ITT population)

Parameter	Statistics	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Weight (kg)	n	xx	xx	xx	Xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Height (meters)	n	xx	xx	x	Xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
BMI Category (kg/m^2)					
<20	n	xx	xx	xx	xx
20-<25	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
25-<30	Median	xx.x	xx.x	xx.x	xx.x
>=30	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Smoking History					
Never	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Former	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Current	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Listing 16.2.4.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.1.2.1B Demographics and Baseline Characteristics (Safety Population)
Table 14.1.2.1C Demographics and Baseline Characteristics (PP Population)

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Table 14.1.3.1

Baseline Migraine Data
(ITT Population)

Parameter	Statistics	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Number of Migraine Days	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Number of Migraine Attacks	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Number of Acute Migraine Specific Medication Days	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Number of Moderate and Severe Headache Days	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Number of Headache Days	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Number of Headache Hours	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics Confidential Page 2 of x
Protocol MGB224-001

Table 14.1.3.1

Baseline Migraine Data
(ITT Population)

Parameter	Statistics	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
MIDAS Score	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
HIT Score	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
MSQL Score	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.1.3.2 Baseline Migraine Data (PP Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB244-001

Table 14.1.4.1

Concomitant Medication by Anatomic Therapeutic Class and Preferred Term
(Safety Population)

ATC Class Preferred Term	Statistics	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
ATC 1					
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					
ATC 2					
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					
Etc.					

Source: Listing xxxx
Note: Concomitant medications are any medications that did not end prior to first dose. If an end date is missing or the medication is ongoing, the medication is included.
Note: Concomitant medications anatomic therapeutic class (ATC) and preferred term (PT) are coded using the WHO Drug Dictionary version March 2017.
This listing does not include Rescue Medications taken to relieve any migraine or headaches.
Source: Listing 16.2.9.3

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB244-001

Table 14.1.5.1

Rescue Medications – Diary
(Safety Population)

ATC Class Preferred Term	Statistics	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
ATC 1					
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					
ATC 2					
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					
Etc.					

Source: Listing 16.2.5.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.1.6.1

Summary of Drug Exposure
(ITT Population)

Parameter	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Cumulative Study Drug Exposure (g)	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Amount of Product Used per Day (g)	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Days of Study Drug Administration	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Percent Compliance	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

[1] Cumulative study drug exposure = weight of the 3 drug bottles at last visit - weight of the 3 drug bottles at first dispense.
[2] Amount of product used per day = change / number of days the subject was on treatment.
[3] Percent compliance = (Net weight of study drug) / (0.56g per day *84 days on study) × 100.
Source: Listing 16.2.5.2
PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.1.6.2 Summary of Drug Exposure (PP Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.1A

Summary of Values and Change from Baseline for Monthly Migraine Days – Mixed Effects Model for Repeated Measures (MMRM)
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28 (Week 4)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16)

Repeat Table 14.2.1.1A for:

Table 14.2.1.1B Summary of Values and Change from Baseline for Monthly Migraine Days – Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.1C Summary of Values and Change from Baseline for Monthly Migraine Days by Race – Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.1D Summary of Values and Change from Baseline for Monthly Migraine Days by Gender – Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.1E Summary of Values and Change from Baseline for Monthly Migraine Days by Age Group – Mixed Effect Repeated Measures (MMRM) Model (ITT Population)

Table 14.2.1.1F Summary of Values and Change from Baseline for Monthly Migraine Days by History of Depression – Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.1G Summary of Values and Change from Baseline for Monthly Migraine Days for subjects having at least 50% diary compliance – Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.1H Summary of Values and Change from Baseline for Monthly Migraine Days for subjects having at least 50% diary compliance – Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.2A

Summary of Values and Change from Baseline for Monthly Migraine Attacks – Mixed Effects Model for Repeated Measures (MMRM)
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28 (Week 4)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16)

Repeat Table 14.2.1.2A for:

