MeiraGTx UK II Ltd

Statistical Analysis Plan

An open label, multi-center, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV5-hRKp.RPGR) for gene therapy of adults and children with X-linked Retinitis Pigmentosa owing to defects in Retinitis Pigmentosa GTPase Regulator Gene

Protocol MGT009; Phase 1/2

MGT-RPGR-009 (AAV5-hRKp.RPGR)

Amendment 1

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

The original SAP (dated 24 May 2019) described analyses of the test-retest variation for each visual function assessment, however, this will not be assessed given that the assessments of efficacy endpoints focus on the effect of the treated eye in immediate treatment group compared to the randomized concurrent control eye in deferred group. The statistics for the test-retest do not fit the purposes of the stated objectives and are not appropriate for the goals of the study. The current SAP describes analyses comparing treated eye in immediate treatment group compared to the randomized concurrent control eye in deferred group. Furthermore, the original SAP did not pre-specify primary/secondary endpoints and hierarchical testing. These are addressed in this SAP.

ABBREVIATIONS

AAV	Adeno-Associated Virus
AE	adverse event
ATC	Anatomical Therapeutic Chemical
ATIMP	advanced therapy investigational medicinal product
BMI	body mass index
CI	confidence interval
RPGR	Retinitis Pigmentosa GTPase Regulator
dB-sr	decibel-steradians
DLE	dose-limiting event
DPS	Data Presentation Specifications
EQ-5D	EuroQol 5-Dimension
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
eCRF	electronic case report form
FAS	Full analysis set
FV	Functional Vision
IDMC	Independent Data Monitoring Committee
IVI	impact of visual impairment
IVI-A	impact of visual impairment adult
IVI-C	impact of visual impairment child
LLQ	Low luminance questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
meanRS	Mean Retinal Sensitivity
PAP	Psychometric Analysis Plan
PCR	polymerase chain reaction
PRO	Patient-reported Outcomes
QoL	Quality of Life
RPGR	Retinitis Pigmentosa GTPase Regulator
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SUSAR	suspected unexpected serious adverse reaction
V30	central 30-degree hill-of-vision
VA	Visual Acuity
VFMA	visual field modeling and analysis
WHO-DD	World Health Organization Drug Dictionary
XLRP	X-linked Retinitis Pigmentosa

1. INTRODUCTION

This Statistical Analysis Plan (SAP) specifies definitions of analysis sets, key derived variables, and statistical methods for the analysis of safety and efficacy data for the Phase I/II RPGR study (MGT009). This SAP is based on the protocol of study MGT009, v12.0 and replaces the original SAP dated 24 May 2019, with the key change related to the analysis of efficacy parameters as further described in Section 5.1. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures, and listings) are provided in a Data Presentation Specifications (DPS).

1.1. Trial Objectives

The primary research objective is to assess the safety of the advanced therapy investigational medicinal product (ATIMP), AAV5-hRKp.RPGR vector for RPGR-ORF15 gene replacement in the retina of patients with RPGR-XLRP based on the primary safety outcome listed in Section 1.3.1. The secondary research objective is to determine whether an AAV5-hRKp.RPGR vector for RPGR-ORF15 gene replacement in the retina can slow/halt progressive deterioration or possibly even improve retinal structure or visual function, functional vision and vision-related quality of life in patients with RPGR-XLRP. Specifically, the secondary research objective is to evaluate the effect of treatment on the following endpoints: perimetry responder, central 30-degree hill-of-vision, walk time in visual mobility assessment, retinal sensitivity in microperimetry, patient reported outcome, low luminance visual acuity, contrast sensitivity and EZ area.

1.2. Trial Design

This is an open-label, phase I/II dose-escalation trial to determine the safety and efficacy of subretinal administration of the study agent (AAV5-hRKp.RPGR) in subjects with genetically confirmed RPGR-XLRP. As shown in Schema of treatment groups with study phases in Figure 1 and Schema of treatment groups within study phases in Figure 2, MGT-RPGR-009 includes three phases, dose escalation phase in adult RPGR patients, dose confirmation phase in pediatric RPGR patients, and randomized expansion phase in adult RPGR patients.

