Janssen Research & Development

Statistical Analysis Plan

An open label, multi-center, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV2/8-hCARp.hCNGB3) for gene therapy of adults and children with achromatopsia owing to defects in CNGB3

Protocol MGT006; Phase 1/2

AAV2/8-hCARp.hCNGB3

Status: Approved

Date: 18 December 2019

Prepared by: Janssen Research & Development, LLC

Document No.: EDMS-ERI-203932413, 1.0

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

TABLE OF CONTENTS

ABBREVIATIONS

AAV	Adeno-Associated Virus
ADL	activities of daily living
AE	adverse event
ATC	Anatomical Therapeutic Chemical
ATIMP	advanced therapy investigational medicinal product
BMI	body mass index
CI	confidence interval
CNGB3	Cyclic Nucleotide-Gated Cation Channel Beta-3
DLE	dose-limiting event
ERG	electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
eCRF	electronic case report form
FST	Full-field Stimulus Testing
IDMC	Independent Data Monitoring Committee
IVI	impact of visual impairment
IVI-A	impact of visual impairment adult
IVI-C	impact of visual impairment child
MedDRA	Medical Dictionary for Regulatory Activities
PA	photoaversion
PCR	polymerase chain reaction
QoL	Quality of Life
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SUSAR	suspected unexpected serious adverse reaction
VA	Visual Acuity
VRQoL	Vision-Related Quality of Life
WHO-DD	World Health Organization Drug Dictionary

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 CNGB3 study (MGT006). This SAP is based on the protocol of study MGT006, v7.0 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 6.1. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures, and listings) are provided in a separate document.

1.1. Trial Objectives

The primary research objective was to assess the safety of an AAV2/8 vector for hCNGB3 gene replacement in the retina based on the primary safety outcome listed in Section 2.1.

The secondary research objective was to determine whether an AAV2/8 vector for hCNGB3 gene replacement in the retina can improve retinal function, visual function and quality of life.

1.2. Trial Design

This was an open-label, non-randomized phase I/II dose-escalation trial to determine the safety and efficacy of subretinal administration of the study agent (ATIMP) in subjects with CNGB3-related achromatopsia. In the dose escalation phase, subjects were administered a single dose of ATIMP in cohorts of 3 subjects at a time (up to a maximum of 18 subjects in total). Based on toxicity data, the Independent Data Monitoring Committee (IDMC) made a recommendation on the dose to administer to the next cohort of 3 subjects.

Once an acceptable safety profile had been established in adults, up to 18 additional subjects (either children or adults), were included. The IDMC agreed to the sponsor's recommendation for the maximum tolerated dose in adults before recommending administering up to this dose in the expansion phase.

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

Safety and efficacy were assessed for 6 months following the intervention by clinical examination and special investigations according to the schedule in Section 5.6 of the protocol.

Due to the rare nature of the disease, there were no formal sample size calculations performed and no formal hypothesis testing was conducted.

2. OUTCOME DEFINITIONS

2.1. Primary Safety Outcome

The primary safety outcome is defined as any of the below events occurring during the 6 weeks following administration, at least possibly related to the ATIMP, not 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 of the protocol)
- Infective endophthalmitis
- Ocular malignancy
- Grade III or above non-ocular suspected unexpected serious adverse reaction (SUSAR) (Protocol MGT006, Section 5.11.3.4.2 Severity or Grading of Adverse Events).

This is the same criteria as the dose limiting event in the dose escalation phase.

Overall safety will be assessed for 6 months after the intervention in this study, and a further 4.5 years in a separate long-term follow-up study (Protocol MGT007).

The adverse events preferred terms are identified in a separate file (AES_OF_INTEREST.xlsx) and saved in the ERIS system.

2.2. Efficacy Outcomes

As listed in the protocol (Section 5.6 Trial Assessments), the following efficacy outcomes will be analyzed or summarized depending on the amount of data collected:

- Visual acuity (VA)
- Contrast sensitivity
- Reading speed
- Color vision
- Static perimetry
- Full field stimulus testing (FST)
- Ocular examination
- Fundus photography
- Spectral domain optical coherence tomography (SD-OCT)
- Adaptive optics imaging
- Fundus autofluorescence
- Photoaversion (PA)
- Microperimetry
- Visual mobility
- Nystagmus
- Electroretinography (ERG)
- Quality of life (QoL) as measured by the Impact of Visual Impairment (IVI) questionnaire adult (IVI-A) and child (IVI-C) versions, and the EQ5D-5L and EQ5D-Y
- Photoaversion questionnaire.