Table 14.2.1.2B Summary of Values and Change from Baseline for Monthly Migraine Attacks - Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.2C Summary of Values and Change from Baseline for Monthly Migraine Attacks by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.2D Summary of Values and Change from Baseline for Monthly Migraine Attacks by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.2E Summary of Values and Change from Baseline for Monthly Migraine Attacks by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.2F Summary of Values and Change from Baseline for Monthly Migraine Attacks by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) Model (ITT Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.3A

Summary of Values and Change from Baseline for Monthly Acute Migraine Specific Medication Days – Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28 (Week 4)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16)

Repeat Table 14.2.1.3A for:

Table 14.2.1.3B Summary of Values and Change from Baseline for Monthly Acute Migraine Specific Medication Days - Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.3C Summary of Values and Change from Baseline for Monthly Acute Migraine Specific Medication Days by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.3D Summary of Values and Change from Baseline for Monthly Acute Migraine Specific Medication Days by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.3E Summary of Values and Change from Baseline for Monthly Acute Migraine Specific Medication Days by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.3F Summary of Values and Change from Baseline for Monthly Acute Migraine Specific Medication Days by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.4A

Summary of Values and Change from Baseline for Monthly Moderate and Severe Headache Days – Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28 (Week 4)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16)

Repeat Table 14.2.1.4A for:

Table 14.2.1.4B Summary of Values and Change from Baseline for Monthly Moderate and Severe Headache Days - Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.4C Summary of Values and Change from Baseline for Monthly Moderate and Severe Headache Days by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.4D Summary of Values and Change from Baseline for Monthly Moderate and Severe Headache Days by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.4E Summary of Values and Change from Baseline for Monthly Moderate and Severe Headache Days by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.4F Summary of Values and Change from Baseline for Monthly Moderate and Severe Headache Days by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.5A

Summary of Values and Change from Baseline for Monthly Headache Days – Mixed Effects Model for Repeated Measures (MMRM)
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28 (Week 4)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16)

Repeat Table 14.2.1.5A for:

Table 14.2.1.5B Summary of Values and Change from Baseline for Monthly Headache Days - Mixed Effects Model for Repeated Measures (MMRM) Model (PP Population)

Table 14.2.1.5C Summary of Values and Change from Baseline for Monthly Migraine Attacks by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.5D Summary of Values and Change from Baseline for Monthly Migraine Attacks by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.5E Summary of Values and Change from Baseline for Monthly Migraine Attacks by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.5F Summary of Values and Change from Baseline for Monthly Migraine Attacks by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.6A

Summary of Values and Change from Baseline for Monthly Headache Hours – Mixed Effects Model for Repeated Measures (MMRM)
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28 (Week 4)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16)

Repeat Table 14.2.1.6A for:

Table 14.2.1.6B Summary of Values and Change from Baseline for Monthly Headache Hours - Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.6C Summary of Values and Change from Baseline for Monthly Headache Hours by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.6D Summary of Values and Change from Baseline for Monthly Headache Hours by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.6E Summary of Values and Change from Baseline for Monthly Headache Hours by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.6F Summary of Values and Change from Baseline for Monthly Headache Hours by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB224-001

Table 14.2.1.7A

Summary of Values and Change from Baseline for MIDAS Score – Mixed Effects Model for Repeated Measures (MMRM)
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 12	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.3

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat Table 14.2.1.7A for:

Table 14.2.1.7B Summary of Values and Change from Baseline for MIDAS Score - Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.7C Summary of Values and Change from Baseline for MIDAS Score by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.7D Summary of Values and Change from Baseline for MIDAS Score by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.7E Summary of Values and Change from Baseline for MIDAS Score by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.7F Summary of Values and Change from Baseline for MIDAS Score by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.8A

Summary of Values and Change from Baseline for HIT-6 Total Score – Mixed Effects Model for Repeated Measures (MMRM)
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 4	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.4

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16)

Repeat Table 14.2.1.8A for:

Table 14.2.1.8B Summary of Values and Change from Baseline for HIT-6 Total Score - Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.8C Summary of Values and Change from Baseline for HIT-6 Total Score by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.8D Summary of Values and Change from Baseline for HIT-6 Total Score by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.8E Summary of Values and Change from Baseline for HIT-6 Total Score by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.8F Summary of Values and Change from Baseline for HIT-6 Total Score by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.9A

