STATISTICAL ANALYSIS PLAN

for

A Phase II Multiple Site, Randomized, Placebo-Controlled Trial of Oral Valproic Acid for Retinitis Pigmentosa #H-13371 (Valproic Acid Protocol (VP1))

Version 1.0
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<td>Alanine Aminotransferase</td>
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<td>AST</td>
<td>Aspartate Aminotransferase</td>
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<tr>
<td>BID</td>
<td>Bis in die (Twice a Day)</td>
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<td>CME</td>
<td>Cystoid Macular Edema</td>
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<td>Case Report Form</td>
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<td>OCT</td>
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<td>PP</td>
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<td>PT</td>
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<td>RHO</td>
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<td>Semi-automated Kinetic Perimetry</td>
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1 INTRODUCTION

Retinitis Pigmentosa (RP) is a severe neurodegenerative disease of the retina characterized initially by night blindness with progression to tunnel vision and eventual loss of central vision and potentially total blindness. Targeted therapies for RP are complicated by the identification of more than 30 genes identified being responsible for dominant and recessive forms of the disease and many more linked to RP but not identified. RP affects approximately 100,000 individuals in the U.S., qualifying it as an orphan disease. While a few new approaches for RP treatment have recently been investigated including nutritional supplementation, light reduction and gene therapy (Delyfer et al., 2004; Gaby, 2008; Hartong et al., 2006), of these, vitamin A supplementation is the most promising, but its benefits are modest and side effects are problematic. Therefore, currently there is no FDA approved therapy to substantially alter or reverse the progression of RP.

In vitro data supports that valproic acid (VPA) has multiple biologic properties that may slow apoptosis thereby potentially slowing or halting retinal degeneration. A small pilot study in seven RP patients treated off-label with oral VPA (250 mg BID) for durations of between three and five months showed six of 7 patients had no detectable progression of their disease and one patient experienced a loss of visual field. Some other patients using VPA off-label that was prescribed by their ophthalmologist reported some improvement in vision and therefore it was determined that VPA needed further investigation.

1.1 Purpose of Document

The purpose of this document is to describe the data tables and analyses that will be produced by Emmes following database lock for the VP1 study. The analysis plan is not intended to be comprehensive of all analyses described in the protocol. Instead it is a plan focused on the primary endpoint as defined in the protocol (kinetic perimetry) and two secondary endpoints (static perimetry and optical coherence tomography (OCT)). The choice of endpoints on which to focus was chosen in conjunction with the Sponsor, based on program priorities.

2 SUMMARY OF STUDY DESIGN

2.1 Study Objective

The purpose of this study is to evaluate the potential efficacy of VPA to slow progression of visual function loss in patients with the autosomal dominant form of RP, and to collect safety and tolerability information.

2.2 Study Design and Procedures

2.2.1 Study Design

This is a multi-site, prospective, randomized, placebo-controlled, double-masked study of 90 participants undergoing 12 months of therapy with oral VPA or a placebo. The study population will be comprised of male and female patients who have been diagnosed with autosomal dominant retinitis pigmentosa and who meet the inclusion/exclusion criteria outlined in section 2.3. Patients who have been genotyped autosomal dominant for RP prior to their baseline visit will undergo clinical examinations and evaluations of retinal function and structure to determine whether the participant is eligible. Clinical examinations will include refraction, static and kinetic perimetry and visual acuity. Spectral-Domain Optical Coherence Tomography (SD-OCT) will be used to measure retinal structure. During these evaluations, medical and ophthalmic histories will be elicited from participants to ensure that there are no co-morbid medical or ocular genetic conditions that may prevent study participation.
2.2.2 Study Procedures

A screening visit will be used to determine whether the participant meets all eligibility criteria. Participants will sign informed consent at the screening visit. Qualified participants will be asked to return to the clinic within 12 weeks after the Screening Visit for the Baseline Visit. Following randomization at the Baseline Visit, participants will be dispensed study drug and will be instructed to begin taking study drug the following day. Participants will be asked to return for in-clinic follow-up visits at Week 8, Week 26, Week 39, Week 52, and Week 65 after initiating VPA treatment for evaluation of their clinical status and to assess adverse events (AEs). At each in-clinic visit (except Weeks 52 and 65), participants will be given a sufficient number of capsules to last until the next scheduled visit plus at least a 15 day overage allowance. Participants will also be followed up with phone calls at weeks 1, 4, 13, 17, 22, 30, 35, 43 and 48. The purpose of these phone calls is to assess adherence to study medication, assess adverse events, schedule additional clinic visits if needed, and clarify study procedures. Participants will be followed for a period of 13 weeks after the participant completes study drug (VPA or placebo) one year post-baseline.