Figure 1: MGT009 Study Design Schematic

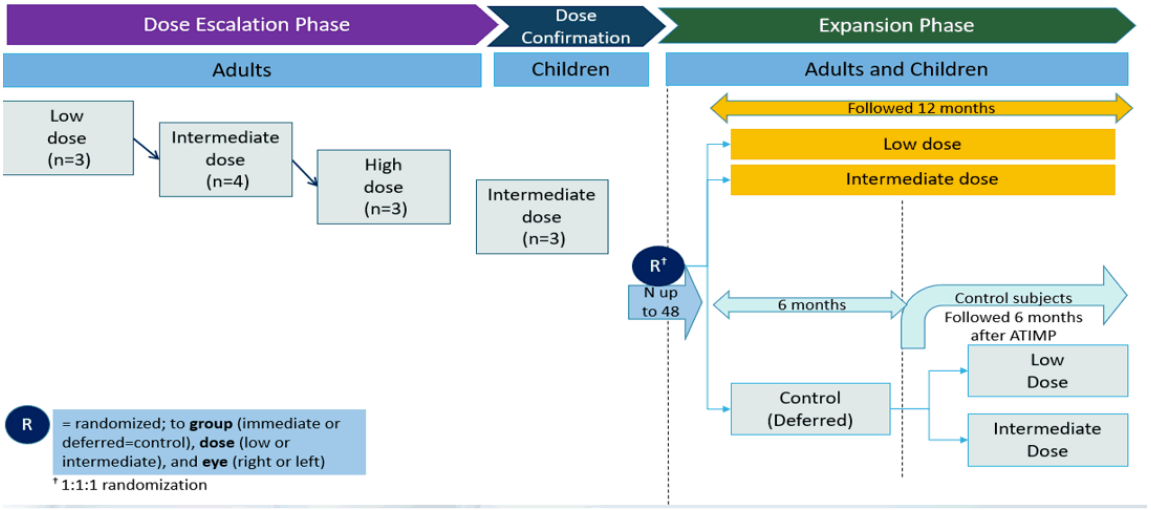
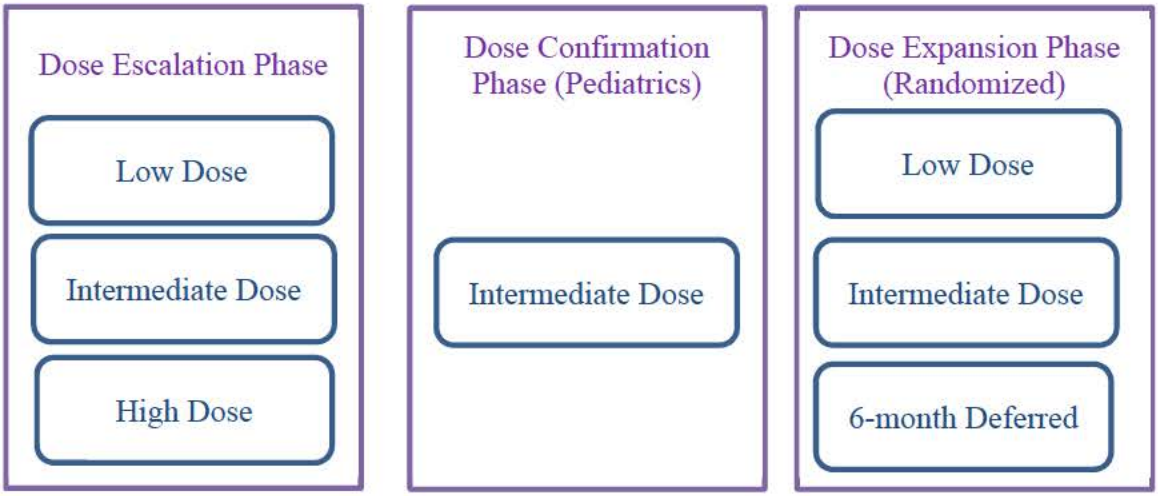


Figure 2: Schema of treatment groups within study phases



In the dose escalation phase, subjects were administered a single dose of ATIMP in cohorts of 3-4 subjects at a time. Based on a review of safety data, the Independent Data Monitoring Committee (IDMC) made recommendations on whether the dose was to be escalated or whether additional subjects were needed to repeat a dose in the cohort. The IDMC concurred on dosing a pediatric cohort at the intermediate dose prior to moving into the expansion cohort.

After an acceptable safety profile had been established in adults, the IDMC agreed to the sponsor's plan for administering the intermediate and low doses in the expansion phase. In the expansion phase, subjects were randomized to either immediate treatment with the low dose, or immediate treatment with the intermediate dose, or to a 6-month deferred-treatment group to receive either the low dose or the intermediate dose. Subjects in the immediate treatment arm were followed for 12 months before migrating to the long-term extension study, MGT-RPGR-010. Subjects in the deferred treatment arm were followed for at least 6 months before crossing them over to active treatment; at the 12-month time point these subjects also migrated to the long-term follow up study, MGT-RPGR-010. 6-month data from deferred arm during deferred period prior to treatment serves as the concurrent control group.

Adults were defined as subjects aged 16+ in the United Kingdom and aged 18+ in the United States.

Safety and efficacy are assessed for 12 months following the intervention by clinical examination and special investigations according to the schedule in Section 5.6 of the protocol.

The study conduct was substantially impacted by the COVID-19 pandemic. In particular, the pandemic caused delayed and missed visits to several subjects in the randomized dose expansion phase of the study. In addition, there were delays beyond the planned 6 months for treatment in the deferred treatment arm of the study. To allow greater flexibility in the management of protocol

deviations and timing of treatments in the deferred treatment arm of the study as a result of the COVID-19 pandemic, the protocol was amended in accordance with Health Authority guidance.