Summary of Values and Change from Baseline for MSQL Transformed Score – Mixed Effects Model for Repeated Measures (MMRM)
(ITT Population)

Domain: Role-Function

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 4	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		LS-Mean (SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		LS-Mean Difference B244-Placebo(SEM)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
		95% CI	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
		P-value [1] (vs Placebo)	0.xx	0.xx	0.xx	
		P-value [1] (vs B244 4X)	0.xx			

The MMRM model includes baseline values, treatment and time as fixed effects, a repeated effect for subject and an interaction term between treatment and time.
[1] P-value is derived from the contrast testing at each visit using the MMRM model.
Source: Listing 16.2.6.5

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16). Repeat all visits for Role Function -Preventive and Emotional Function Domains.

Repeat Table 14.2.1.9A for:

Table 14.2.1.9B Summary of Values and Change from Baseline for MSQL Transformative Score - Mixed Effects Model for Repeated Measures (MMRM) (PP Population)

Table 14.2.1.9C Summary of Values and Change from Baseline for MSQL Transformative Score by Race - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.9D Summary of Values and Change from Baseline for MSQL Transformative Score by Gender - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.9E Summary of Values and Change from Baseline for MSQL Transformative Score by Age Group - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

Table 14.2.1.9F Summary of Values and Change from Baseline for MSQL Transformative Score by History of Depression - Mixed Effects Model for Repeated Measures (MMRM) (ITT Population)

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB224-001

Table 14.2.1.10A

Summary of Values for CGI Score
(ITT Population)

Domain	Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
CGI-I (Global Improvement)	Week 4	Actual	n	xx	xx	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x	xx.x
			Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

Source: Listing 16.2.6.6

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16). Repeat all visits for CGI-E (Efficacy Index)

Repeat for:
Table 14.2.1.10B Summary of Values for CGI Score (PP Population)

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB224-001

Table 14.2.1.11A

Shift Table for MIDAS Score Grade by Treatment Group
(ITT Population)

Treatment Group:

	MIDAS Score Grade at Week 12			
MIDAS Score Grade at End of 4 Weeks of Baseline	I	II	III	IV
I	xx	xx	xx	xx
II	xx	xx	xx	xx
III	xx	xx	xx	xx
IV	xx	xx	xx	xx

Source: Listing 16.2.6.3

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for all treatment groups.

Repeat for:
Table 14.2.1.11B Shift Table for MIDAS Score Grade by Treatment Group (PP Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.12A

Shift Table for HIT-6 Score Grade by Treatment Group
(ITT Population)

Treatment Group:

	HIT-6 Score Grade at Week 12			
HIT-6 Score Grade at End of 4 Weeks of Baseline	I	II	III	IV
I	xx	xx	xx	xx
II	xx	xx	xx	xx
III	xx	xx	xx	xx
IV	xx	xx	xx	xx

Source: Listing 16.2.6.4

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for all treatment groups.

Repeat for:
Table 14.2.1.12B Shift Table for HIT-6 Score Grade by Treatment Group (PP Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.13A

Reduction in Monthly Migraine Days – Fisher's Exact Test
(ITT Population)

Proportion Reduction in Monthly Migraine Days from Baseline to Day 28 (Week 4)	Statistic	B244 1X (N=xx)	B244 4X (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
>50%	n(%)	xx	xx	xx	xx
	p-value	0.xxxx	0.xxxx	0.xxxx	
>75%	n(%)	xx	xx	xx	xx
	p-value	0.xxxx	0.xxxx	0.xxxx	
=100%	n(%)	xx	xx	xx	xx
	p-value	0.xxxx	0.xxxx	0.xxxx	

Note: p-value is calculated using Fishers Exact test comparing treatment group to placebo.
Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16).