2.2.3 Randomization

Ninety participants will be randomized in a 1:1 fashion to either treatment with VPA or with a placebo. Randomization will be stratified by site. The randomization plan will be developed and stored at the Coordinating Center.

The Coordinating Center will create the master randomization list and provide the drug distributor the drug kit numbers to assign to the active treatment and to the placebo, as well as communicate which drug kit numbers to distribute to each of the participating sites. The master randomization list for all sites will be maintained at the Coordinating Center.

A secure Internet-based eligibility, enrollment and randomization system is integrated into the electronic data capture system AdvantageEDC to control and document the randomization assignments. Investigators will access AdvantageEDC to enroll and randomize qualified participants. Upon randomization, the investigator will be informed of the drug kit number to provide to the participant.

2.2.4 Masking and Unmasking

Participants and investigators will be masked to the treatment assignments. Only designated personnel responsible for packaging and labeling study drug, select individuals at the Coordinating Center and the Data and Safety Monitoring Board (DSMB) will have access to the study treatment assignments. Participants will be unmasked if deemed clinically necessary by the examining physician and if the Medical Monitor agrees the unblinding is justified. A written request for unmasking, after approval by the Medical Monitor, will be made to the Coordinating Center, who will inform the site Principal Investigator of the treatment assignment. Attempts should be made to maintain the masking of the investigators prior to the study-wide unmasking.

2.3 Inclusion and Exclusion Criteria

2.3.1 Inclusion Criteria

To be eligible for the study, participants must fulfill all of the following criteria:

1. Understand and sign the IRB-approved informed consent document for the study.
2. Age ≥ 18 years, no upper age limit
3. Males and non-child bearing females* must weigh ≥ 40 Kg and ≤158.9 Kg; Females of child bearing potential* must weigh ≥40 Kg and ≤74.9 Kg.
4. Diagnosis of Retinitis Pigmentosa (RP) including photoreceptor degeneration established by visual field constriction, night blindness, marked reduction of electroretinography responses, and the clinical signs of RP including waxy pallor of the optic nerve, vascular attenuation and/or the presence of intraretinal pigment on clinical examination.

5. Visual acuity of greater than or equal to 35 letters in at least one eye as measured by the EVA-ETDRS (equivalent to 20/200 on a Snellen chart).

6. Genotyped as autosomal dominant form of RP.

7. Female subjects of childbearing potential* and male subjects able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, be completely abstinent from intercourse or must commit to practice at least two acceptable methods of contraception to minimize the chance of pregnancy during the study and for the 13 week period after stopping the study drug. Acceptable methods of contraception include hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring), intrauterine device, barrier methods (diaphragm, condom) with spermicide, or surgical sterilization (tubal ligation).

8. Female subjects of childbearing potential must have a negative urine pregnancy test at study entry and throughout the duration of the study.

9. Willingness to comply with the protocol.

* The following definition will be used to determine childbearing potential:
A female subject who is considered non-childbearing due to a medical condition (i.e., subject has previously undergone a hysterectomy) does not need a pregnancy test or contraception. Women over age 55 who have not had a period for one year will be considered menopausal and do not need a pregnancy test or contraception. Women under 55 must undergo pregnancy testing and use contraception as outlined in the protocol.

2.3.2 Exclusion Criteria

Potential participants meeting any of the following criteria will be excluded from the study:

1. Medical problems that make consistent follow-up over the treatment period unlikely (e.g. stroke, severe MI, end stage malignancy), or in general a poor medical risk because of other systemic diseases or active uncontrolled infections.

2. Other retinal diseases: Glaucoma, retinal inflammatory disease (CME is allowable), cataract worse than +2 NS, or herpes simplex virus of the eye.

3. Intact visual field of 5° or less.

4. Subject unable to provide reliable perimetry measurements in both eyes for both static and kinetic visual field, as determined by the Reading Center.

5. Diabetes.

6. History of cancer (other than non-melanoma skin cancer) diagnosed, or requiring treatment within the past 2 years.

7. A hemoglobin concentration, a platelet count or an absolute neutrophil count below the lower limit of normal at study entry. The limits of normal are defined by each site and are agreed to by the medical monitor.

