STATISTICAL ANALYSIS PLAN

Protocol Title:	Long-term follow-up study of participants following an open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3) for gene therapy of adults and children with achromatopsia owing to defects in CNGB3 or CNGA3
Protocol Number:	MGT007
Protocol Version/Date:	Version 6.0/03Dec2021
Investigational Product:	AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3
Sponsor:	MeiraGTx UK II Ltd. 92 Britannia Walk London N1 7NQ
SAP Version/Date:	Version 2.0/22August2024

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature		**Date**
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VERSION HISTORY

Version	Version Date	Description
1.0	Version 1.0/23July2024	Original signed version
2.0	Version 2.0/22August2024	Reduced the number of analyses, including all those comparing the treated eye to the fellow eye and analyses by dose level.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AO	Adaptive optics
ATIMP	Advanced therapy investigational medicinal product
BCEA	Bivariate contour ellipse area
BMI	Body mass index
CF	Counting fingers
CI	Confidence interval
CMT	Clinical Management Team
CSF	Contrast Sensitivity Function
CTCAE	Common Terminology Criteria for Adverse Events
DA	Dark adapted
ELISA	Enzyme-linked Immunosorbent Assay
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus Autofluorescence
FAS	Full Analysis Set
FST	Full-field Stimulus Testing
HM	Hand motion
IDMC	Independent Data Monitoring Committee
ISCEV	International Society for Clinical Electrophysiology of Vision
IVI	Impact of visual impairment
KG	Kilograms
LP	Light perception
MedDRA	Medical Dictionary for Regulatory Activities
mfERG	Multifocal electroretinography
mL	Millilitre
NLP	No light perception
PCR	Polymerase chain reaction
PERG	Pattern electroretinography

Abbreviation	Definition
PT	Preferred term
RPGR	Retinitis Pigmentosa GTPase Regulator
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SOC	System organ class
SUN	Standardisation of uveitis nomenclature
TEAE	Treatment emergent adverse event
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VG	Vector genome
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number MGT007. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary research objective is to assess the longer-term safety of AAV8-hCARp.hCNGB3 for CNGB3 gene replacement and AAV8-hG1.7p.coCNGA3 for CNGA3 gene replacement in the retina administered to participants in the CNGB3 and CNGA3 trials, measured by the presence or absence of adverse events, the assessment of visual acuity, and loss of light perception.

2.1.2 Secondary Objective

The secondary research objective is to explore the longer-term efficacy of AAV8-hCARp.hCNGB3 and AAV8-hG1.7p.coCNGA3 in improving visual and retinal function, and quality of life.

2.2 Study Design

2.2.1 Overview

Participants will be invited to provide consent for this longer-term follow-up study during the CNGB3 (MGT006) trial or CNGA3 (MGT012) trial. During this longer-term follow-up study participants will be assessed for safety for up to 60 months following AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3 administration in study MGT006 or study MGT012.

The duration of long-term follow-up is therefore consistent with the recommendations of the current CHMP Guideline on Follow-up of Patients Administered with Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/60436/2007) of 22 October 2009, where it is stated that, for viral vectors without integration, latency or reactivation potential, a brief clinical history and sample testing should be performed pre-treatment, at 3, 6 and 12 months after treatment, and then yearly thereafter for a minimum of 5 years (and, if non-clinical tests or evidence from other clinical trials using identical vectors or modifications of vectors indicate a potential for integration or late re-activation, the monitoring should be extended to continue yearly after those 5 years until data indicate that there is no longer any risk to be followed). Further, although the Food and Drug Administration (FDA) Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006) recommends a standard 15-year period of follow-up, it is also noted that a shorter period of follow-up may be possible if the vector does not integrate and has no potential for latency and reactivation. The follow-up study will be a non-intervention study designed to collect data on longer-term safety and efficacy at the equivalent of 9, 12, 18, 24, 36, 48, and 60 months following ATIMP administration.

2.2.2 Randomization and Blinding

The study is an open-label non-randomized study.

2.2.3 Sample Size Determination

This is a long-term follow-up study; therefore, there is no formal sample size calculation.

23 and 11 participants were randomized and dosed in the MGT006 and MGT012 studies, respectively. All participants enrolled in the MGT006 and MGT012 studies were invited to participate in this follow-up study.

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint is to assess the longer-term safety of AAV8-hCARp.hCNGB3 for *CNGB3* gene replacement and AAV8-hG1.7p.coCNGA3 for *CNGA3* gene replacement in the retina administered to participants in the MGT006 and MGT012 studies, measured by the occurrence of any adverse events that are related to the study drug and loss of light perception as measured by a deterioration in visual acuity by 15 or more early treatment diabetic retinopathy study (ETDRS) letters.