1.3. Statistical Hypotheses for Trial Objectives

1.3.1. Primary Safety Hypothesis

The objective of the dose escalation phase is to estimate the proportion of subjects who experienced the primary safety outcome. No formal hypothesis testing will be conducted.

The primary safety outcome is defined as any of the events delineated below and occurring during the 9 weeks following administration, at least possibly related to the ATIMP, not the surgery alone:

- Reduction in visual acuity by 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or more
- Severe unresponsive inflammation (defined in Section 4.2.1 of the protocol)
- Infective endophthalmitis
- Ocular malignancy
- Grade III or above non-ocular suspected unexpected serious adverse reaction (SUSAR) (Protocol MGT009, Section 5.11.3.4.2 Severity or Grading of Adverse Events).

Safety will be assessed for 12 months following ATIMP administration for immediate treatment participants in this study (Protocol MGT009) by study phases (dose escalation, dose confirmation and expansion phases) and overall, comparing with 6 months data in deferred treatment arm prior to treatment. Safety outcome captured in a separate long-term follow-up study (Protocol MGT010) for a further 4 years will be summarized separately.

1.3.2. Primary Efficacy Hypothesis

The objective of the dose expansion phase is to provide preliminary evidence of efficacy by comparing immediate treatment to a concurrent randomized control group. The randomized concurrent control eye refers to an untreated eye in a participant who was randomized to deferred treatment; these eyes are randomized and will receive treatment after completion of the 6-month deferral period. For the purposes of the primary efficacy analyses, these eyes represent the randomized concurrent control group. The primary comparisons of efficacy outcome assessments will be at Week 26 (immediate treatment vs. deferred treatment) in randomized expansion phase. Here immediate treatment group include subjects randomized to immediate low dose and immediate intermediate dose. Sensitivity analysis will also be conducted by pooling adult subjects from dose escalation and expansion phases together comparing immediate with deferred subjects.

The primary efficacy endpoint is responder/non-responder evaluated based on point-by-point data in full field from the 185-point (excluding 3 loci near blind spot) static perimetry assessed through Week 26 in the randomized immediate treatment subjects compared with randomized deferred subjects in the 26-week deferred period (prior to treatment). Subjects will be considered a responder if they experience at least 7 dB improvement from baseline at 5 or more loci at Week

26 and Week 13; this determination will be based on the treated eye for subjects in the immediate treatment group and for the deferred participant treatment eye in the deferred group, who had static perimetry assessments at both Week 13 and Week 26. The null hypothesis is that there is no difference in proportion of responders between randomized immediate treatment subjects and deferred treatment subjects. The alternative hypothesis is that the proportion of responders in the randomized immediate treatment subjects is greater than that in deferred subjects. The proportion of responders at Week 52 in subjects randomized for immediate treatment will also be estimated.

Table 1: loci near blind spot to be excluded from 185 loci grid for pointwise responder definition

Eye	XPOS	YPOS
Left	-16	-5.2
Left	-13.9	-1.2
Left	-15	0
Right	16	-5.2
Right	13.9	-1.2
Right	15	0

1.3.3. Secondary Efficacy Hypothesis

For the expansion phase, the null hypothesis for each secondary endpoint listed below is that there is no difference between the treated eye in subjects for the immediate treatment at Week 26 and the deferred participant treatment eye in the deferred group during 26-Week deferred period prior to treatment. The alternative hypothesis for each secondary endpoint listed below is that the improvement in the ATIMP treated eye in immediate treatment subjects is greater than that on the deferred participant treatment eye during deferred period prior to treatment.

a) Central 30-degree hill of vision (V30) in static perimetry using visual field modeling and analysis (VFMA) (Richard Weleber, 2015)

b) Average threshold in mesopic microperimetry

c) Maze walk time in Vision Mobility Assessment (VMA) under lux 1 and lux 4, separately

d) Low Luminance visual acuity (LLVA)

e) Patient report outcome, Low luminance questionnaire (LLQ) for the assessment of functional vision in low light conditions

f) Contrast sensitivity (Log CS) as measured by Pelli-Robson

g) Area of Intact EZ under the fovea from Optical Coherence Tomography (OCT)

1.4. Randomization and Blinding

In dose escalation phase, up to 18 adult participants will be administered one of 3 different doses of the ATIMP in cohorts of 3 participants at a time. Based on toxicity data, the IDMC will make a recommendation on the dose to administer to the next cohort of 3 participants.

Once an acceptable safety profile has been established in adults, the IDMC will agree the maximum tolerated dose in adults, which will be confirmed in 3 pediatric participants.

In the expansion phase, up to 48 subjects were randomized to 1 of 3 arms in a 1:1:1 ratio (Immediate low dose administration: Immediate intermediate dose administration: deferred administration). Subjects randomized to the deferred administration group were further randomized to receive the low or intermediate dose in a 1:1 ratio. The eye selected for administration was also randomized at the start of the expansion cohort. All aspects of randomization occurred on completion of screening. The three treatment groups of the randomized expansion phase will be stratified by age at date of informed consent (<25 years, ≥25 years) to balance for disease severity between treatment groups with age used as a surrogate for severity.