3. ANALYSIS DEFINITIONS

3.1. Analysis Sets

For safety analyses, the safety analysis set includes all enrolled subjects who were administered ATIMP.

For efficacy analyses, the full analysis set includes all enrolled subjects who were administered ATIMP and have both a baseline and at least 1 visit after ATIMP administration.

3.2. Baseline

In general, baseline is defined as the closest visit prior to ATIMP administration 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 will be used as the baseline value.

3.3. Study Day/Relative Day

Study Day 1 or 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 Day 1
- Visit date - date of Day 1, if the visit date is before Day 1

3.4. Visit Windows

The following rules are applied to assign actual visits to analysis visit windows other than baseline. 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.

Table 1: Visit Windows

Visit Window Label	Time Interval	Target Day
Baseline	-6 Months - < Day 1	< Day 1
Day 1	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 20	Day 15
Week 4	Day 21 – Day 36	Day 29
Week 6	Day 37 – Day 59	Day 43
Week 12	Day 60 – Day 127	Day 85
Week 24	Day 128 – Day 225	Day 169

3.5. 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.

3.6. Imputation Rules for Missing Adverse Event Dates

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.

4. SUBJECT INFORMATION

Summary statistics (arithmetic mean, standard deviation [SD], median, minimum and maximum for continuous variables) will be presented by age group and dose level. Frequency tables for categorical data will also be provided.

4.1. Demographics and Baseline Characteristics

Table 2 list the demographic and baseline characteristic variables that will be summarized by age group, dose level (see Table 3) and overall.

Table 2: 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)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Sex (male, female)	Frequency distribution with the number and percentage of subjects in each category.
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Study Eye (left, right)	

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

4.2. Definition of Subgroups

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

Table 3: Subgroups

Subgroup	**Definition**
Age Group	• Adults • Children (<16 years old [United Kingdom] or <18 years old [United States])
Dose Level	• Low • Intermediate • Other • High
Country	• United Kingdom • United States
Sex	• Female • Male

4.3. Disposition Information

A subject will be considered to have completed the study if the subject completes the Week 24 visit.

The number of subjects in the following disposition categories will be summarized throughout the study by age group, dose level and overall for safety 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.

4.4. Genetic Testing

A listing of genetic testing data based on screening for CNGB3 mutations prior to enrollment will be provided.

4.5. ATIMP Administration

ATIMP administration volume and study eye data will be summarized. All ATIMP administration data will be listed.

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. 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 dose level, 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 provided.

4.8. Protocol Deviations

Subjects with major protocol deviations will be summarized and an accompanying listing will be provided.

5. SAFETY ANALYSES

5.1. Primary Safety Outcome

The proportion of subjects who experience the primary safety outcome and the corresponding 95% confidence interval (CI) using for the binomial proportion based on the normal approximation with continuity correction will be provided (by age group, dose level and overall). The primary safety outcome will also be listed.

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

5.2. 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 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 occurrence of the given event will be summarized by age group, dose level 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

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.

5.3. 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.

Summary statistics of hematology and clinical chemistry observed values and change from baseline by parameter (unit) will be summarized by age group, dose level and overall.

All hematology and clinical chemistry values will be listed.

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

All PCR values will be summarized by tissue and listed.

5.4. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including height, weight, pulse, blood pressure (systolic and diastolic), pulse, respiration rate, arterial oxygen saturation, temperature will be summarized at each assessment time point. Change from baseline will be summarized through Week 24 using descriptive statistics (mean, standard deviation, median, minimum and maximum).

Individual physical examination data will be listed by subject.

5.5. Other Safety Parameters

All pregnancy test data will be listed.

6. EFFICACY

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

6.1. 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 assessment of safety is the primary objective of the study and the secondary objectives for efficacy focus on the effect of the treated eye compared to the untreated eye. 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.

6.2. Analysis Methods

Summaries by age group, dose level and time point (and study eye when appropriate) using descriptive statistics will be provided for each outcome. Descriptive statistics such as mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables, and counts and percentages will be used to summarize categorical variables; 95% CIs may be provided for descriptive statistics. Data from each individual will also be plotted across time by age group and dose level for the treated eye compared to the untreated eye, if available. Change from baseline will be summarized, if appropriate.