8. Suspected liver dysfunction determined by having alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin values elevated above the upper limit of normal.

9. History of pancreatitis by clinical features and/or laboratory abnormalities in the last 12 months.

10. Renal dysfunction based on serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation.
11. Urea cycle disorders.
12. History of neurological conditions including epilepsy, history of brain injury, encephalitis, or any organic brain syndrome.
13. History of schizophrenia, schizoaffective disorder, bipolar disorder, suicidality or organic mental disorders.
14. Currently receiving valproic acid or other anti-convulsants.
15. Sensitive to or have ever had an allergic reaction to valproic Acid.
16. Sensitive to or have ever had an allergic reaction to peanuts as peanut oil is an inactive ingredient in valproic acid capsules and the placebo.
17. Has taken one of the following drugs at least 2 weeks prior to randomization as these drugs are specifically known to interact with valproic acid: aspirin (daily prophylactic use of 'low-dose’ aspirin (≤81 mg) is not excluded), felbamate, rifampin, amitriptyline/nortriptyline, carbamazepine, clonazepam, diazepam, ethosuximide, lamotrigine, phenobarbital, primidone, phenytoin, tolbutamide, topiramate, warfarin, or zidovudine.
18. Pregnant women.
19. Lactating mothers who are breast feeding their babies.
20. RP patients involved in other clinical trials within the last 3 months.
21. Require enrollment by consent of a legally authorized representative.
22. Persons who are unable to read are not allowed to consent for themselves or others to participate in this study.
23. The potential participant lives in the same household as a current participant in this protocol.

3 GENERAL DEFINITIONS AND PROCEDURES

3.1 Study Population Definitions

3.1.1 Screened Population

The screened population consists of all participants who provide informed consent at the initiation of the screening process.

3.1.2 Intent-to-Treat (ITT) Population

The ITT population consists of all randomized participants.

3.1.3 Per-Protocol Population

There are a number of ways of defining a per-protocol population, some of which require a significant amount of time to review each participant’s data profile to decide whether they should be included in the population. The definition that will be used for this analysis is as follows. The Per-Protocol (PP) population consists of all randomized participants who meet the following:

- Achieve an overall 90% to 110% study drug exposure (see Section 6.2 for the definition of treatment exposure)
- Attend the Baseline, Week 26 and Week 52 in-clinic visits
- Have kinetic visual fields measurements at Baseline, Week 26 and Week 52
- Meet all eligibility criteria, regardless of whether an exception was granted by the Sponsor at the time of randomization.

3.1.4 Safety Population

The Safety population will include all participants who provide informed consent. This population is identical to the Screened Population.
3.1.5 RHO Subgroup

Participants with a mutation in the rhodopsin (RHO) gene will be included in a subgroup analysis. Participants with both the RHO and PRPH2 mutations will not be included in this subgroup due to the RHO mutation being autosomal dominant and the PRPH2 mutation being semi-dominant. Participants with both the RHO and ROM1 mutations will be included in the RHO subgroup because the ROM1 mutation has no phenotype.

3.2 Treatment Emergence

Treatment emergent AEs are defined as those that occur between the date of the first dose of study drug and the date of the last dose of study drug plus 7 days. Adverse events that start on the same day as the date of first dose of study drug will be assumed to be treatment emergent.

3.3 Treatment Period

The treatment period begins on the day the first dose of study medication is taken and ends on the date of the last dose of study drug.

3.4 Early Medication Termination

Study procedures indicate that participants should receive study drug until they return to the site for their Week 52 visit, therefore an early medication termination is defined as a participant who stops study drug prior to the Week 52 visit.

3.5 Analysis Procedures

All summaries and analyses described in this document will be presented by treatment arm. Additionally, some summaries will also presented by site. Refer to Section 12 for a listing of planned tables, figures and listings.

For all summaries of the ITT population, participants will be analyzed according to the treatment arm to which they were randomized regardless of the subsequent sequence of events. In other words, participants will be considered to belong to the randomized arm regardless of actual treatment received, adherence to treatment protocol, and eligibility.

Descriptive statistics will include mean, standard deviation, median, minimum, and maximum values for continuous variables and counts and percentages for each level of categorical variables. Graphical displays of the data will be used when analyzing primary and secondary outcomes.