Visual function assessors and reading centers are masked to treatment (dose levels and immediate vs. deferred treatment). Neither study site nor sponsor personnel were masked to treatment.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

The following rules are applied to assign actual visits to analysis visit windows. If a subject has two or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important outcomes. If two actual visits are equidistant from the target day within a visit window, the later visit is used. All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point. If a visit falls outside of the visit window, then this visit will be assigned to the closest window according to the distance to the target day and visit description, if there is no visit assigned to the visit window.

Table 1: Visit Windows

Dose Escalation Phase, Pediatric Dose Confirmation Phase, and Immediate Treatment Arms of Expansion Phase		
Visit Window Label	**Time Interval**	**Target Day**
Baseline	-6 Months - Day -1	< Day 1
Day 1 (ATIMP admin.)	Day 1	Day 1
Day 2	Day 2	Day 2
Day 4	Day 3 – Day 5	Day 4
Week 1	Day 6 – Day 10	Day 8
Week 2	Day 11 – Day 21	Day 15
Week 4	Day 22 – Day 36	Day 29
Week 6	Day 37 – Day 56	Day 43

Week 9		Day 57 – Day 72	Day 64
Week 13		Day 73 – Day 160	Day 92
Week 26		Day 161 – Day 259	Day 183
Week 39		Day 260 – Day 350	Day 274
Week 52		Day 351 – Day 393	Day 365
Deferred Treatment Arms of Expansion Phase			
Period	**Visit Window Label**	**Time Interval**	**Target Day**
Deferred Period (prior to treatment)	Baseline	-6 Months - Day 1	≤ Day 1
	Week 13	Day 73 – Day 168	Day 92
	Week 26	Day 169 – Day 365 ł	Day 183
Post treatment period	Day 1 (ATIMP admin.)	Day 1	Day 1¶
	Day 2	Day 2	Day 2¶
	Day 4	Day 3 – Day 5	Day 4¶
	Week 1	Day 6 – Day 10	Day 8¶
	Week 2	Day 11 – Day 21	Day 15¶
	Week 4	Day 22 – Day 36	Day 29¶
	Week 6	Day 37 – Day 56	Day 43¶
	Week 9	Day 57 – Day 72	Day 64¶
	Week 13	Day 73 – Day 160	Day 92¶
	Week 26	Day 161 – Day 365 ł	Day 183¶
¶: after ATIMP administration day for deferred subjects ł : Any scheduled visits after week 26 in deferred treatment arm will be summarized as week 26 visits given COVID-19 delays			

2.2. Pooling Algorithm

In the primary efficacy analysis, randomized immediate treatment arm subjects (pooled low and intermediate doses) in the dose expansion phase will be compared with deferred treatment arm subjects in the dose expansion phase. As a supportive analysis, immediate treatment arm subjects at low, intermediate and high doses in the dose escalation phase and dose confirmation phases will be also compared with deferred treatment subjects prior to treatment in the dose expansion phase, respectively.

A sensitivity analysis will include subjects assigned to low and intermediate doses pooled across both dose escalation phase and expansion phases and compared with deferred subjects prior to treatment from the dose expansion phase of the study.

The MGT011 study is an ongoing long-term natural history non-interventional study of RPGR-XLRP subjects. Sixteen MGT009 subjects participated in the MGT011 study prior to enrolling into MGT009. The study procedures and timing of assessments in both MGT009 and MGT011 are similar thereby facilitating a longitudinal analysis. To do so, data from the deferred subjects prior to treatment from MGT009 (i.e., during their enrollment in the natural history study) will be included to create a more robust longitudinal data set that will help enhance the precision of the corresponding model estimates for this group and expand the deferred period data. This sensitivity analysis will be conducted using this pooled dataset to assess the progression of the disease prior to and post treatment.

2.3. Analysis Sets

2.3.1. All Enrolled Analysis Set

The analysis set of all enrolled subjects includes all subjects who were assigned to a treatment group and therefore excludes screen failures.

2.3.2. Efficacy Analysis Set(s)

For efficacy analyses, the Full Analysis Set (FAS) includes all subjects treated with ATIMP who completed both a baseline and at least one visit after ATIMP administration from the dose escalation and dose confirmation phases, and all immediate treatment subjects who were administered ATIMP and have both a baseline and at least one visit after ATIMP administration and all deferred subjects who completed at least one baseline visit and one post baseline visit prior to ATIMP administration from the expansion phase. Efficacy analyses will be performed according to the randomized/assigned treatment assignment.

2.3.3. Safety Analysis Set

Safety analyses will be performed using the safety analysis set, which includes all immediate treatment subjects (regardless of study phase) who were administered ATIMP, and all deferred subjects who completed their last baseline assessment during the deferred period prior to treatment. Safety analyses will be performed according to actual treatment received.