Mixed linear effects models may be used to assess differences between the treated and the untreated eye with covariates including age group, dose level, time and the interaction of dose level by time. An unstructured correlation structure will be used to model within-subject correlations when possible. Possible transformations of the response (i.e., logarithm) may also be considered for some outcomes.

Sensitivity analyses with demographics such as sex and race may be explored.

Quality of life patient reported outcome measures may be used to correlate a subject's feeling about their own well-being with clinical observations. The IVI-C and IVI-A will be summarized by the 3 domains of reading and accessing information, mobility and independence, and emotional well-being.[123] The EQ-5D-5L[4] and EQ-5D-Y[5] will also be summarized (see Attachment 1 for details).[6]

For specialized ophthalmologic assessments, data may be analyzed by the expert team member(s) who are best qualified to analyze and interpret those assessments. Final data will be reported descriptively.

REFERENCES

1. Goldstein JE et al. Calibrating the impact of vision impairment (IVI): creation of a sample-independent visual function measure for patient-centered outcomes research. Translational Vision Science & Technology; December 2018; Vol.7, 38
2. Lamoureux EL et al. The impact of vision impairment questionnaire: an evaluation of its measurement properties using Rasch analysis. Invest Ophthalmology & Vision Science; November 2006; 47(11):4732-41
3. Lamoureux EL et al. The impact of vision impairment questionnaire: an assessment of its domain structure using confirmatory factor analysis and Rasch analysis. Invest Ophthalmology & Vision Science. March 2007; 48(3):1001-6
4. Herdman M et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research, December 2011;20(10), 1727-36.
5. Wille N et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Quality of Life Research, August 2010;19(6), 875-86
6. EuroQol Research Foundation. EQ-5D User Guide, 2019 Available from: https://euroqol.org/publications/user-guides

ATTACHMENT 1

1. DESCRIPTION OF QUESTIONNAIRE DATA

The impact of visual impairment (IVI) vision-related quality of life (VRQoL) questionnaire queries the level of restriction of participation in common daily experiences due to visual impairment. For this study, there will be 2 sets of IVI questionnaires. The adults will complete a 28-item questionnaire (IVI-A) and the children will complete a 24-item questionnaire (IVI-C). The impact of photoaversion (extreme sensitivity to light) on activities of daily living (ADLs) will be assessed with the Photoaversion (PA) patient-reported questionnaire.

For adults, the IVI questionnaire covers a broad range of issues in 3 separate domains of functioning. The domains and the items that they contain are:

- Reading and accessing information domain contains items 1, 3, 5, 6, 7, 8, 9, 14, 15. Items 1, 3 and 5 to 9 will be rated on a 5-level scale (0 = a lot, 1 = a fair amount, 2 = a little, 3 = not at all and 8 = don't do this for other reasons). Items 14 and 15 will be rated on a 4-level scale (0 = a lot, 1 = a fair amount, 2 = not at all and 8 = don't do this for other reasons).
- Mobility and independence domain contains items 2, 4, 10, 11, 12, 13, 16, 17, 18, 19, 20. Items 2, 4 and 10 to 13 will be rated on a 5-level scale (0 = a lot, 1 = a fair amount, 2 = a little, 3 = not at all and 8 = don't do this for other reasons). Items 16 to 20 will be rated on a 4-level scale (0 = a lot, 1 = a fair amount, 2 = a little and 3 = not at all).
- Emotional well-being domain contains items 21 to 28. These items will be rated on a 4-level scale (0 = a lot of the time, 1 = a fair amount of time, 2 = a little of the time and 3 = not at all).

The EQ-5D is a standardized measure of health status. The EQ-5D-5L questionnaire will be completed by adults while EQ-5D-Y will be completed by children.

- The 5 dimensions of both questionnaires are:
  - Mobility
  - Self care
  - Usual activities
  - Pain/discomfort
  - Anxiety/depression
- Each of the dimensions of EQ-5D-5L have 5 levels:
  - Level 1: indicating no problems
  - Level 2: indicating slight problems
  - Level 3: indicating moderate problems

  - Level 4: indicating severe problems
  - Level 5: indicating extreme problems

- Each of the dimensions of EQ-5D-Y have 3 levels:

  - Level 1: indicating no problems
  - Level 2: indicating some problems
  - Level 3: indicating a lot of problems

In addition, there are 13 questions focused on photoaversion questionnaire.