4 ENROLLMENT, PARTICIPANT DISPOSITION AND FOLLOW-UP

A summary of the reasons for screening failure during the pre-screening period (i.e., prior to signing informed consent) will be provided by site. A summary of the reasons for screen failure for the participants who signed informed consent but subsequently did not meet all eligibility criteria will also be provided by site. In addition, a summary of the number of participants who were screened more than once for the study, along with corresponding screen failure reasons, will be prepared by site.

A graphical display of the trajectory of randomizations over time will be provided. The completion status and the reasons for early study termination will be summarized with descriptive statistics by site and by treatment arm.

The number and reasons for missed visits by site and type of visit (in-clinic versus telephone assessments) will be provided.
5 PARTICIPANT CHARACTERISTICS AT BASELINE

Baseline characteristics will be summarized by site and treatment arm. Because randomization is expected to produce balance at baseline between the two treatment groups, statistical comparisons of treatment groups with respect to baseline characteristics should be more informal. If differences between treatments arms are suspected, statistical testing will be performed.

Participants will be asked about their medical history relating to a host of different body systems and ocular history relating to various ocular conditions. A summary of medical history data will present the number and percent of participants with each captured condition organized by body system and treatment group. Summaries of ocular history data (one for all conditions and one for active conditions at screening) will present the number and percent of participants with each captured ocular condition organized by treatment group.

Genotyping will be performed to determine the genetic mutation leading to RP. The gene with the mutation will be summarized by site, by treatment group and overall.

6 TREATMENT EXPOSURE AND COMPLIANCE

6.1 Early Medication Terminations

Study medication completers, early medication terminations with reasons for early study termination and length of treatment period will be summarized by treatment arm with descriptive statistics. Total length of exposure in days will be based on the number of days on study drug calculated as last dose date minus the first dose date plus 1.

6.2 Drug Accountability

Assessments of the actual exposure to study medication will be based on the drug accountability data. A capsule count is performed at every post-baseline in-clinic visit and is used to calculate the number of capsules taken. Percent treatment exposure will be calculated as the dose taken divided by the protocol-recommended dose according to weight and child-bearing potential. This calculation assumes all participants should have taken study drug until the Week 052 visit, with the exception of participant death causing the participant to terminate study medication early. Percent treatment exposure will be summarized by treatment arm with descriptive statistics. Exposure will also be assessed by average daily dose in milligrams and will be summarized with descriptive statistics.

Percent compliance with study medication will be calculated as the number of capsules administered divided by the expected number of capsules administered. Participants who experience dose reductions or temporary dose stoppages due to AEs will have their expected number of capsules reduced for the compliance calculation. Participants will also not be penalized for temporary dose stoppages due to expired study drug. Descriptive statistics will be used to summarize percent compliance by treatment group.

A listing of treatment exposure and compliance will be presented by treatment arm. A graph of treatment exposure versus treatment compliance will also be provided.

6.3 VPA Serum levels

Serum VPA levels were measured beginning with Protocol Amendment 3.0. As a result, participants do not have VPA serum levels available for visits occurring before the amendment. The following information will be summarized: the number of participants having detectable levels of VPA at the Baseline and Week 65 visits, the number of placebo participants having a detectable VPA level during the treatment period, the number of VPA participants and visits with
levels below the seizure therapeutic range (50 – 100 μg/mL) during the treatment period, and the number of participants with critical high VPA serum levels during the treatment period. A listing of VPA serum levels by treatment arm will be presented.

7 DEFINITION AND ANALYSIS OF OUTCOME MEASURES

7.1 Primary Endpoint

7.1.1 Definition of Primary Endpoint

The primary objective of the study is to compare the degree of improvement in visual function in participants who receive VPA versus those who receive a placebo. This objective will be determined by testing the following hypothesis:

H0: \( \mu_{\text{VPA}} = \mu_{\text{PL}} \)

H1: \( \mu_{\text{VPA}} \neq \mu_{\text{PL}} \)

where \( \mu_{\text{VPA}} \) and \( \mu_{\text{PL}} \) are the true mean change in visual field area from Baseline to Week 52 in the VPA and placebo arms, respectively.

The primary outcome measure is the difference in visual field area between Baseline and Week 52 using the III4e isopter. Visual field area will be measured twice in both eyes at each time point with the semi-automated kinetic perimetry (SKP) module using the Octopus 900. The two most reliable sessions for analysis may differ by eye.

7.1.2 Analysis of Primary Endpoint

The primary analysis of the primary endpoint will test the significance of a VPA-Placebo treatment effect based on change in visual field area and will be done using a linear mixed model as noted below, while accounting for the variability related to site, participant, eye within participant (right and left), and the two replicates measured on each eye at each visit (Ibrahim and Molenberghs, 2009).