2.4. Definition of Subgroups

Descriptive summaries of safety and/or efficacy may be done by considering, but not limited to, the following subgroups:

Table 2: Subgroups

Subgroup	Definition
Age Group	• Adults • Children (<16 years old [United Kingdom] or <18 years old [United States])
Country	• United Kingdom • United States
Sex	• Female • Male
Baseline mean Retinal sensitivity (meanRS) from static perimetry	• meanRS <= 10 dB • meanRS > 10 dB

2.5. Study Day and Relative Day

Study Day 1 refers to the day of ATIMP administration for subjects in the dose escalation phase and dose confirmation phase, as well as immediate treatment subjects in dose expansion phase. For deferred treatment subjects during the deferred period prior to treatment, Study Day 1 refers to the end date of the last baseline visit. For deferred treatment subjects during the post-treatment

period, Study Day 1 refers to the day of ATIMP administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day (or relative day) for a visit is defined as:

- Visit date - (date of Study Day 1) +1 day, if the visit date is on or after Study Day 1
- Visit date - date of Study Day 1, if the visit date is before Study Day 1

2.6. Baseline

In general, baseline is defined as the closest visit prior to Study Day 1 and will exclude any screening observations (unless there are no other observations prior to ATIMP administration). However, for efficacy parameters with multiple planned assessments in the baseline window, the arithmetic mean of scheduled baseline visits will be used as the baseline value.

2.7. Imputation Rules for Missing AE Date and Resolution

Partial adverse event (AE) onset dates will be imputed as follows:

- If the onset date of an AE is only missing the day, it will be imputed as:
  - First day of the month that the AE occurred, if month/year of the onset of the AE is different than the month/year of ATIMP administration
  - The day of ATIMP administration, if the month/year of the onset of AE is the same as month/year of ATIMP administration and month/year of the AE resolution date is different
  - The day of ATIMP administration or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of ATIMP administration and month/year of the AE resolution date are same
- If the onset date of an AE is missing both day and month, it will be imputed to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after ATIMP administration
  - Month and day of ATIMP administration, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of ATIMP administration,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.

- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

Completely missing resolution dates will not be imputed.

3. ADMINISTRATIVE INTERIM ANALYSIS

An administrative interim analysis was conducted summarizing both safety and efficacy endpoints to help plan Phase 3 study (MGT-RPGR-021) on data cutoff date 02NOV2020. All available data (including visits after 6 months and up to 12 months for subjects enrolled earlier) were used for this interim analysis. Given the administrative nature of this interim analyses which is intended to support subsequent planning, there is no impact to type I error rate. Results of primary and secondary efficacy endpoints as well as key safety analyses were summarized.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized by treatment group and overall. In addition, the distribution of subjects by country and site will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 3 list the demographic and baseline characteristic variables that will be summarized by study Phase, treatment group and overall for the Safety Analysis Set and All Enrolled Analysis set, respectively.

Table 3: Demographic Variables and Baseline Characteristics

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, SD, median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Categorical Variables	
Age group (adult, pediatric)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Baseline meanRS (<= 10 dB, > 10 dB)	
Race	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'.

4.2. Disposition Information

A subject will be considered to have completed the study if the subject completes the Week 52 visit.

The number of subjects in the following disposition categories will be summarized throughout the study by age group, treatment group and overall, for the All Enrolled Analysis Set.

- Subjects who were administered ATIMP

- Subjects who completed the study
- Subjects who prematurely discontinued from the study and their reasons for discontinuation

Listings will also be provided.

4.3. ATIMP Administration

ATIMP administration volume and study eye data will be summarized by study phase and dose and listed.

4.4. Protocol Deviations

Subjects with major protocol deviations will be identified prior to database lock. Subjects with major protocol deviations will be summarized and an accompanying listing will be provided.

Delayed and missing visits due to COVID-19 will be tabulated and listed.

4.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy initiated before the day of ATIMP administration. Concomitant medications are defined as any therapy used on or after the day of ATIMP administration, including those that started before and continue on or after ATIMP administration.

Summaries of prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) term will be presented by treatment group, age group and overall. The proportion of subjects who receive each medication will be summarized as well as the proportion of subjects who receive at least 1 medication.

Concomitant medications of interest (e.g., medication for management of inflammation/corticosteroids) will also be presented.

4.6. Medical History and Ophthalmic History

Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) by Primary System Organ Class/High Level Term.

Ophthalmic history apart from the study condition will be summarized and an accompanying listing will be provided.

4.7. Genetic Testing

A listing of genetic testing data on nucleotide and protein sequence based on screening for RPGR mutations prior to enrollment will be provided.

5. EFFICACY

Unless otherwise specified, efficacy analyses will be based on the efficacy analysis set and statistical tests will be interpreted at a two-sided significance level of 0.05, with confidence intervals presented at a 2-sided level of 95%.

5.1. Changes to the Protocol

This SAP will not define slowing or halting of progressive deterioration using baseline variation, as defined in Protocol v12.0. Instead, this SAP will assess the visual function endpoint readout in immediate treatment group compared with deferred treatment group.