2.3.2 Secondary Endpoints

The secondary outcomes are measures of the efficacy of the ATIMP; these will be performed on an individual participant basis and will be descriptive in nature:

1) Any improvements in visual function from baseline that are greater than the test-retest variation and are sustained for at least two consecutive assessments.
2) Any improvement in retinal function from baseline that is greater than test-retest variation and measurable by electrophysiology (pattern ERG, or full-field ERG).
3) Quality of life will be measured by the Impact of Visual Impairment (IVI) questionnaire and the EQ5D-5L.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Definition of Baseline

The baseline values of MGT006 and MGT012 final analyses will be used for the MGT007 final analyses.

3.1.2 Incomplete Dates

For calculation purposes, incomplete dates will be completed using the most conservative values. For example, AEs with missing start dates, but with stop dates either overlapping the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the administration of ATIMP. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered treatment-emergent. Actual data values as they appear in the original eCRFs will be presented in the listings.

3.1.3 Non-numeric Values Recorded in a Numeric Field

In the case where a variable is recorded as “>x”, “≥x”, “<x” or “≤x”, then 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.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, Q1, Q3, minimum, and maximum.

3.1.5 Data Presentations

All data will be summarized by dose level. For each study, a separate study-specific total should summarize all dose levels for that study. In addition, an overall column that includes all participants of both studies should also be presented.

The following table summarizes the number of dosed participants and the associated dose levels in studies MGT006 and MGT012.

Dose Level (vg/mL)	Number of MGT006 Participants Dosed	Number of MGT012 Participants Dosed
[redacted]	3	3
[redacted]	12	3
[redacted]	3	NA
[redacted]	5	5
Study Total	23	11

Unscheduled measurements and repeat measurements not due to technical failure will be listed but not summarized. If a repeat measurement is due to a technical failure, it will be included in the summaries.

3.2 Analysis Populations

3.2.1 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all enrolled participants who have been administered vector in the parent study (MGT006 or MGT012).

3.2.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) includes all enrolled participants who were diagnosed with CNGA3- or CNGB3-related achromatopsia, who were administered vector, and who had at least one post-baseline assessment for efficacy. Participants will be presented according to the dose level they received.

Study completion/withdrawal and protocol deviations will be summarized using the FAS set. Background and demographic characteristics will be summarized using the SAF. The primary and secondary efficacy endpoints will be summarized using the FAS. Prior/concomitant medications, administration of study treatment, and exposure and safety will be summarized using the SAF.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition will include the number and percentage of (1) all participants enrolled, (2) participants included in the safety analysis set, (3) participants in the full analysis set, (4) participants who completed the study, and (5) participants who prematurely discontinued follow-up. The number and percentage of participants will be summarized by their reasons for withdrawal from follow-up. Individual reasons for withdrawal will be presented in a listing.

Eligibility for each of the analysis sets, along with reasons for exclusion, will be listed. Study completion/withdrawal data will be listed.

3.3.2 Protocol Deviations

Counts and percentages of subjects with protocol deviations by deviation category will be summarized by treatment and in total based on all enrolled subjects. Major deviations will be summarized separately.

3.3.3 Demographic and Baseline Characteristics

Demographic characteristics (age, sex, ethnic origin, race, country, and adult or pediatric) and body measurements (height, weight, and body mass index (BMI)) will be carried over from the respective parent studies.

All participant demographic data, including informed consent, will be listed.

3.3.4 Concomitant Medications

Medications will be coded using the latest World Health Organization (WHO) Drug Dictionary version, which will be indicated in the data summaries and listings.

Medications that are ongoing at the time of MGT007 study enrollment will be deemed to be concomitant medications. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of participants taking concomitant medications will be summarized by medication class and standardized medication name, where medication class and standardized medication name will be presented in decreasing frequency of the total number of participants with medications. In summary tables, participants taking multiple medications in the same medication class or having the same standardized medication recorded multiple times in the study will be counted only once for that specific medication class and standardized medication name.

Medication data will be listed, and concomitant medications will be flagged.

3.4 Safety Evaluation

3.4.1 Adverse Events

AE will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings.

A TEAE is defined as an AE that started on or after the start of the administration of ATIMP. If adverse event dates are incomplete and it is not clear whether the adverse event was treatment-emergent, it will be assumed to be treatment-emergent.