In mathematical terms, denote \( Y_{ijklmn} \) as the value of the primary outcome measure (visual field area based on kinetic perimetry) and consider the following model for the primary analysis:

\[
Y_{ijklmn} = \beta_0 + \text{time}(i) + \text{treatment}(j) + \text{time*treatment}(ij) + \text{site}(k) + \text{participant}(l) + \text{eye}_m(l) + \text{eps}(ijklmn)
\]

where

- \( i \) indexes time (Baseline, Week 26 or Week 52);
- \( j \) indexes treatment (either placebo or VPA);
- \( \text{time*treatment}(ij) \) interaction;
- \( k \) indexes the site;
- \( l \) indexes study participant;
- \( m(l) \) indexes eye (right and left) nested within participant;
- \( \text{eps}(ijklmn) \) is measurement error that contains the replicate measurements (n) on each eye; and
- random effects are underlined.

The model can be fit and tested with the SAS MIXED procedure as follows:

```sas
proc mixed data = file covtest;
```

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 12/29/2019
class time treatment site participant eye;
model VF = time|treatment / ddfm=kr s;
random site participant eye(participant);
estimate "Week 52 treatment effect" time*treatment 1 -1 0 0 -1 1;
run;

Inclusion of the estimate statement in the above syntax will provide us the results for the primary analysis.

With 90 study participants in the study, and a fairly complex model to assess the impact of treatment on visual field area, there is the potential for difficulties in the model converging. If difficulties in fitting the model arise, the model may be simplified by reducing the number of random effects in the model. In addition, if any estimated covariance component from the above random effect model is zero, the corresponding random effect may be dropped.

The Intent-to-Treat Population will be used for the primary analysis.

Transformation of the outcome variable will be considered to better approximate normality.

7.2 Secondary Endpoints Analyses

All analyses of secondary endpoints will utilize the Intent-to-Treat population.

7.2.1 Other Kinetic Perimetry Measurements

For each eye of each participant, duplicate kinetic perimetry measurements for the I4e and V4e isopters will be attained using the SKP module on the Octopus 900 at Baseline and at Weeks 26 and 52. Analyses using the mixed model approach similar to those used for the analysis of the primary outcome and described in section 7.1.1 will be applied to the analysis of these endpoints.

7.2.2 Static Perimetry Measurements

For each eye of each participant, duplicate static perimetry measurements in the visual field, including the volume of 30 degree hill of vision and volume of the full field hill of vision, will be collected at Baseline with the Octopus 900 Perimeter using German Adaptive Thresholding Estimation (GATE) static perimetry and custom made grids. All participants will receive an initialization GATE (GATEi), which measures the static visual field of a subject without any prior knowledge of the participant’s visual function.

Duplicate testing is optional at weeks 26 and 52. Only sessions that are deemed to be reliable by the Reading Center will be used in the analysis. The mixed model approach described in section 7.1.1 will be used to examine the change from baseline in hill of vision measurements at Week 26 and Week 52. It is anticipated that few participants will have two reliable measurements at the Weeks 26 and 52 as duplicate testing is not required; therefore, if model convergence is an issue, only the first reliable session will be used in the analysis. The most reliable session for analysis may differ by eye.

7.2.3 Retinal Anatomy

For each eye of each participant, Spectral–Domain optical coherence tomography (OCT) will be used to estimate the existence and the extent of retained photoreceptors at Baseline and Week 52. The mixed model approach described in section 7.1.1 will be used to examine the change from baseline in central macular thickness and macular volume at Week 52. No random effect for replicate will be needed in this model, as OCTs are performed once at each visit. The presence of cystoid macular edema will also be assessed at baseline and Week 52 with a Cochran-Mantel-Haenszel test, stratifying by site (Mantel and Haenszel, 1959). Descriptive
statistics will be presented for central macular thickness, macular volume, and presence of cystoid macular edema.

7.3 Additional Analyses
The analyses described in Sections 7.1 and 7.2 will be repeated in the subset of participants with a RHO mutation.

8 OTHER STATISTICAL CONSIDERATIONS

8.1 Correlated Data from Related Participants
A small number of related participants are expected to enroll in the study, but these relationships will not be recorded in the database. No analysis adjustment for correlated data due to some participants being related will be made.