5.2. Changes to the SAP

The original SAP (dated 24 May 2019) described analyses of the test-retest variation for each visual function assessment, however, this will not be assessed given that the assessments of efficacy endpoints focus on the effect of the treated eye in immediate treatment group compared to the deferred participant treatment eye in deferred group. The statistics for the test-retest do not fit the purposes of the stated objectives and are not appropriate for the goals of the study.

5.2.1. Data Handling Rules

In the case where a variable is recorded as ">x", "≥x", "<x" or "≤x", for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken. For example, if a laboratory safety parameter is reported as being below the limit of quantification or <x, the value of the limit will be used in the calculation of summary statistics. The recorded value will be reported in listings. As sensitivity analysis, for endpoints from static perimetry assessment, including pointwise responder, mean retinal sensitivity, central 30 degree hill of vision (V30), assessment with reliability factor greater than 19% is deemed not reliable and will be excluded according to MeiraGTx Working Practice on Octopus 900 Static perimetry.

For safety, there will be no imputation for missing values for physical examination results, ocular examination, vital sign measurements, clinical laboratory test results and other safety endpoints in the analyses.

5.3. Primary Efficacy Endpoint

5.3.1. Definition

The primary efficacy endpoint is evaluated in subjects from the dose expansion phase based on point-by-point data from 185-point static perimetry assessed through Week 26 in the randomized immediate treatment subjects and compared with randomized deferred subjects in the 26-week deferred period (prior to treatment). Subjects will be considered a responder if they experience at least 7 dB improvement from baseline at 5 or more loci at Week 13 and Week 26; this determination will be based on the treated eye for subjects in the immediate treatment group and for the deferred participant treatment eye for subjects in the deferred group, who had static perimetry assessments at both Week 13 and Week 26. Subjects with missing visits in either Week 13 or Week 26 will not be counted as responder or non-responder and will not contribute to number of subjects in the denominator when calculating proportion of responders.

Treated eye refers to a treated eye in a participant who was assigned or randomized to immediate treatment in any period of the study. Randomized concurrent control eye refers to an untreated eye in a participant who was randomized to deferred treatment; these eyes will receive treatment after completion of the 6-month deferral period. For the purposes of the primary efficacy analyses, these eyes represent the randomized concurrent control group.

5.3.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following components:

- Population: subjects of age 5 years or above with *RPGR*-XLRP
- Treatment: subretinal administration of AAV5-hRKp.RPGR at low and intermediate doses (pooled) for immediate treatment arm and 6-month deferred treatment for deferred treatment arm
- Variable: retinal sensitivity response defined by point-by-point data from 185-point static perimetry
- Intercurrent event: none
- Strategy for addressing intercurrent events: treatment policy strategy
- Population-level summary: Difference in the proportion of responders in retinal sensitivity between immediate treatment subjects and deferred treatment subjects and associated 95% confidence interval

5.3.3. Analysis Methods

Descriptive summaries by treatment group and time point (and study eye when appropriate) using descriptive statistics will be provided. Descriptive statistics such as mean, median, standard deviation, 95% CIs (when applicable), minimum, and maximum will be used to summarize continuous variables; counts and percentages will be used to summarize categorical variables. Change from baseline will be summarized in the same format and plotted across time by treatment group for primary and secondary endpoints.

The primary efficacy endpoint will be evaluated based on point-by-point data from 185-point static perimetry (excluding 3 loci near blind spot). Subjects will be considered a responder if they experience at least 7dB improvement from baseline in at 5 or more loci at Week 13 and Week 26. Subjects with missing visits in either Week 13 or Week 26 will not be counted as responder or non-responder and will not contribute to number of subjects in the denominator when calculating proportion of responders.

A Stratified Fisher's exact test (two-sided) will be used to evaluate the number of responders and non-responders in immediate (pooled low and intermediate doses) versus deferred treatment group

from the dose expansion phase of the study. The stratification factor is age at time of informed consent (<25 years, ≥25 years). Point estimates with corresponding 95% confidence intervals will be provided for the difference in proportion of responders comparing between immediate vs. deferred treatment group. The proportion of responders and 95% confidence interval at week 52 in immediate treatment group (pooled low and intermediate doses) will also be estimated, where the responder is defined as a subject who experiences at least 7 dB improvement from baseline at 5 or more loci at Week 52 and one or more time point prior to Week 52.

The proportion of responders and 95% confidence interval through week 26 will be estimated and summarized by dose level (low and intermediate) and overall in a separate table for deferred subjects post treatment.