Repeat for:
Table 14.2.1.13B Reduction in Monthly Migraine Days – Fisher's Exact Test (PP Population)
Table 14.2.1.13C Reduction in Monthly Migraine Days for subjects having at least 50% diary compliance – Fisher's Exact Test (ITT Population)
Table 14.2.1.13D Reduction in Monthly Migraine Days for subjects having at least 50% diary compliance – Fisher's Exact Test (PP Population)

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Table 14.2.1.14A

Change in Monthly Migraine Days from End of Treatment to Follow-up Period
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Day 84 (Week 12)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28P (Week 16)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

Source: Listing 16.2.6.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.2.1.14B Change in Monthly Migraine Days from End of Treatment to Follow-up Period (PP Population)

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB224-001

Table 14.2.1.15A

Monthly Migraine Related Symptom Days
(ITT Population)

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 28 (Week 4)	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

Note: Migraine related symptoms include nausea /vomiting, photophobia and sonophobia.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Repeat for Day 56 (Week 8), Day 96 (Week 12), Day 112 (Week 16).

Repeat for:
Table 14.2.1.15B Monthly Migraine Related Symptom Days (PP Population)

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB244-001

Table 14.3.1.1

Overall Summary of Treatment-Emergent Adverse Events
(Safety Population)

	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Subjects with at Least 1 Treatment-Emergent Adverse Event (TEAE)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Treatment-Related TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Grade 3 or 4 TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Treatment-Related Grade 3 or 4 TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Serious TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 Treatment-Related Serious TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 TEAE that led to Treatment Discontinuation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at Least 1 TEAE that led to Study Discontinuation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with 1 TEAE that led to Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

If a subject experiences multiple occurrences in the category of Adverse event, the subject will be counted only once for that PT/SOC.
If a subject experiences the same AE more than once with different CTCAE grades, the event with the highest grade will be tabulated.
TEAE is defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug.
Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug.
Severity will be graded based on the NCI CTCAE, Version 4.03.
Adverse events are coded using MedDRA v20.0.
Source: Listing 16.2.7.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB244-001

Table 14.3.1.2

Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Any TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					
System Organ Class 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					
Etc.					

TEAE is defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug.
If a subject experiences multiple occurrences in the same PT/SOC, the subject will be counted only once for that PT/SOC.
Adverse events are coded using MedDRA v20.0.
Source: Listing 16.2.7.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat Table 14.3.1.2 for the following tables:

Table 14.3.1.3 Treatment-Related Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for at least possibly related to the study drug. Add footnote "Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug."

Table 14.3.1.4 Grade 3 or 4 Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for grade = 3 or 4. Add footnote "Severity will be graded based on the NCI CTCAE, Version 4.03." AND "If a subject experiences the same AE more than once with different CTCAE grades, the event with the highest grade will be tabulated."

Table 14.3.1.5 Treatment-Related Grade 3 or 4 Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for grade = 3 or 4 and at least possibly related to the study drug. Add footnote "Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug." AND "Severity will be graded based on the NCI CTCAE, Version 4.03." AND "If a subject experiences the same AE more than once with different CTCAE grades, the event with the highest grade will be tabulated."

Table 14.3.1.6 Serious Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for SERIOUS = YES.

Table 14.3.1.7 Treatment-Related Serious Treatment-Emergent Adverse Events (TEAE) by MedDRA System Organ Class and Preferred Term (Safety Population)
PROGRAMMING NOTE: filter for SERIOUS = YES and at least possibly related to the study drug. Add footnote "Treatment-related TEAE is defined as TEAE that was considered by the Investigator to be at least possibly related to the study drug."

Repeat Listing 16.2.7.1 for the below table listings.

Table 14.3.2.1 Serious Adverse Events
PROGRAMMING NOTE: filter for SERIOUS = YES and remove Serious Column.

Table 14.3.2.2 Adverse Events Leading to Early Discontinuation
PROGRAMMING NOTE: filter for subjects who discontinued early.

Table 14.3.2.3 Subject Deaths
PROGRAMMING NOTE: filter for subject deaths, remove Outcome column and accompanying footnote and renumber other footnotes accordingly.

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB244-001

Table 14.3.3.1

Summary of Values and Change from Baseline for Hematology Parameters
(Safety Population)

Parameter:

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Screening	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 4	Actual	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Etc.						