8.2 Multiplicity
Although a number of secondary and exploratory analyses are planned, no formal method for controlling Type 1 error will be implemented. Caution will be used when interpreting results to avoid overstatement of results.

8.3 Missing Data Procedures
A mixed linear model will be implemented using maximum likelihood methodology to estimate the means, variances, and covariances given the sample data (Kackar and Harville). This methodology is appropriate to account for missing data in the sample under a missing at random assumption (Ibrahim and Molenberghs).

8.4 Adjustment for Site
Site will be included in statistical models to account for any influence site has on primary and secondary endpoints.

8.5 Change from Baseline
Change from baseline will be calculated as:
Change = (Post-baseline Value) – (Baseline Value).

8.6 Software to be Used for Analyses
All analyses will be performed using SAS® Version 9.3 software.

8.7 Sample Size Justification
This study was undertaken to assess trends towards slowing progression of disease over 1 year of therapy. To determine the sample size for this study, data on longitudinal rates of change in patients with autosomal dominant RP and RHO mutations (Berson 2002) was used. Among patients with normal baseline function in visual field area measured in deg², there was an estimated annual decline of -0.0449 with a standard deviation of 0.0395.

When the sample size in each treatment group is 35, an α=0.05 two-sided t-test of means based on a 60% treatment effect (placebo mean change of -0.0449, VPA mean change of -0.0180) and equal standard deviation of 0.0395, will have 80% power to detect a difference in mean change.

Assuming approximately a 10% drop-out, this would indicate a sample size of 40. There may be a small number of siblings enrolled in the study and the siblings will not be truly independent observations. An additional 5 patients were added to adjust for the small intraclass correlation.
that these siblings may create in the outcomes. This results in a final sample size of 45 per treatment group and a total of 90 participants.

9 SAFETY ANALYSIS

9.1 Adverse Events

Treatment emergent adverse events will be summarized by treatment arm by presenting the number of events, by counts and frequencies for the number of participants with treatment emergent AEs, and the severity and relatedness of each adverse event to study product and study procedures. A similar summary will be provided for non-treatment emergent AEs in randomized participants by treatment arm. Detailed listings of treatment emergent adverse events by treatment arm, non-treatment emergent adverse events in randomized participants and non-treatment emergent adverse events in screen failures will be provided.

All adverse events will be coded using MedDRA® dictionary version 18.1. Treatment emergent adverse event incidence rates will be summarized by System Organ Class (SOC) and Preferred Term (PT). The incidence rate of an AE is calculated as the number of participants who experience the event at least once divided by the number of participants at risk (times 100). Incidence rates will be calculated at the PT level and at the SOC level. If a participant experiences multiple episodes of an event, then the event is only counted once.

Information on any pregnancies will be reported.

9.2 Serious Adverse Events

Treatment emergent Serious Adverse Events (SAEs) will be summarized by treatment arm by presenting the number of events, by counts and frequencies for the number of participants with treatment emergent AEs, and the severity and relatedness to study product and study procedures of each SAE. A summary of treatment emergent MedDRA coded serious adverse events using incidence rates, as defined in Section 9.1, will be provided by treatment arm. Detailed listings of all SAEs by treatment arm will also be provided, along with a narrative summary.

9.3 Best Corrected ETDRS Visual Acuity

For each eye of each participant, visual acuity is measured at a distance of 3 meters on a calibrated computer screen, using the program EVA-ETDRS, at Baseline and Weeks 8, 26, 52 and 65. Descriptive statistics will be provided for number of letters read at each visit and the change from baseline in numbers of letters read. Participants losing greater than 5 letters, greater than 10 letters, and greater than 15 letters will be evaluated with descriptive statistics.

9.4 Laboratory Values

Listings of liver function tests (ALT, AST, total and direct bilirubin), serum ammonia levels, pancreatic function tests (amylase, lipase) and platelet counts will be provided by treatment arm. Only those participants who have elevations in one or more of these parameters will be included in these listings. Narratives summarizing the clinically significant cases will be provided.

10 PROTOCOL DEPARTURES

Protocol departures will be summarized. The number of participants with departures as well as frequencies and percents for the types of protocol departures will be presented by treatment arm. All protocol departures for randomized participants will be provided in a listing. A separate
listing will be presented for departures observed in participants who screen failed along with those departures not associated with a particular participant.

## 11 REFERENCES


## 12 LIST OF PLANNED TABLES, FIGURES AND LISTINGS

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