A treatment-related TEAE is defined as a TEAE that is possibly, probably, or definitely related to ATIMP or ATIMP surgery. If the TEAE has a missing relationship it is assumed to be related to ATIMP for analysis purposes.

A summary table will present the following by dose group in the dose escalation and dose expansion phase:

- TEAEs (events and participants).
- Serious TEAEs (events and participants).
- Serious study treatment-related TEAEs (events and participants).
- TEAEs by severity (CTCAE grade version 4.0) (events and participants).
- TEAEs by relationship to ATIMP and the pooled ATIMP-related [possibly, probably, and related] category (events and participants).
- TEAEs by relationship to ATIMP surgery and the pooled ATIMP-related [possibly, probably, and related] category (events and participants).
- TEAEs leading to withdrawal from study (participants only).
- TEAEs leading to death (participants only).

If a participant experienced more than one TEAE, the participant will be counted once using the most related event for the "by relationship to study treatment" and "related to study treatment" summaries and at the worst severity for the "by severity" summary.

The following tables will be presented:

- TEAEs by SOC and PT.
- TEAEs by SOC, PT, and severity (CTCAE grade version 4.0).
- TEAEs by SOC, PT, and relationship to ATIMP and the pooled related categories (related [possibly, probably, and related]).
- TEAEs by SOC, PT, and relationship to ATIMP surgery and the pooled related categories (related [possibly, probably, and related]).

For all of the above, SOC and PT will be presented in decreasing frequency of the total number of participants with TEAEs.

Further details of the above five tables are given below:

- If a participant experienced more than one TEAE the participant will be counted once for each SOC and once for each PT
- If a participant experienced more than one TEAE the participant will be counted once for each PT.
- If a participant experienced more than one TEAE the participant will be counted once for each SOC and once for each PT at the worst severity.
- If a participant experienced more than one TEAE the participant will be counted once for each SOC and once for each PT using the most related event.

Adverse event data will be listed in full, and this will also include a treatment-emergent flag, the time of onset and cessation of event relative to first administration of ATIMP and duration of AE.

3.4.2 Clinical Laboratory Evaluation

No current plans to analyze the sample collected in study MGT007 for immunological response.

3.4.3 Pregnancy Test

All pregnancy data will be listed.

3.4.4 Other Safety Analyses

Ocular examination

Ocular examination by slit lamp biomicroscopy will be used to assess the anatomical integrity of the eyes and quantify any intraocular inflammation. During the examination, intraocular pressure will be determined by tonometry.

The arithmetic mean of the multiple observations at baseline will be used as the baseline value.

Summary statistics of the intraocular pressure (mmHg) observed values and change from baseline for study eye and fellow eye by assessment and dose level in the dose escalation and dose expansion phase and for all participants will be presented.

All intraocular pressure (mmHg) observed values will be listed.

Slit lamp observation data of the condition of the lids, cornea, conjunctiva, iris, lens, anterior chamber – cell, anterior chamber – flare, vitreous haze, and fundus will be listed for all participants.

Fundus Autofluorescence (FAF)

FAF imaging allows visualization of CNGA3 and CNGB3 by using the intrinsic fluorescence derived from their lipofuscin content.

FAF data will be listed.

Fundus Photography

Retinal imaging will be performed by color fundus photography (ETDRS 7 standard fields).

All fundus photography data will be listed.

3.5 Efficacy Evaluation

3.5.1 Test-Retest

The test-retest values from studies MGT006 and MGT012 will be used for the MGT007 final analyses.

The protocol describes efficacy as being indicated by:

Any improvement in visual function from baseline that is greater than the test-retest variation for that test and is sustained for at least 2 consecutive assessments.

Participants who have a post baseline reading greater than the test-retest value for at least 2 consecutive assessments will be classed as a visual function improvement for the relevant test.

The test-retest variation for each visual function assessment will be calculated for each participant who has at least one set of test-retest data as:

$$Test - retest = 1.96\sqrt{S_p^2}$$

where S_p^2 is the within-participant variance for each participant and will be derived as:

$$\frac{(\boldsymbol{n1}-\boldsymbol{1})\sum_{\mathbf{(yi1-ybar1)}}\mathbf{2} + (\mathbf{n2}-\mathbf{1})\sum_{\mathbf{(yi2-ybar2)}}\mathbf{2}}{\boldsymbol{n1}+\boldsymbol{n2}-\boldsymbol{g}}$$