Source: Listing 16.2.8.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Continue for all parameters and visits.

Repeat for:
Table 14.3.3.2 Summary of Values and Change from Baseline for Chemistry Parameters (Safety Population)
PROGRAMMING NOTE: Update source to Listing 16.2.8.2
Table 14.3.3.3 Summary of Values and Change from Baseline for Urinalysis Parameters (Safety Population)
PROGRAMMING NOTE: Update source to Listing 16.2.8.3

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol ADB244-001

Table 14.3.4

Summary of Values and Change from Baseline for Vital Signs
(Safety Population)

Parameter: Systolic Blood Pressure

Visit	Actual/ Change	Statistic	B244 1x (N=xx)	B244 4x (N=xx)	Pooled B244 (N=xx)	Placebo (N=xx)
Screening	Actual	N	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Week 4	Actual	N	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	N	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

Etc.

Source: Listing 16.2.9.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Continue for all parameters and visits.

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB224-001

Table 14.3.5

Responder Analysis - Blood Pressure
(ITT Population)

Parameter	Visit	Number of Subjects	B244 1X (N=xx)	B244 4X N=xx	Pooled B244 N=xx	Placebo N=xx
Subjects with ≥10 mmHg reduction in systolic blood pressure or ≥5 mmHg reduction in diastolic blood pressure	Week 4	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Week 8	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Etc.					
Subjects whose blood pressure recorded ≥130 mmHg systolic blood pressure or ≥80 mmHg diastolic blood pressure	Week 4	n(%)	xx (xx.x)	xx(xx.x)	xx (xx.x)	xx (xx.x)
	Etc.					
Subjects with >120 mmHg systolic blood pressure at baseline visit (V3)		n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Listing 16.2.9.1

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol ADB244-001

Table 14.3.6

Electrocardiogram Results
(Safety Population)

Visit	Parameter	Statistic	B244 1x (N=XX)	B244 4x (N=XX)	Pooled B244 (N=XX)	Placebo (N=XX)
Screening	Reported Electrocardiogram Results	n	XX	XX	XX	XX
	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Clinically Significant Abnormal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
End of Baseline	Received Treatment and Reported Electrocardiogram Results	n	XX	XX	XX	XX
	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Clinically Significant Abnormal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 12						

Source: Listing 16.2.9.4

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.1.1

Study Completion Status

Treatment Group:

Subject Number	End of Study Date (Rel Day)	Early Withdrawal or Discontinuation?	Primary Reason
	DD-MMM-YYYY	Yes	Death
		No	Lost to follow-up
			Other, specify
			Etc.

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.2.1

Inclusion/Exclusion Criteria Not Met

Treatment Group:

Subject Number	Did the Subject Meet All Eligibility Criteria?	Criterion ID Not Met	Was a Waiver Provided so the Subject Can Continue on the Trial?	Date of Waiver	Continue to the Next Visit?
	Yes	Inclusion 1	Yes	DD-MMM-YYYY	Yes
	No	Exclusion 1	No		No
		Etc.			

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Page 1 of x

Listing 16.2.2.2

Protocol Deviations

Treatment Group:

Subject Number	Date of Deviation (Rel Day)	Visit	Deviation Code	Description
	DD-MMM-YYYY		Informed Consent Procedures	
			Concomitant medication/therapy	
			Etc.	

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Page 1 of x

Listing 16.2.4.1

Demographics and Baseline Information

Treatment Group:

Subject Number	Age (years)	Sex	Race	Ethnicity	Is Female Subject of Child-Bearing Potential?	If No, Reason
			American Indian or Alaska Native	Hispanic or Latino	Yes	Post-Menopausal
			Asian	Not Hispanic or Latino	No	Surgically Sterile
			Black or African American	Not Reported		Hysterectomy
			Native Hawaiian or Other Pacific Islander	Unknown		Tubal Ligation
			White			Other, Specify
			Other			

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Listing 16.2.4.2

Medical History

Treatment Group:

Subject Number	Date Diagnosed	Ongoing at Screening?	End Date	Medical History Condition/Event Description	MedDRA System Organ Class	Preferred Term	Currently Being Treated with Concomitant Medication for this Condition/Event?
		Yes					Yes
		No					No

Medical history is coded using MedDRA v21.0.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Page 1 of x

Listing 16.2.4.3

Smoking History

Treatment Group:

Subject Number	Does Subject Have Smoking History?	Type of Product Smoked	Date Subject Started to Smoke	Still Smoking?	Date Stopped Smoking	Number of Cigarettes Per Day (Tobacco Products)	Number of Times Smoking Occurs Per Week (Non-Tobacco Products)
	Yes	Tobacco Products		Yes			
	No	Non-Tobacco Products		No			
		Both					

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.5.1

Rescue/Acute Migraine Specific Medication

Treatment Group:

Subject Number	Medication Taken to Treat Headache/Migraine Since Last Diary Entry?	Rescue Medication Name	Date Medication was Taken (Rel Day)	Time Medication was Taken (24-hour clock)	Dose (mg)	Administration Route
	Yes	Sumatriptan (Imitrex)	DD-MMM-YYYY	HH24:MM		Oral
	No	Sumatriptan (Zembrace)				Injection
		Sumatriptan (Sumavel DosePro)				Other, Specify
		Other, Specify				
		Etc.				

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Page 1 of x

Listing 16.2.5.2

Dose Administration

Treatment Group:

Subject Number	Morning Dose Administered?	Reason for Missing Morning Dose	Date (Rel Day)/Time of Morning Dose	Night Dose Administered?	Reason for Missing Night Dose	Date (Rel Day)/Time of Night Dose
	Yes		DD-MMM-YYYY HH24:MM	Yes		DD-MMM-YYYY HH24:MM
	No			No		

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.5.3

Study Drug Compliance

Treatment Group:

Subject Number	IP Weight Measured	Date (Rel Day)	Kit ID	Bottle Number	Date of IP Response	Weight of Bottle at Dispense (g)	Priming Weight	Date of Bottle Return	Weight of Bottle when Returned	Percentage Compliance
	Yes	DD-MM-YYYY (XX)								
	No									

Rel Day = Relative to first dose of study medication, Day 1.
IP = Investigational Product

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.6.1

Migraine Attacks and Headache Days

Treatment Group:

Subject Number	End of Week	Number of Migraine Days	Number of Migraine Attacks	Number of Acute Migraine Specific Medication Days	Number of Moderate and Severe Headache Days	Number of Headache Days	Number of Headache Hours
	Baseline	DD-MM-YYYY (XX)					
	4						
	8						
	12						

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.6.2

Migraine Pain Intensity Score

Treatment Group:

Subject Number	Visit	Date of Assessment (Rel Day)	Migraine Pain Intensity Score
		DD-MMM-YYYY	0
			1
			2
			3

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.6.3

Migraine Disability Assessment (MIDAS) Questionnaire

Treatment Group:

		Days in the last 3 months						
Subject Number	Date (Rel Day)	Patient Missed Work/School	Productivity at Work/School reduced by Half or More	Patient did not do Household work	Productivity at Household work reduced by Half or More	Patient missed Family/Social/Leisure Activities	Patient Have Any Headache	Pain of Headaches on a Scale of 1-10

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.6.4

Headache Impact Test-6 (HIT-6) Questionnaire

Treatment Group:

Subject Number	Date (Rel Day)	How often is the Pain of Headaches Severe?	How Often do Headaches Limit Subject's Ability to do Usual Daily Activities?	How Often Subject Wishes to Lie Down when having a Headache?	How Often in the Past 4 Weeks Patient Felt too Tired to do Daily Activities Because of Headaches?	How Often in the Past 4 Weeks Patient Felt Irritated Because of Headaches	How Often in the Past 4 Weeks Headaches Limit Patients Ability to Concentrate on Work/Daily Activities
		Never	Never	Never	Never	Never	Never
		Rarely	Rarely	Rarely	Rarely	Rarely	Rarely
		Sometimes	Sometimes	Sometimes	Sometimes	Sometimes	Sometimes
		Very Often	Very Often	Very Often	Very Often	Very Often	Very Often
		Always	Always	Always	Always	Always	Always