5.4. Secondary Endpoints

5.4.1. Definition

Secondary efficacy endpoints will be analyzed as change from baseline through the week 26 assessment on treated eye in immediate treatment group and compared with deferred participant treatment eye in deferred treatment group at 26 weeks. Major secondary efficacy endpoints include the following:

a) Central 30-degree hill of vision (V30) in static perimetry using visual field modeling and analysis (VFMA) (Richard Weleber, 2015)

b) Average threshold in mesopic microperimetry

c) Maze walk time in Vision Mobility Assessment (VMA) under 1 lux and 4 lux, where 4 lux will be tested first

d) Low Luminance best corrected visual acuity (BCVA)

e) Patient report outcome, Low Luminance Questionnaire (LLQ) for the assessment of functional vision in low light conditions

f) Contrast sensitivity (Log CS) as measured by Pelli-Robson

g) Area of Intact EZ under the fovea from Optical Coherence Tomography (OCT)

5.4.2. Analysis Methods

A linear mixed model will be used to model change from baseline V30 with treatment group, baseline V30, and visit month as fixed effect, subject as random effect and age group (<25 years vs. ≥25 years) as strata in expansion phase. An unstructured correlation structure will be used to model within-subject correlations between different visits. Point estimates with corresponding 95% confidence intervals will be estimated for the difference in mean change from baseline between treated eye in immediate treatment group and deferred participant treatment eye in

deferred treatment group at week 26. Two-sided p-values will be reported. The mean change from baseline in V30 and 95% confidence interval at week 52 in immediate treatment group will also be estimated.

Other secondary endpoints will be analyzed through week 52 with the same methodology as described for V30. Possible transformations of the response (ie, logarithm) may also be considered as appropriate.

The mean change from baseline on V30 and other secondary endpoints and corresponding 95% confidence interval at week 26 will be estimated and summarized by dose level (low and intermediate) and overall in a separate table for deferred subjects post treatment.

For LLQ endpoint, the endpoint will be the change from baseline in average score across all item measures related to functional vision in low light conditions. The change from baseline in average score will be analyzed using the same methodology as described above for V30. The detailed analysis plan on patient reported outcome (PRO) will be documented in a supplementary PRO SAP separately.

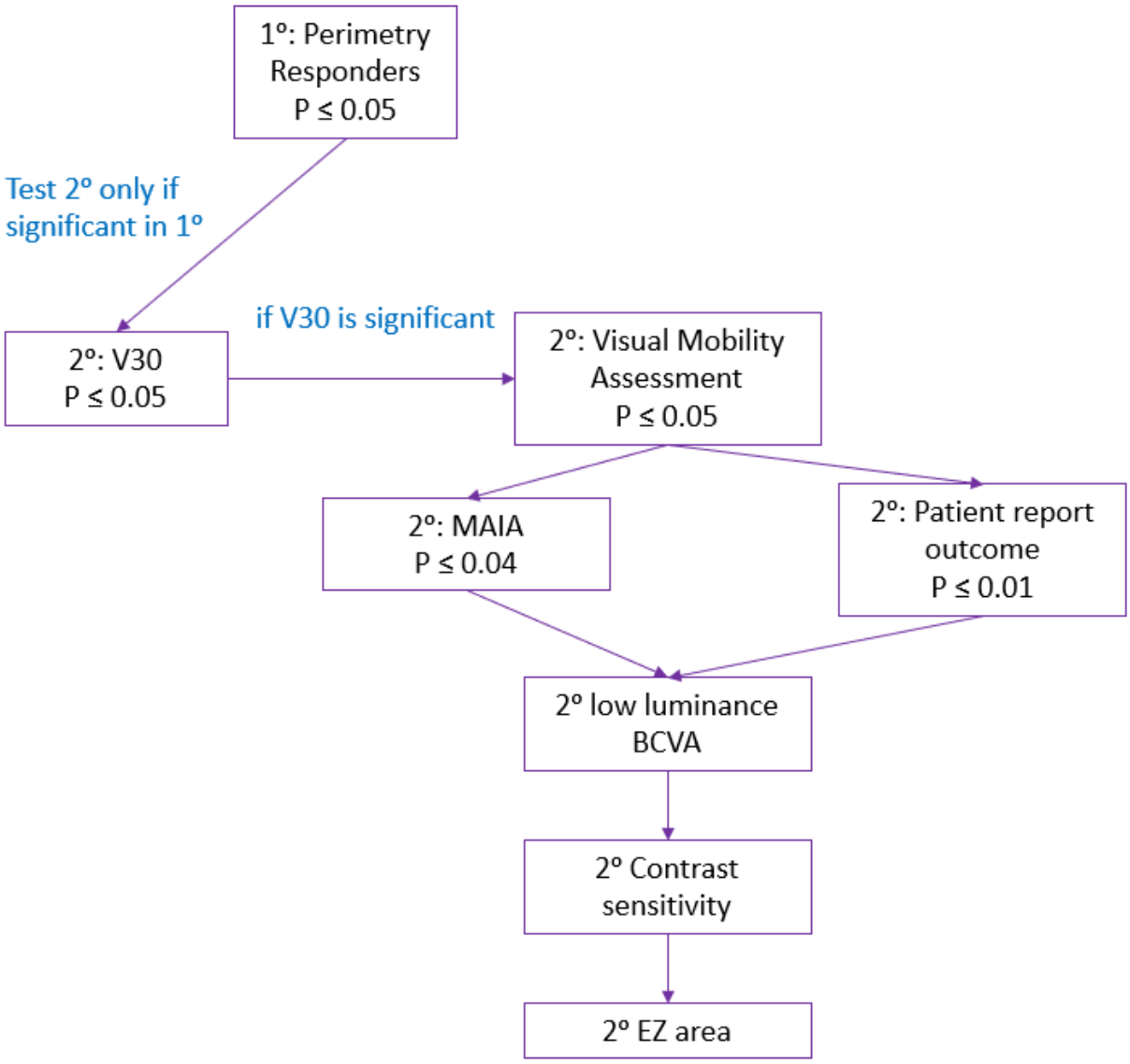
For efficacy, if appropriate, a model-based imputation will be applied.