Where:

yi1 is the ith baseline observation in the left eye

ybar1 is the mean of baseline observations in the left eye

yi2 is the ith baseline observation in the right eye

ybar2 is the mean of baseline observations in the right eye

n1= number of baseline observations in the left eye

n2= number of baseline observations in the right eye

g is the number of eyes =2

The test-retest variation for each visual function assessment of the difference between the study eye and fellow eye will also be calculated for each participant who has at least one set of test-retest data using the same formula except S_p^2 will be derived as

$$\frac{\sum_{(yi-ybar)} \mathbf{2}}{\boldsymbol{n-g}}$$

Where:

yi is the ith baseline observation in the difference of the study eye and fellow eye

ybar is the mean of baseline observations in the difference of the study eye and fellow eye

n= number of baseline observations in the difference of the study eye and fellow eye (vary from 2 to 3)

g is 1

3.5.2 Visual Acuity

Visual acuity was assessed at the Month 9, 12, 18, 24, 36, 48, and 60 visits.

4 meter refraction of the sphere, cylinder, and axis of each eye will be measured. Best-corrected ETDRS visual acuity will be measured.

The arithmetic mean of the multiple observations at baseline will be used as the baseline value.

Achievement of visual improvement above the test-retest variation (yes/no) as measured by a number of ETDRS letters will be summarized for study eye and the difference between eyes (study eye minus fellow eye) for all participants.

The 4-meter refraction (sphere, cylinder, and axis) observed values will be summarized for the study eye for all participants.

Summary statistics of all ETDRS visual acuity observed values and the change from baseline by study eye and the difference between eyes (study eye minus fellow eye) for all participants will be presented.

The difference between the study eye and the fellow eye of ETDRS letters, the difference at each visit, along with its change from baseline data, will be summarized. At each post-baseline visit, the change from baseline in the difference between the study eye and the fellow eye will be tested by a nonparametric Wilcoxon signed rank test as the primary method. The p-value from the t-test and the Shapiro-Wilk Normality test will also be provided.

All visual acuity data will be listed.

In-text displays:

- Average Plot of BCVA (ETDRS Letters) Change from Baseline Over Time
- Individual Plot of BCVA (ETDRS Letters) Change from Baseline Over Time

3.5.3 Contrast Sensitivity

Contrast sensitivity was assessed at the Month 9, 12, 18, 24, 36, 48, and 60 visits.

Contrast sensitivity (LogCS) will be measured using the Pelli-Robson chart. Measurements for each eye and both eyes will be taken.

The arithmetic mean of the multiple observations at baseline will be used as the baseline value.

Achievement of any visual improvement above the test-retest variation (yes/no) as measured by the contrast sensitivity (LogCS) will be summarized for study eye and the difference between eyes (study eye minus fellow eye) for all participants.

Summary statistics of the contrast sensitivity observed values and change from baseline by study eye and assessment by distance at testing for all participants will be presented.

The difference between the study eye and the fellow eye of contrast sensitivity, the difference at each visit, along with its change from baseline data, will be summarized. At each post-baseline visit, the change from baseline in the difference between the study eye and the fellow eye will be tested by a nonparametric Wilcoxon signed rank test as the primary method. The p-value from the t-test and the Shapiro-Wilk Normality test will also be provided.

All contrast sensitivity observed values will be listed.

In-text displays:

- Average Plot of Contrast Sensitivity Change from Baseline Over Time
- Individual Plot of Contrast Sensitivity Change from Baseline Over Time

3.5.4 Reading Speed

Reading speed was assessed at the Month 9, 12, 18, 24, 36, 48, and 60 visits.

Reading ability, including reading distance (cm), reading acuity (LogMAR), maximum reading speed (words/minute), and critical print size (LogMAR) will be assessed with MNRead and International Reading Speed Texts.

The arithmetic mean of the multiple observations at baseline will be used as the baseline value.

Achievement of visual improvement above the test-retest variation (yes/no) as measured by maximum reading speed will be summarized for study eye and difference between eyes (study eye minus fellow eye) for all participants.

The number and percentage of participants with a reading distance of 40 cm or 25 cm will be presented for the study eye for all participants.

Summary statistics of the maximum reading speed observed values and change from baseline by study eye for all participants will be presented.

The difference between the study eye and the fellow eye of reading speed (words/minute), the difference at each visit along with its change from baseline data will be summarized. At each post-baseline visit, the change from baseline in the difference between the study eye and the fellow eye will be tested by nonparametric Wilcoxon signed rank test as the primary method. The p-value from the t-test and the Shapiro-Wilk Normality test will also be provided.