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Listing 16.2.6.5

Migraine Specific Quality of Life (MSQL) Questionnaire

The MSQL questionnaire has 14 questions as below:

Q1: In the past 4 weeks, how often have migraines interfered with how well you dealt with family, friends and others who are close to you? (Select only one response)

Q2: In the past 4 weeks, how often have migraines interfered with your leisure time activities, such as reading or exercising? (Select only one response)

Q3: In the past 4 weeks, how often have you had difficulty in performing work or daily activities because of migraine symptoms?

Q4: In the past 4 weeks, how often did migraines keep you from getting as much done at work or at home?

Q5: In the past 4 weeks, how often did migraines limit your ability to concentrate on work or daily activities?

Q6: In the past 4 weeks, how often have migraines left you too tired to do work or daily activities?

Q7: In the past 4 weeks, how often have migraines limited the number of days you have felt energetic?

Q8: In the past 4 weeks, how often have you had to cancel work or daily activities because you had a migraine?

Q9: In the past 4 weeks, how often did you need help in handling routine tasks such as everyday household chores, doing necessary business, shopping, or caring for others, when you had a migraine?

Q10: In the past 4 weeks, how often did you have to stop work or daily activities to deal with migraine symptoms?

Q11: In the past 4 weeks, how often were you not able to go to social activities such as parties, dinner with friends, because you had a migraine?

Q12: In the past 4 weeks, how often have you felt fed up and frustrated because of your migraines?

Q13: In the past 4 weeks, how often have you felt like you were a burden on others because of your migraines?

Q14: In the past 4 weeks, how often have you been afraid of letting others down because of your migraines?

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.6.5

Migraine Specific Quality of Life (MSQL) Questionnaire

Treatment Group:

Subject Number	Date (Rel Day)	Q1	Q2	Q$	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
	DD-MM-YYYY (XX)														

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.6.6

Clinical Global Impression (CGI) Questionnaire

Treatment Group:

Subject Number	Date (Rel Day)	Severity of Illness	Global Improvement	Efficacy Index
		0	Never	00
		1	Rarely	01
		2	Sometimes	02
		3	Very Often	03
		4	Always	04
		5		05
		6		06
		7		07
				08
				09
				10
				11
				12
				13
				14
				15
				16

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.7.1

Adverse Events by Subject

Treatment Group:

Subject Number	Start Date/Time (Rel Day)	Stop Date/Time (Rel Day)	System Organ Class/ Preferred Term	Grade [1]	Serious?	Outcome [2]	Relationship to Study Drug [3]	Relationship to Study Procedure [3]	Action [4]
				Grade 1	Yes				
				Grade 2	No				
				Grade 3					
				Grade 4					
				Grade 5					

Rel Day = Relative to first dose of study medication, Day 1.
Note: Adverse events are coded using MedDRA v21.0.
[1] Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life Threatening, Grade 5 = Fatal.
[2] Recovering/Resolving, Recovered/Resolved with Sequelae, Recovered/Resolved, Not Recovered/Not Resolved, Fatal.
[3] Unk = Unknown, Rel = Definite Related, Prob = Probably Related, Poss = Possibly Related, Unl = Unlikely Related, Unr = Definitely Not Related.
[4] None = None, Conmed = Concomitant Medication, Addper = Additional Percutaneous Procedures, Surg = Surgery, Hosp = Hospitalization, Oth = Other, Unk = Unknown.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.7.2

Serious Adverse Events

Treatment Group:

Subject Number	System Organ Class/ Preferred Term	Serious Criteria	Start Date (Rel Day)	End Date (Rel Day)	Lead to Temporary Treatment Interruption?	Lead to Permanent Treatment Discontinuation?	Lead to Study Discontinuation?
		Death			Yes	Yes	Yes
		Life Threatening			No	No	No
		Significant Disability					
		Hospitalization					
		Prolonged					
		Congenital Anomaly/Birth Defect					
		Associated with Other SAEs					