For a subject who either refuses or is unable to navigate the visual mobility assessment under a certain lux level, the missing data will be imputed using the predicted value from an imputation model based on Rubin's imputation strategy using SAS® PROC MCMC and MI, by leveraging data relevant to visual mobility assessment, such as age, lux level, test eye, treatment group and other baseline clinical covariates including static perimetry.

5.5. Multiplicity Adjustment

A branched fixed sequence method will be used to control the family-wise type I error rate at 0.05 for testing the primary and key secondary endpoints comparing immediate treatment subjects (pooled low and intermediate doses) with deferred treatment subjects in the expansion phase as illustrated in Figure 3. Alpha of 0.05 will be allocated to the primary endpoint, static perimetry responder by pointwise analysis. If statistically significant, the alpha of 0.05 will be passed down to the first secondary endpoint, V30. If V30 is statistically significant, the alpha of 0.05 will be passed down to the visual mobility assessment. If the visual mobility assessment is statistically significant, MAIA microperimetry and patient report outcome (Impact of Vision Impairment – 'Reading and Accessing Information' domain) will be tested under alpha=0.04 and 0.01, respectively. If one or both endpoints are statistically significant, the remaining alpha will be passed down to test low luminance BCVA, contrast sensitivity and EZ area, conditional on the statistical significance of the prior test. If any of the endpoint(s) are not statistically significant, the allocated alpha for testing cannot be passed and testing will stop after all alpha has been spent.

Figure 3: Illustration of alpha distribution



Key: V30=central 30-degree hill of vision. MAIA =microperimetry

5.6. Exploratory Efficacy Variable(s)

5.6.1. Definition

[redacted]

[redacted]

5.6.2. Analysis Methods

[redacted]

[redacted]

6. SAFETY

The proportion of subjects who experience the primary safety outcome and the corresponding 95% confidence interval (CI) based on the normal approximation with continuity correction will be provided for the immediate treatment subjects and deferred subjects prior to treatment in the safety analysis set. The analysis will be performed by study phase, treatment group and overall. The primary safety outcome for all deferred subjects post-treatment will be tabulated separately. A listing of primary safety outcome events will also be provided.

A similar analysis will also be conducted for dose-limiting events (DLEs) in dose escalation phase.

6.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Any AE occurring on or after the initial administration of ATIMP within 6 months is considered to be treatment emergent. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 (one) occurrence of the given event will be summarized by age group, treatment group and overall.

Summary tables will be provided for the frequency and incidence of subjects experiencing the following treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs leading to termination of study participation
- AEs by severity
- AEs by relationship to ATIMP
- AEs by relationship to ATIMP surgery
- Death
- AEs of interest related to ocular inflammation

- Inflammation in cohorts before and after the addition of subTenons triamcinolone injection to the protocol

Summaries of adverse events by system organ class and dictionary-derived (preferred) term will also be provided.

In addition to the summary tables, accompanying listings will be provided for subjects who experience:

- AEs
- SAEs
- AEs leading to termination of study participation
- Death (if any)
- AEs of interest related to ocular inflammation.

6.2. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the subjects included in the safety analysis set. Hematology, clinical chemistry, glucose, serology and polymerase chain reaction (PCR) laboratory tests will be presented.

Hematology and clinical chemistry observed values will be summarized at each assessment time point using shift table by parameter (unit). Number of subjects and percentage with values outside of normal range will be summarized through Week 52.

Individual hematology and clinical chemistry values outside of normal range will be listed by subject.

Serology data will be listed and summarized at each assessment by age group, treatment group and overall.

All PCR values will be summarized by tissue and listed.

6.3. Vital Signs and Physical Examination Findings

Vital sign parameters including height, weight, pulse, blood pressure (systolic and diastolic), respiration rate, arterial oxygen saturation, temperature will be summarized at each assessment time point using shift table. Number of subjects and percentage with values outside of normal range will be summarized through Week 52.

Individual physical examination data outside of normal range will be listed by subject.

6.4. Other Safety Parameters

All pregnancy test data will be listed.

REFERENCES

FDA. (2017). *Multiple Endpoints in Clinical Trials Guidance for Industry.*

Richard Weleber, T. S. (2015). VFMA: Topographic Analysis of Sensitivity Data From Full-Field Static Perimetry. *Transl Vis Sci Technol*, 4(2):14.