All reading speed data will be listed.

In-text displays:

- Average Plot of Maximum Reading Speed Change from Baseline Over Time
- Individual Plot of Maximum Reading Speed Change from Baseline Over Time

3.5.5 Quality of Life

3.5.5.1 Impact of Visual Impairment (IVI) Questionnaire

IVI was assessed at the Month 12, 24, 36, 48, and 60 visits.

The IVI quality of life questionnaire queries the level of restriction of participation in common daily experiences. For this study, there will be 2 sets of questionnaires. The adults will complete a 28-item questionnaire (IVI-A) and the children will complete a 24-item questionnaire (IVI-C).

For adults, the 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).

Domain scores will be calculated by first reversing scores (0, 1, 2, 3) to (3, 2, 1, 0) to allocate the better IVI scores to the less impaired. The higher the score, the worse the quality of life. Category 8 (don't do this for other reasons) will be excluded from the domain scores derivation as it does not relate to impairment. The domain scores are calculated by summing the reversed scores across relevant items within each domain.

Domain scores will be calculated for each participant at baseline and any other assessments where data is captured. There are no domains specified on the children's version of the questionnaire, so domain scores will not be calculated.

The total IVI score represents the overall impact of vision impairment on an individual's participation in daily activities. It is obtained by summing the domain scores (emotional well-being, reading/accessing information, and mobility/independence).

Summaries will be reported for adults, with summary statistics of the calculated total scores per domain and change from baseline summarized by assessment and dose level.

All IVI data will be listed.

In-text displays:

- Histogram of IVI Questionnaires for Adults - Total score
- Histogram of IVI Questionnaires for Children - Part 1
- Histogram of IVI Questionnaires for Children - Part 2

3.5.5.2 EQ-5D-5L and EQ-5D-Y

EQ-5D-5L and EQ-5D-Y were assessed at Month 12, 24, 36, 48, and 60 visits.

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 has 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

A total of 3125 health states are possible. Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problem on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with self-care, moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression.

Only one response should be provided for each dimension, and missing values will be coded as 9. If 2 levels are selected for a dimension, the dimension will be treated as missing.

For participants who complete the EQ 5D 5L questionnaire, the health states will be converted into a single index value for each participant that has complete data for the 5 dimensions. The conversion will be done using the crosswalk value sets provided by the EuroQol research foundation (Euroqol.org, 2019). The crosswalk value sets for the UK will be used for UK participants and the crosswalk value sets for the US will be used for US participants.

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

- Level 1: indicating no problems
- Level 2: indicating moderate problems
- Level 3: indicating extreme problems

Due to the absence of a mapping scale for the youth questionnaire, the 5 dimensions will be analyzed individually.

Both questionnaires also contain a visual analog scale (EQ-VAS) where the participant is asked to rate their health state on a 0 to 100 scale between the worst health imaginable (0) and best health imaginable (100).

For EQ-5D-5L and EQ 5D Y separately, the number of participants and percentage of participants who reported problems at each level for each dimension will be presented. The summaries will be presented by dose level in the dose escalation and dose expansion phase and for all participants.

In addition, a single index will be derived for each participant who completed the EQ 5D-5L questionnaire. The derived EQ 5D index value and the change from baseline will be summarized.

The EQ-VAS observed and changes from baseline data will be summarized for the EQ-5D-5L and EQ-5D-Y questionnaires separately.

All EQ 5D-5L and EQ 5D Y data will be listed.

In-text displays:

- EQ-5D-5L Individual Dimensions: Percentage of Subjects Reporting Problems at Baseline and End of Study
- EQ-5D-Y Individual Dimensions: Percentage of Subjects Reporting Problems at Baseline and End of Study

3.5.6 Multiplicity

No adjustments for multiple comparisons will be made.

4 CHANGES FROM PROTOCOL-SPECIFIED ANALYSIS

- Samples for immunological response will be stored and will not be analyzed at this time.
- Videos of photoaversion test will be stored for future use and will not be analyzed at this time.
- Data from the following assessments will not be analyzed:
    - computerised (achromatic) spatial contrast sensitivity function tests
    - Colour Vision
    - Octopus Perimetry
    - Optical Coherence Tomography
    - Photoaversion
    - Full field electroretinography
    - Pattern electroretinography
    - Adaptive optics imaging
    - Full Field Stimulus Testing

5 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

1. EuroQol Research Foundation. EQ-5D User Guide, 2019 Available from: https://euroqol.org/publications/user-guides