Rel Day = Relative to first dose of study medication, Day 1.
Note: Adverse events are coded using MedDRA v21.0.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.8.1

Laboratory Testing - Hematology

Treatment Group:

Subject Number	Visit	Date/Time of Collection	Rel Day	Subject Fasting	Lab Parameter	Units	Specimen Type	Result	Reference Range

H = High, L = Low, CS = Clinically Significant, NCS = Abnormal, Not Clinically Significant.
Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for all Chemistry Parameters in:
Listing 16.2.8.2 Laboratory Testing – Chemistry
Repeat for all Urinalysis Parameters in:
Listing 16.2.8.3 Laboratory Testing - Urinalysis

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Listing 16.2.8.4

Urine Pregnancy Test

Treatment Group:

Subject Number	Visit	Date Performed	Rel Day	Pregnancy Test Done?	Test Result
					Positive
					Negative

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

PROGRAMMING NOTE: Report for females only.

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.9.1

Vital Signs

Treatment Group:

Subject Number	Visit	Date Performed (Rel Day)	Time Performed	Height (m)	Weight (kg)	BMI	Average Heart Rate (beats/min)	Respiration Rate (breaths/min)	Average Systolic Blood Pressure (mmHg)	Average Diastolic Blood Pressure (mmHg)

Rel Day = Relative to first dose of study medication, Day 1.
Note: Readings with ≥10 mmHg systolic blood pressure reduction from baseline or ≥5 mmHg diastolic blood pressure reduc
baseline in the clinic are indicated with *.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Listing 16.2.9.2

Physical Examination

Treatment Group:

Subject Number	Visit	Date of Examination	Rel Day	Body System	Assessment Result	Clinical Significance Description
				General Appearance	Normal	
				Dermatologic	Abnormal, not clinically significant	
				Head		
				Eyes	Abnormal, clinically significant	
				Ears		
				Nose	Not assessed	
				Mouth/throat/neck		
				Thyroid		
				Lymph nodes		
				Respiratory		
				Cardiovascular		
				Gastrointestinal		
				Extremities		
				Musculoskeletal		
				Neurological Systems		

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics | Confidential | Page 1 of x
Protocol MGB224-001

Listing 16.2.9.3

Concomitant Medications

Treatment Group:

Subject Number	ATC/ Generic Name/ Verbatim Name	Start Date (Rel Day)/ End Date (Rel Day)	Ongoing?	Indication	Taken to treat AE	Dose per Administration	Dose Units	Dosing Frequency	Route of Administration
			Yes		Yes				
			No		No				

Rel Day = Relative to first dose of study medication, Day 1.
Concomitant medications are any medications that did not end prior to first dose. If an end date is missing or the medication is ongoing, the medication is included.
Concomitant medications Anatomic Therapeutic Class (ATC) and Preferred Term (PT) are coded using the World Health Organization (WHO) Drug Dictionary March 2018.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics
Protocol MGB224-001

Confidential

Listing 16.2.9.4

Electrocardiogram

Treatment Group:

Subject Number	Visit	ECG Performed?	Date (Rel Day)	Subject resting supine for at least 5 minutes?	PR Interval (msec)	QRS Interval (msec)	QTcB Interval (sec)	Assessment Result	Description of Abnormal Findings
		Yes		Yes				Normal	
		No		No				Abnormal, not clinically significant	
								Abnormal, clinically significant	

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

DATE: HH:MM/DDMMMYYYY

AOBiome Therapeutics Confidential Page 1 of x
Protocol MGB224-001

Listing 16.2.9.5

Nasal Inspection

Treatment Group:

Subject Number	Visit	Date of Examination (Rel Day)	Nasal Inspection Performed?	Location	Assessment Result	Clinical Significance Description
				Nasal Mucosa	Normal	
				Sinuses	Abnormal, not clinically significant	
				Upper Airway	Abnormal, clinically significant	
					Not assessed	

Rel Day = Relative to first dose of study medication, Day 1.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY