NOVARTIS

Clinical Development

UNR844

CUNR844A2202 / NCT04806503

A randomized, placebo-controlled, double-masked, multi-center, dose-ranging study to evaluate the safety, and efficacy of UNR844 in subjects with presbyopia

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

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21-May-2021	*Prior to DB lock*	*Creation of final version*	*N/A - First version*	*NA*
28-July-2022	*Prior to DB lock*	*Creation of amendment 1*	*Update the list of abbreviations*	
			Clarify the second interim analysis	*Section 1*
			Clarify the data analyses scope of this document (IA1 and final CSR)	*Section 1* *Section 2.1*
			Clarify the responsibilities of different teams on the interim analyses and final CSR	*Section 1* *Section 1.1* *Section 2.7*
			Change the decimal of logMAR and revise typos	*Section 1.1* *Section 1.2* *Section 2.2.1* *Section 2.4* *Section 2.7* *Section 2.13* *Section 2.14.1*
			Clarify the exclusion criteria in run-in period	*Section 1.1*
			Change in the definition of Baseline and study day	*Section 2.1.1.2*
			Modify the allocation rule for unplanned visit	*Section 2.1.1.3*
			Exclude unscheduled visits from 'by-visit' tabulations, graphs, or analyses	*Section 2.1.1.4*
			Add the rule for multiple unscheduled visits	*Section 2.1.1.4*

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Change in the definition of on-treatment period and post-treatment period	*Section 2.1.1.5* *Section 2.8* *Section 2.8.1*
			Add a rule to deal with cases with multiple entries for the same assessment and exclude physiologically implausible DCNVA	*Section 2.1.1.8*
			Change the definition of FAS	*Section 2.2*
			Use PD terms to identify subjects infected by COVID-19	*Section 2.2.1* *Section 2.5.3.1*
			Delete summary of prior, concomitant and post therapies by SOC	*Section 2.4.1*
			Add descriptions for candidate dose-response model assumptions and update the dose-response curve	*Section 2.5.2*
			Refine the descriptions for primary and supportive estimands	*Section 2.5.3.1*
			Add one sensitivity analysis to investigate the impact of subjects with unexpected fluctuations	*Section 2.5.4*
			Delete the paragraphs for supportive analyses	*Section 2.5.5*
			Change the success criteria for gaining of 3 lines in binocular DNCVA	*Section 2.7.2* *Section 2.13* *Section 4*
			[redacted]	
			Add required part for CTSD	*Section 2.8.1*
			Remove the summary and shifting tables	*Section 2.8.3* *Section 2.8.4.2*
			[redacted]	[redacted]
			[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	
			[redacted] *1*	
			Update the interim analysis team members	*Section 2.14.2*
			Add the description of Five Macros for multiple imputation	*Section 5.4.1*
			Remove the Type III analysis in logistic regression and add the sample code	*Section 5.4.2*
			[redacted]	
23-November-2022	*Prior to DB lock*	*Creation of amendment 2*	*Reflect early study termination*	*Section 1, Section 2.14, Section 4*
			Delete second interim analysis	*Section 1.1, Section 2.14*
			Define end of study/end of treatment mapping rule	*Section 2.1.1.3*
			Define the wording of unscheduled visits mapping rule	*Section 2.1.14*
			Delete the summary of significant non-drug therapies and procedures	*Section 2.4.1*
			Define secondary endpoints	*Section 2.7*
			Defined safety endpoints	*Section 2.8.1*
			Delete " i.e. until 1 day after the date of the last study treatment"	*Section 2.8.1*
			Add ophthalmic examinations and refractive status in the listings	*Section 2.8.4.3*
			[redacted]	[redacted]
			[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Define changes to protocol analyses	*Section 4*
			Delete the imputation of CM end date for ongoing record	*Section 5.1.2.1*
			Delete medical history partial date of diagnosis imputation	*Section 5.1.2.3*

NOVARTIS

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AIC	Akaike information criterion
ATC	Anatomical Therapeutic Chemical Classification System
[redacted]	[redacted]
BSE	Better-seeing eye
CIR	Copy Increment from Reference
COVID-19	Coronavirus Disease - 19
CTT	Clinical Trial Team
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical study report
DBL	Database Lock
DCNVA	Distance-corrected near visual acuity
DI-C&S	Novartis Development Informatics – Clinical and Safety Systems
ED50	Median Effective dose
EMA	European Medicines Agency
Emax	Maximum Effect
EOS	End of Study
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
GPH	Global Program Head
IA	Interim Analysis
ICE	Intercurrent event
IRT	Interactive Response Technology
IAT	Interim Analysis Team
MAR	Missing at Random
MCP-Mod	Multiple Comparison Procedure - Modeling
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Multilevel Modelling for Repeated Measures
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PD	Protocol Deviation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred term
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SOC	System Organ Class

[redacted]	[redacted]
VA	Visual Acuity
WSE	Worse-seeing eye

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1 Introduction

The study is being terminated early as Novartis has made the decision to stop UNR844A2202 for the treatment of presbyopia based on the results from the interim analysis. All subjects who are ongoing at the time of the decision of study termination will be discontinued from the study at their next visit.

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study CUNR844A2202.

The analyses will be conducted at two time points as described below:

- The Interim Analysis (IA) will be conducted on data from all subjects up to the Month 3 Visit, when all subjects complete (or discontinue prior to) the Month 3 Visit;
- The final analysis will be conducted on data obtained after Month 3 Visit once all active subjects have terminated the study and final Database Lock (DBL) achieved.

This document refers to the data analysis for:

- the Interim Analysis (at Month 3 visit), which is also the final analysis of the Month-3 endpoints;
- the final analysis for some key endpoints determined by the team, including data collected beyond Month-3.

Data will be analyzed according to the data analysis plan described in this document that will be incorporated into Section 9.7 and Appendix 16.1.9 of the CSR.

The Interim Analysis has been completed according to the plan on 24th August 2022.

1.1 Study design

This is a randomized, placebo-controlled, double-masked, multi-arm, parallel-group, multi-center study. The total duration of the study will be approximately 13 months and there will be around 225 male or female presbyopic participants aged 45 to 55 years enrolled in this study.

The 13-month study will consist of:

- A 1-week run-in period
- A 3-month treatment course with UNR844 and/or placebo
- A 9-month treatment holiday period

Participants will be randomized equally to one of five treatment arms, consisting of:

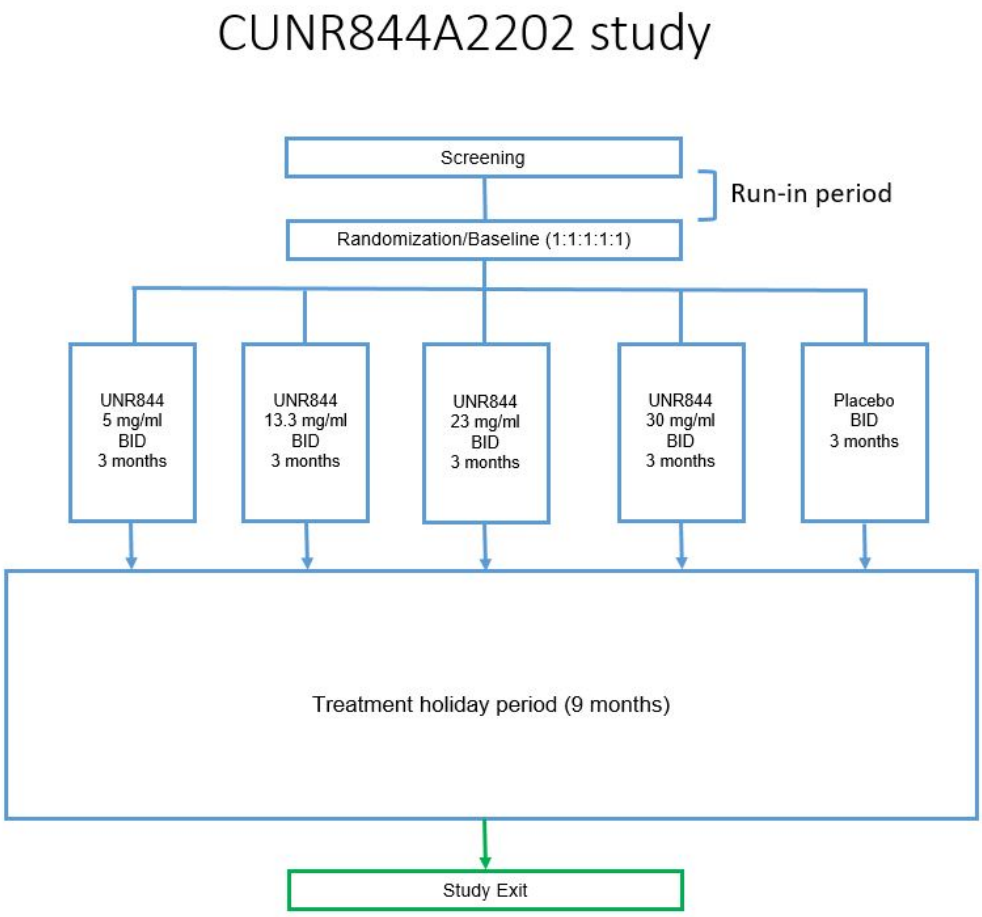
- Placebo eye drops, twice-a-day for three months
- UNR844 5 mg/mL eye drops, twice-a-day for three months
- UNR844 13.3 mg/mL eye drops, twice-a-day for three months

- UNR844 23 mg/mL eye drops, twice-a-day for three months
- UNR844 30 mg/mL eye drops, twice-a -day for three months

Participants will undergo a 1-week run-in period where they will be assessed for entry criteria during the Screening visit. During the run-in period, participants will administer 1 drop of artificial tears twice-a-day (1 drop in the morning and 1 drop in the evening) in each eye at home. This run-in period is designed to help minimize potential variability in distance-corrected near visual acuity (DCNVA) caused by initial ocular surface issues and help to establish an accurate baseline prior to randomization. The run-in period will exclude participants with a change in DCNVA more than 0.10 logMAR (5 letters) difference between Screening and Baseline. The study design is schematically depicted in Figure 1-1.

Randomization will be stratified based on binocular DCNVA (0.50 logMAR or less; 0.52 logMAR or more) and age (45 to 50 years and 51 to 55 years) at baseline, and region. Participants will be randomized 1:1:1:1:1 within each stratum to one treatment arm. The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

Figure 1-1 Study Design



The primary objective of this study is to characterize dose-response of UNR844 in presbyopic subjects aged 45 to 55 years by assessing the change in binocular DCNVA from baseline after three months of treatment.

The interim analysis will be performed when all subjects completed (or discontinue prior to) the Month 3 visit to assess the primary objective. The analysis was completed and the outcome led to the discontinuation of the program due to lack of efficacy.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**

Objective(s)	Endpoint(s)
• Characterize the dose-response of UNR844 for change from baseline in binocular DCNVA at Month 3	• Change from baseline in binocular DCNVA assessed using letters at Month 3
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Characterize the dose response of UNR844 as measured by change from baseline in monocular DCNVA at Month 3	• Change from baseline in monocular DCNVA, assessed using letters (i.e. worse-seeing eye and better-seeing eye) at Month 3
• Assess the duration of effect using change in DCNVA after Month 3 with various dose concentrations of UNR844	• Binocular and monocular DCNVA assessed using letters, over time after Month 3 (i.e. Month 4 to Month 12)
• Evaluate the efficacy of improving DCNVA in presbyopic participants, as measured by proportion of participants gaining at least 0.30 logMAR DCNVA at Month 3	• Proportion of participants gaining at least 0.30 logMAR in binocular and monocular (worse-seeing eye and better-seeing eye) DCNVA assessed using letters (without near correction) from baseline at Month 3

2 Statistical methods

2.1 Data analysis general information

The Interim Analysis will be performed by independent Analytics and statistical programming group of Novartis, while the final analysis will be performed by the Biostatistics and statistical programming of the CTT.

This document refers to the data analysis for the Interim Analysis (at Month 3 visit), which is also the final analysis of the Month-3 endpoints, as well as the final analysis, including data beyond Month-3. Analyses will be performed using SAS 9.4. In addition, the dose finding R package will be used for the dose finding analysis focusing on Month-3 endpoint.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. These summary statistics will be presented by treatment group unless otherwise specified. Where appropriate, point estimates and confidence intervals of treatment group differences will be provided.

In general, the randomization stratification factors will be included as factors in the primary efficacy analysis, and the corresponding supportive analyses.

2.1.1 General definitions

2.1.1.1 Study treatment

The following treatment groups will be presented:

- Placebo eye drops, one drop twice-a-day for three months
- UNR844 5 mg/mL eye drops, one drop twice-a-day for three months
- UNR844 13.3 mg/mL eye drops, one drop twice-a-day for three months
- UNR844 23 mg/mL eye drops, one drop twice-a-day for three months
- UNR844 30 mg/mL eye drops, one drop twice-a-day for three months

2.1.1.2 Baseline and post-Baseline

Baseline (Day 1) is the first study treatment in the study. The baseline value for efficacy and safety variables is the last available value (scheduled or unscheduled) collected prior to or at the date of first study treatment.

All data collected after the date of first study treatment are defined as post-baseline.

The *study day* for a baseline or post-baseline, scheduled or unscheduled visit, is defined as:
Study day = (Date of visit) - (Date of first study treatment) + 1;
The *study day* for a scheduled or unscheduled visit before baseline is defined as:
Study day = (Date of visit) – (Date of first study treatment).

2.1.1.3 End of study/end of treatment mapping

The *end of study* date (from 'Study disposition' CRF) is the date when a subject completes or discontinues the study. The *end of treatment* date (from 'Treatment disposition' CRF) is the date when a subject completes or discontinues the treatment.

To report data by visit in the outputs, the end of study with early discontinuation will be allocated to Month 12 /End of Study (Month 12/EOS) visit. To be more specific, any visit name equal to "Early Exit Visit" will be allocated to "Month 12/EOS" and analyzed as "Month 12/EOS".

2.1.1.4 Unscheduled visits

Data collected at unscheduled visits will only be used in 'by-visit' tabulations, graphs or analyses when it can be mapped to a missed scheduled visit by the 1/3 – 2/3 rule mentioned above. If multiple unscheduled visits are allocated to the same missed scheduled visit:

- The unscheduled visit closest to the missed scheduled visit will be used;
- If there are multiple unscheduled visits with the same distance/interval to the missed scheduled visit, the latest one will be used;

To be more specific, suppose such a visit falls between two adjacent scheduled visits (e.g. visits A and B) corresponding to visit days X and Y. If the assessment day of such a visit falls within rounding (1/3*(Y-X+1)) after Day X, then it will be allocated to visit A, otherwise, it will allocated to visit B. Figure 2-1 shows a graphical illustration of how this 1/3 – 2/3 rule of visit allocation is done.

Table 2-1 shows an example of the allocation of end of study/end of treatment visit to a scheduled main visit, when an assessment is scheduled to be done at every scheduled visit; and Table 2-2 shows another example of visit allocation when an assessment is only done at Baseline, Month 1 - 4, 7, 10 and 12.

All data collected at unscheduled visits will be listed.

Figure 2-1 Graphical illustration of visit allocation using the 1/3 – 2/3 rule

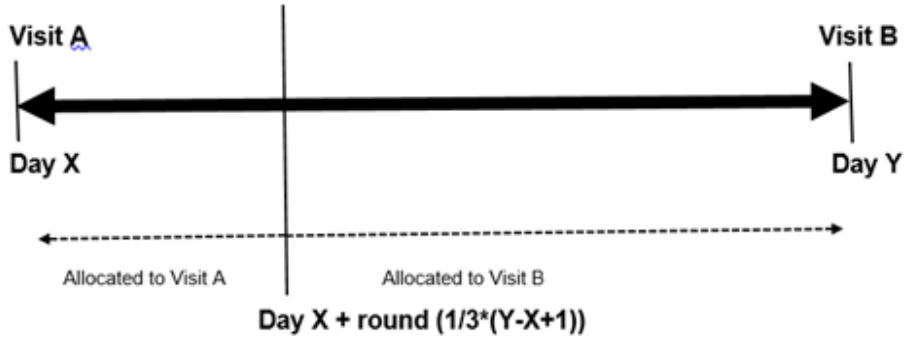


Table 2-1 Allocation of unscheduled visit for an assessment to be done at each scheduled visit

Scheduled main visit name/label	Scheduled visit study day	Scheduled visit window in days	Comment
Screening	-7	-7 – -1	Screening
Baseline	1	1	Baseline
W2	14	2 – 19	
M1	30	20 – 40	
M2	60	41 – 70	

M3	90	71 – 100
M4	120	101 – 130
M5	150	131 – 160
M6	180	161 – 190
M7	210	191 – 220
M8	240	221 – 250
M9	270	251 – 280
M10	300	281 – 310
M11	330	311 – 340
M12	360	>=341

Table 2-2 Allocation of unscheduled visit for an assessment to be done at Baseline, Month 1-4, 7, 10, and 12

Scheduled main visit name/label	Scheduled visit study day	Scheduled visit window in days	Comment
Baseline	1	1	Baseline
M1	30	2 – 40	
M2	60	41 – 70	
M3	90	71 – 100	
M4	120	101 – 150	
M7	210	151 – 240	
M10	300	241 – 320	
M12	360	>= 321	

2.1.1.5 Analysis periods

The on-treatment period of this study lasts from date of the first administration of study treatment to the date of the last administration of study treatment. If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

The post-treatment period is after the on-treatment period, which starts from 1 day after the date of the last actual administration of any study treatment until end of study (EOS).

2.1.1.6 Missing baseline and post-baseline data

Missing baseline data will not be imputed.

Observations with values ‘not done’, ‘not evaluable’, ‘not applicable’ will be treated as missing values.

2.1.1.7 Worse-seeing and better-seeing eyes

The worse-seeing eye (WSE) is defined as the eye that has the higher monocular logMAR value at baseline and the better-seeing eye (BSE) is defined as the eye that has the lower logMAR

value at baseline. For subjects with identical logMAR value of monocular DCNVA for both eyes at baseline, the right eye is defined as the worse-seeing eye.

2.1.1.8 Rule applicable to VA data collected with the digital device (M&S)

Physiologically non-plausible records

Any score of "100" for DCNVA in ETDRS letter will be considered not physiologically plausible and the value will be excluded before the analyses.

Multiple entries

If multiple entries for the same assessment are observed within one visit, the latest assessment will be used.

2.2 Analysis sets

Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization and received at least one dose of the study treatment. According to the intent to treat principle, participants will be analyzed according to the treatment and strata (if applicable) they have been assigned to during the randomization procedure. FAS will be used for all efficacy variables, unless otherwise stated.

Safety Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment, if the patient took at least one dose of that treatment, or the first treatment received if the randomized/assigned treatment was never received.

Rules of exclusion criteria of analysis sets with protocol deviations and subject classification are specified in Section 5.5.

The number and percentage of subjects within each of the above analysis sets will be summarized.

2.2.1 Subgroups of interest

Subgroup analysis will be done by classifying the population according to stratification factors at randomization (See Section 2.13). In addition, analyses based on the following subgroups will be performed to assess any potential impact of the COVID-19 pandemic on key study endpoints, if there is a sufficient number of subjects in each subgroup:

- According to the internal guidance (http://go/covid19info), the start and end dates of the COVID-19 pandemic for different geographical regions/countries participating in Study CUNR844A2202 are defined below:

Region/Country	Start Date	End Date
Japan	21-Feb-2020	End date has not yet been defined
Rest of the World (including US, Canada, and Australia)	01-Mar-2020	End dates have not yet been defined

The following subgroups will be defined once the end dates of the regions are available:

- Exposed subjects to COVID-19 pandemic: subjects who are recruited prior to the end date;
- Non-exposed subjects to COVID-19 pandemic: subjects who are recruited on or after the end date.

- Subgroups of subjects who are infected and non-infected will be defined and identified through data in the following way:
  - Subjects infected by COVID-19: subjects who discontinue study treatment due to COVID-19 infection, or are infected by COVID-19 as identified from COVID-19 infection and health related PD term;
  - Subjects not infected by COVID-19: subjects who don't meet any of the above conditions.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

Subject disposition will be summarized separately by treatment group and total for the FAS. Specifically, the number and proportion of subjects who discontinued the study will be summarized by treatment and total. The primary reason for premature study discontinuation will be summarized in the table.

In addition, protocol deviations (PDs) will be summarized through presenting the number and percentage of subjects with each deviation.

2.3.2 Subject demographics and other baseline characteristics

Demographic (including age, sex, race, ethnicity) and other baseline data including baseline characteristics (DCNVA, [redacted] cycloplegic refraction) will be listed and summarized descriptively by treatment group for the FAS.

Relevant medical histories and current medical conditions at baseline will be summarized by primary system organ class (SOC) and preferred term (PT), by treatment group separately for ocular and non-ocular histories/conditions. This includes any abnormalities noted during baseline evaluation of anterior and posterior eye segment health.

2.4 Treatments (study treatment, concomitant therapies, compliance)

The SAF will be used for the analyses below.

The duration of exposure in days to UNR844, placebo will be summarized by means of descriptive statistics using the SAF. The duration of exposure in days to UNR844 or placebo is defined as the date of the last administration of different doses of UNR844 or placebo (from

'Study treatment' CRF), and date of the first administration of different doses of UNR844 or placebo (from 'Study treatment' CRF) + 1.

Moreover, the on-treatment period (corresponding to the safety observation period) will also be summarized descriptively. The definition of the on-treatment period can be found from Section 2.1.1.5.

Compliance will be presented by summarizing the total number of days with the use of study treatment twice, once, or none, and the total number of times of using study treatment by treatment group and by eye. This information will be obtained from the CRF by counting the number of days with the use of study treatment twice, once, or none in each eye. The total number of times of using study treatment will be to count all the recorded use of study treatment at the subject level for each eye during the treatment phase.

The reason for premature discontinuation of study treatment will also be summarized.

In addition, to assess any potential impact of the COVID-19 pandemic on study treatment compliance, summary tables on the duration of exposure, and the total number of days with the use of study treatment twice, once, or none, will be provided for the subgroups of exposed/non-exposed, and infected/not infected subjects, as defined in Section 2.2.1, if there is a sufficient number of subjects in each subgroup.

2.4.1 Prior, concomitant and post therapies

Prior medications are defined as drugs taken and stopped prior to the first administration of study treatment. Any medication given at least once between the day of the first dose of the study treatment and the last study visit will be a concomitant medication, including those that were started pre-baseline visit and continued into the treatment period. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of taking the medication.

Prior and concomitant medications will be summarized by treatment group (separately for ocular and non-ocular medications/therapies), and presented in alphabetical order by ATC classification codes and preferred term. The tables will be presented with the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular preferred term. Medications will be coded according to the WHO Drug Reference List dictionary. In addition, prior and concomitant medications, and significant non-drug therapies and procedures will be listed including the reported name, laterality if applicable, and treatment start/end date, etc.

2.5 Analysis of the primary objective

The primary objective of the study is to characterize the dose response relationship among UNR844 doses 0 (placebo), 5 mg/mL, 13.3 mg/mL, 23 mg/mL and 30 mg/mL dosed twice-daily at Month 3. This will be evaluated by measuring the DCNVA (letters) in logMAR using the electronic visual acuity system.

2.5.1 Primary endpoint

The primary efficacy variable is defined as the change from baseline in binocular DCNVA assessed using letters at Month 3.

2.5.2 Statistical hypothesis, model, and method of analysis

MCP-Mod methodology is utilized to test for a dose-response signal and estimate the dose-response relationship.

Testing an overall dose-response signal

The null hypothesis of flat dose-response relationship for change from baseline in binocular DCNVA at Month 3 as compared to placebo will be tested at a one-sided significance level of 2.5% against the alternative hypothesis of a monotonic decreasing dose response relationship.

Five candidate models to describe the potential dose-response shape (defined in terms of change from baseline in binocular DCNVA at Month 3 as compared to placebo, the placebo effect is set to -0.08 logMAR and the maximum treatment effect is assumed to be -0.08 logMAR), were selected (see Figure 2-2. of the plot of the candidate models)

1. E_{max} model 1 (with ED_{50} = 0.079%)
2. E_{max} model 2 (with ED_{50} = 0.375%)
3. Sigmoid-E_{max} model 1 (with ED_{50} = 1.500% and Hill coefficient= 4.301)
4. Sigmoid-E_{max} model 2 (with ED_{50} = 1.089% and Hill coefficient= 2.643)
5. Exponential model (with delta=1.770)

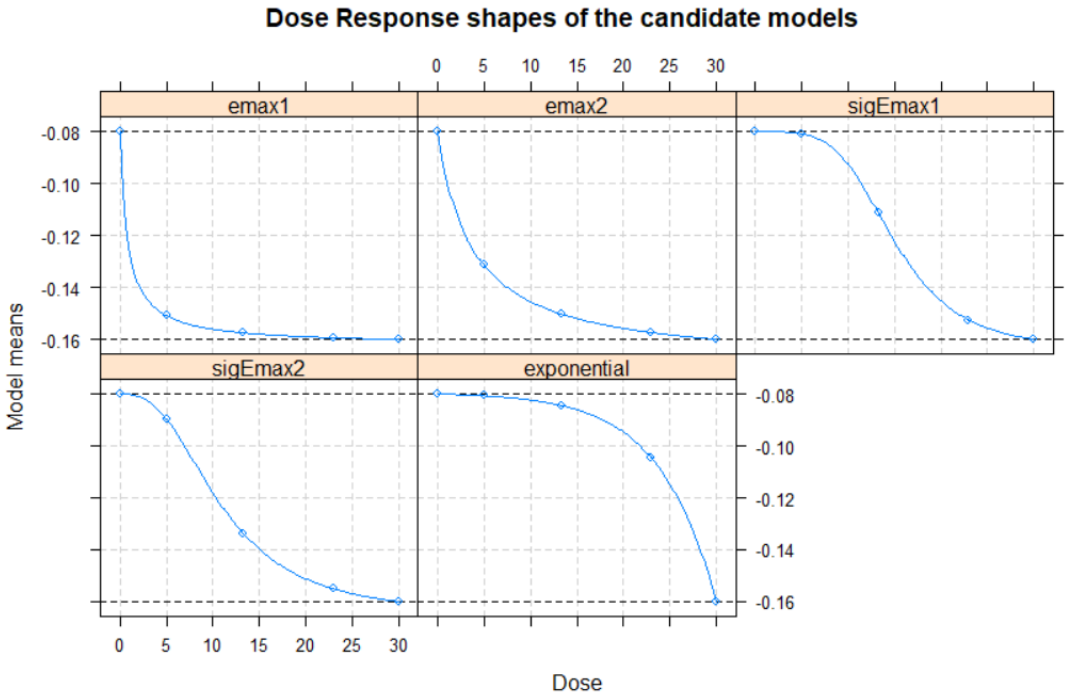
For each of the underlying candidate models an optimal contrast will be derived. Then for each contrast (m, m=1, …, 5), a t-statistic T_m based on multiplying mean responses per dose group with model-derived contrast vectors will be derived. For the purpose of derivation of the contrasts, the dose is used to allow calculation of optimal contrasts.

Response estimates at the dose will be based on the least square means per dose based on an MMRM model.

The model will include the change from baseline in binocular DCNVA (mean of the two assessments) as the dependent variable, binocular DCNVA at the baseline as the covariate, region, dose, age group, assessment visit, interaction of dose and assessment visit as the fixed effect and participant as a random effect. For subjects who do not have a binocular DCNVA assessment at Month 3, the predicted values of the individual subject based on the multiple imputation will be used as dependent variable.

Under a normality assumption on the primary endpoint based on the least-squared estimates across the doses, a critical value q for testing each individual candidate model contrast is determined under the null hypothesis and under the constraint that the family-wise error rate is controlled at the desired one-sided 2.5% level. If $T_{max} = max_m\ T_m > q$, the overall null hypothesis of a flat dose-response curve is rejected and the procedure will move on to the next step of dose-response curve estimation as well as estimation of the dose that achieves a decrease of 0.08 logMAR correct as compared to placebo (if there are multiple such doses, the smallest is chosen).

Figure 2-2 Dose-response shapes of the candidate models



Otherwise, if no contrast test is statistically significant, then no overall dose response signal can be detected from the observed data and the procedure stops without proceeding to dose estimation.

Bootstrap model averaging will be used to estimate the dose-response curve, the target dose and to derive confidence intervals. Parametric bootstrap simulation will be performed using the least-squares dose group estimates based on their multivariate normal distribution.

Each simulated vector of dose estimates will be fitted by generalized least-squares fitting of the resulting simulated values (Pinheiro, Bornkamp et al. 2014) with the Emax model, the sigmoid Emax model and the exponential model. The best model for each simulated bootstrap sample (based on generalized Akaike information criterion, AIC) will be recorded and used for prediction of the dose-response curve and the target dose. The final reported estimates will be based on the median of the obtained predictions. Approximate confidence intervals for the dose-response curve and the target dose will be calculated based on the bootstrap quantiles.

2.5.3 Handling of missing values/censoring/discontinuations

2.5.3.1 Missing data related to intercurrent event

Primary estimand:

The underlying question for the primary estimand is: what is the efficacy attributable to different doses of UNR844 received after 3 months of treatment, taking into account any unfavorable effect of the drug such as discontinuation due to unsatisfactory therapeutic effect or Adverse Events (AE). The estimand definition that addresses this question is the dose-specific difference

in mean change from baseline in DCNVA at Month 3 attributable to the initially randomized medication accounting for beneficial and detrimental effect of the drug.

Three types of intercurrent events (ICEs) listed below will be addressed for this estimand:

- ICE 1: treatment discontinuation due to unsatisfactory therapeutic effect or AE;
- ICE 2: treatment discontinuation due to other reasons;
- ICE 3: use of prohibited medication or therapy, or changes in prohibited medication, which would potentially affect efficacy (as captured by 'Protocol Deviations' CRF).

For this estimand, data following the above three types of intercurrent events will be dealt with in three specific ways:

- For ICE 1, include data collected post discontinuation if available. If not available, impute assuming no further benefit, i.e. Copy Increment from Reference (CIR) method will be used for imputation;
- For ICE 2, exclude data collected post discontinuation, treat them as missing and impute assuming Missing at Random (MAR);
- For ICE 3, exclude data collected post-use of prohibited medication, treat them as missing and impute assuming MAR.

If a subject has multiple intercurrent events, treatment discontinuation due to unsatisfactory therapeutic effect or AE will be considered as the priority intercurrent event, and data handling following this intercurrent event will be according to what is specified above, by ignoring the other intercurrent event(s) of the same subject. If only the other two intercurrent events (non-priority) happen to the same subject, consider the event which occurs earliest. Data handling following this earliest intercurrent event will be according to what is specified above.

Supportive estimand 1:

The underlying question for the supportive estimand 1 is: what is the true efficacy of different doses of UNR844, when administered as planned for 3 months, in participants who had no relevant intercurrent events such as discontinuation or use of prohibited medications? The estimand definition that addresses this question is: dose-specific difference in mean change from baseline in DCNVA at Month 3 attributable to the study treatment received, excluding the effect of intercurrent events such as discontinuation or use of prohibited medications.

For this estimand, data following the three types of intercurrent events will be dealt with in three specific ways:

- For ICE 1, exclude data collected post discontinuation, treat them as missing and impute assuming MAR;
- For ICE 2, exclude data collected post discontinuation, treat them as missing and impute assuming MAR;
- For ICE 3, exclude data collected post-use of prohibited medication, treat them as missing and impute assuming MAR.

If a subject has multiple intercurrent events, consider the event which occurs earliest. Data handling following this earliest intercurrent event will be according to what's specified above.

Supportive estimand 2:

The underlying question for the supportive estimand 2 is: what is the efficacy attributable to the randomly assigned doses of UNR844 after 3 months of treatment, considering the impact of any intercurrent events as inherent part of the assigned treatment? The estimand definition that addresses this question is: dose-specific difference in mean change from baseline in DCNVA at Month 3 attributable to the randomized treatment.

For this estimand, data following the three types of intercurrent events will be dealt with in three specific ways:

- For ICE 1, include data collected post discontinuation, if available. If not available, impute assuming no further benefit, i.e. CIR method will be used for imputation;
- For ICE 2, include data collected post discontinuation, if available. If not available, impute assuming no further benefit, i.e. CIR method will be used for imputation;
- For ICE 3, include data collected post-use of prohibited medication, if available. If not available, impute assuming no further benefit, i.e. CIR method will be used for imputation.

If a subject has multiple intercurrent events, consider the event which occurs earliest. Data handling following this earliest intercurrent event will be according to what's specified above.

Supportive estimand 3:

The underlying question for the supportive estimand 3 is: what is the efficacy attributable to each UNR844 arm/dose group, after 3 months of BID treatment, taking into account any unfavorable effect of the drug such as discontinuation due to unsatisfactory therapeutic effect or Adverse Events (AE), as based on the primary estimand, assuming the subjects had no relevant intercurrent events due to COVID-19 infection. The estimand definition that addresses this question is: dose-specific difference in mean change from baseline in DCNVA at Month 3 attributable to the initially randomized medication accounting for beneficial and detrimental effect of the drug, by excluding the effect of COVID-19 infection related intercurrent events.

For this estimand, in addition to the data handling for the three types of intercurrent events, as described for the primary estimand, data following the below types of COVID-19 infection related intercurrent events will be dealt with in the following ways:

- Treatment discontinuation due to COVID-19 infection: exclude data collected post discontinuation, treat them as missing and impute assuming MAR;
- Infected by COVID-19 (identified from COVID-19 infection and health related PD term): exclude data collected post infection, treat them as missing and impute assuming MAR.

The priority rule for the primary estimand is still applicable for the supportive estimand. In addition to the priority rule for the primary estimand, if a subject has multiple intercurrent events, consider the event which occurs earliest. Data handling following this earliest intercurrent event will be according to the specifications stated above. An exception to apply only the rule of the

first intercurrent event, is when treatment discontinuation due to lack of efficacy or AEs other than COVID-19 infection (as defined by the above intercurrent events) occurs first, and infection by COVID-19 infection occurs later. In such a case, in order to rule out the effect due to COVID-19, while still being consistent with the primary estimand definition, both of these events need to be accounted for by applying the corresponding data handling rule following each event.

2.5.3.2 Missing data not related to intercurrent event

In the case of missing data occurring in other scenarios, i.e. independent of intercurrent events related to response to study treatment, the estimand based on MAR approach will be considered specifically for each treatment arm the participants are assigned. This will result in a reasonable estimate of the true outcome based on the treatment effect observed for up to 7 months after study treatment discontinuation in prior completed clinical study with UNR844.

2.5.4 Sensitivity analyses for primary endpoint/estimand

There will be two sensitivity analyses corresponding to the primary estimand, refer to Section 2.5.3.1 for more details.

Sensitivity analysis #1:

The efficacy endpoint is the same as the primary efficacy analysis, with the only change to exclude data collected post treatment discontinuation due to unsatisfactory therapeutic effect or AE, and impute assuming no further benefit, i.e. the CIR method.

Sensitivity analysis #2:

In this study, a subject with unexpected fluctuations is defined as a subject who has a change in DCNVA equal to or more than 15 letters between two consecutive scheduled visits. In cases that data records showing a difference of 0.30 logMAR or larger between two consecutive scheduled visits, data collected on or after the second visit will be excluded from primary and secondary analyses to remove the impact of unexpected fluctuations.

- If any intercurrent event happened before the first visit of the two consecutive scheduled visits, missing data imputation will follow the data handling rule specified in the primary estimand. For example, CIR method will be used for missing data post treatment discontinuation due to unsatisfactory therapeutic effect or AE. The priority rule for the primary estimand is still applicable for this analysis.
- Otherwise, intercurrent events happening on or after the first visit of the two consecutive scheduled visits will be ignored, and all missing data will be imputed as missing at random (MAR).

2.5.5 Supportive analyses

There will be three supportive analyses corresponding to the three supportive estimands, refer to Section 2.5.3.1 for more details.

2.6 Analysis of the key secondary objective

There is no key secondary objective for the study.

2.7 Analysis of secondary efficacy objective(s)

There are three secondary objectives:

1. Characterize dose response of UNR844 as measured by change from baseline in monocular DCNVA assessed using letters at Month 3;
2. Assess the duration of effect using change in DCNVA after Month 3 with various dose concentrations of UNR844;
3. Evaluate the efficacy of improving DCNVA in presbyopic participants, as measured by the proportion of participants gaining at least 0.30 logMAR DCNVA at Month 3.

2.7.1 Secondary endpoints

The corresponding secondary endpoints are:

1. Change from baseline in monocular DCNVA assessed using letters (i.e. worse-seeing eye and better-seeing eye) at Month 3;
2. Binocular and monocular (worse-seeing eye and better-seeing eye) DCNVA assessed using letters over time after Month 3 (i.e. Month 4 to Month 12);
3. Proportion of participants gaining at least 0.30 logMAR in binocular and monocular (worse-seeing eye and better-seeing eye) DCNVA assessed using letters (without near correction) from baseline at Month 3.

2.7.2 Statistical hypothesis, model, and method of analysis

1. Change from baseline in monocular DCNVA assessed using letters (i.e. worse-seeing eye and better-seeing eye) at Month 3:

- MCP-Mod as described in Section 2.5.2 will be applied to the worse-seeing eye and better-seeing eye , with intercurrent events and missing data handled in the same way as the for the primary estimand and supportive estimand 2 (Section 2.5.2 and Section 2.5.3).

2. Gain of 3 lines (change from baseline of ≤ - 0.30 logMAR and < + 0.10 logMAR in BCDVA) in binocular, worse-seeing eye and better-seeing eye, respectively at Month 3:
   - For the endpoints of gaining of 3 lines in binocular, worse-seeing eye and better-seeing eye, respectively at Month 3. Missing data imputation will be done in the same way as the primary endpoint (Section 2.5.3), defined for the primary estimand, based on their corresponding continuous endpoints, i.e. binocular and monocular DCNVA. After imputation, these endpoints will be dichotomized to generate the endpoints of gaining of 3 lines in both eyes, worse-seeing eye and better-seeing eye, respectively, at Month 3. Then a logistic regression model, by adjusting for baseline DCNVA and age (grouped as 45 to 50 years and 51 to 55 years), will be fitted to each imputed data set for each of the three endpoints. By applying Rubin's rule to combine results of these individual data sets, pairwise comparison of each dose versus placebo will be obtained for each of the three endpoints.
3. Change from Month 3 in binocular and monocular (worse-seeing eye and better-seeing eye) DCNVA over time after Month 3 (i.e. Month 4 to Month 12):

- Only observed data for these endpoints will be analyzed with no imputation for missing data.
- For binocular, worse-seeing eye and better-seeing eye, DCNVA over time after Month 3 will be summarized by treatment group and scheduled visits, and the mean line plots for the change from Month 3 over time will also be presented. In addition, the binocular and monocular DCNVA will be listed.

2.7.3 Handling of missing values/censoring/discontinuations

Missing data handling of secondary analyses for different endpoints are specified in Section 2.7.2.

2.8 Safety analyses

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

[redacted]. The on-treatment period lasts from the date of first administration of study treatment to the date of the last administration of study treatment. Where appropriate, baseline data or change from baseline data will also be summarized.

Note:

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

2.8.1 Adverse events (AEs)

[redacted]

A subject with multiple adverse events within a primary SOC is only counted once towards the total of the SOC.

[redacted]

In addition, all AEs (from the first date of treatment to the end of study) will be summarized separately for ocular and non-ocular AEs by treatment in the following ways:

- AEs by primary SOC and PT;
- Study treatment related AEs, by primary SOC and PT;
- SAEs by primary SOC and PT;
- Study treatment related SAEs, by primary SOC and PT.

All AEs, deaths and serious adverse events (including those from the pre-treatment period and from the first date of treatment to the end of study) will be listed.

In addition, in order to assess the impact of the COVID-19 pandemic, summary tables will be provided for the subgroups of exposed/non-exposed, infected/not-infected subjects (as defined in Section 2.2.1) by treatment, for the following safety endpoints, if there is a sufficient number of subjects in each subgroup:

[redacted]

For the ClinicalTrials.gov and EudraCT requirements, two tables are mandatory:

- all adverse events which are not serious adverse events with an incidence greater than X% will be provided by PT on the safety set population. Detailed threshold (X%) will be determined by safety disclosure;
- and all serious adverse events and SAE suspected to be related to study treatment will be provided by primary SOC and PT on the safety set population.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is less than or equal to 1 day gap between the end date of the preceding AE and the start date of the consecutive AE;
- more than one occurrence will be counted if there is more than 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

If at least one SAE is occurring in a less than or equal 1 day gap, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs, irrespective of study treatment relationship, will be provided by primary SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

All deaths will be listed.

2.8.3 Laboratory data

All laboratory data for hematology, chemistry and urinalysis will be listed by treatment group, subject, and visit/time.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

All vital signs data (including systolic/diastolic blood pressure, and heart rate measurements) will be listed by treatment group, subject, and visit/time.

[redacted]

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

[redacted]

[redacted]

2.12 Biomarkers

Not applicable.

[redacted]

[redacted]

2.14 Interim analysis

2.14.1 Planned Interim analysis

The interim analysis will be performed when all subjects complete (or discontinue prior to) the Month 3 visit as described in Section 2.5. The major objective of this interim analysis is to determine if the overall null hypothesis of a flat dose-response curve can be rejected. For this interim analysis, the following analyses will be presented:

- Key information of subject disposition, demographics and other baseline characteristics;
- Duration of exposure, on-treatment period, and compliance;
- Analysis corresponding to the primary objective, as described in Section 2.5;
- Analysis corresponding to the secondary objective: to characterize dose response of UNR844 as measured by change from baseline in monocular DCNVA at Month 3, as described in Section 2.7;
- Analysis corresponding to the secondary objective: to evaluate the efficacy of improving DCNVA in presbyopic participants, as measured by the proportion of participants gaining at least 0.30 logMAR DCNVA at Month 3, as described in Section 2.7;

[redacted]

2.14.2 Interim Analysis Team

Interim Analysis Team (IAT) is an independent group of individuals who have experience and expertise in the management of patients within this disease area, experience in statistical methods, experience in efficacy and safety monitoring and experience in the monitoring of randomized clinical trials. The members of the IAT for this study are appointed by Novartis.

Table 2-3 Interim Analysis Team Members

Expert (Specialty)	Institution, City, Country	Phone, Fax and email address
MD	Novartis Pharmaceuticals, Basel, Switzerland	
PhD	Novartis Pharmaceuticals, Dallas, TX USA	
MD	Novartis Pharmaceuticals, New Jersey, USA	
PhD Statistician ( )	Novartis Pharmaceuticals, Shanghai, China	
PhD Statistician ( )	Novartis Pharmaceuticals, Dallas, TX, USA	
MPH (	Novartis Pharmaceuticals, Shanghai, China	
,	Novartis Pharmaceuticals, Paris, France	

* UNR844A2202 Team members, will be involved in the daily activities of the trial until the start the process at the beginning of the first IA and cease the involvement of daily activities thereafter.

Further appointments to the IAT may be made if there are resignations from the initial membership, or if the IAT members believe that additional expertise is required. Any such appointments would be formally made by Novartis after consultation with the members of the IAT.

2.14.3 Conflict of interest

IAT members must abide by the Novartis Conflict of Interest Policy.

2.14.4 Insider Trading

It is prohibited for any IAT member to use any material non-public information received in connection with their role as IAT member to make decisions about buying or selling shares or other securities in Novartis Pharma AG or any other company of the Novartis group or with which Novartis does business and to which the information pertains. It is also prohibited to disclose to any person such material non-public information, whether or not the disclosing person has actual knowledge of the use of the information by the recipient. An IAT member using or disclosing "insider" information may commit a severe criminal offence, the penalty of which may be fines and imprisonment.

IAT members must abide by the Novartis Global Corporate Policy and Procedure on Insider Trading.

2.14.5 Responsibilities

2.14.5.1 The IAT

The IAT will function independently of all other individuals associated with the conduct of this trial, including investigators, and Novartis personnel involved in the project.

The IAT is responsible for monitoring the efficacy and safety of the trial participants, ensuring that the trial is being conducted with the highest scientific and ethical standards, and making appropriate recommendations based on the data seen. The IAT will be responsible for:

- reviewing the planned contents of the interim analysis report i.e. table/figure/listing shells, and making recommendations regarding changes or adjustments that may be required to ensure the IAT has the information it requires for fulfilling its obligations;
- reviewing reports relevant to trial conduct and assumptions, efficacy and safety variables, and outcomes leading to discontinuation of the trial treatment, and making recommendations regarding changes or adjustments that may be required to ensure patient safety and preserve trial integrity;
- suggesting modifications to the trial protocol, which may include, but are not limited to: changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in trial procedures or trial conduct, or discontinuation of one or more trial treatment groups if applicable;
- recommending continuation of the trial according to the protocol and any relevant amendments OR to discontinue the trial (with provisions for orderly discontinuation in accordance with good clinical practice).

2.14.5.2 Clinical Trial Team (CTT)

The Novartis Clinical Trial Team (CTT) is responsible for the following activities related to the operation of the IAT:

- Designating the Novartis leadership team who are involved in the review of IAT recommendation(s) (see Section 2.14.5.4 for details).
- Designating the Independent Statisticians and Independent Programmers from within Novartis Analytics.
- Ensuring the proper secure handling of the treatment codes from the Interactive Response Technology (IRT) provider (who is responsible for generating the randomization list).
- Writing the analysis plan and programs that produce the interim analysis report. Note: trial statistician and trial programmer will have no access to treatment decodes
- Requesting from the Novartis Randomization Office (RO) the release of the randomization codes in accordance with Novartis SOPs in time for production of the interim analysis
- Implementing agreed-upon recommendation(s) and/or trial modifications received from the IAT.
- Monitoring trial conduct, and the collection and quality control of trial data.
- Communicating all pertinent regulatory information to the national regulatory bodies of the countries in which the trial is conducted.
- Informing the IAT of any amendments to the trial protocol, changes to the design or endpoints, or any new clinically relevant information on the trial medication.

2.14.5.3 Randomization Office (RO)

Upon receipt and approval of the randomization release request form for the first IA (or if randomization list was extended since previous release), the RO will:

- Request DI-C&S to upload the randomization list including the treatment group description into the restricted area in Global Programming and Statistical Environment (GPS II), which will only be accessible to the Novartis Independent Statistician and Independent Programmer after the data is available. The data can be uploaded any time before the interim analysis database lock.

The personnel at the RO and DI-C&S will have no access to the non-randomization trial data, nor play any other role in the trial or project.

2.14.5.4 Independent Statistician and Independent Programmer

The Independent Statistician (IS) and Independent Programmer (IP) will not be involved in daily activities of the trial CUNR844A2202 or project UNR844 other than those involved in preparing and providing information to the IAT. They will be situated in a separate location from the rest of the CTT, or if this cannot be achieved, a firewall will be in place to avoid disclosure of confidential information. They will be responsible for generating data analyses for the IAT, including tables, figures and listings produced according to the pre-specified interim analysis plan.

In this study, the IS responsible for Biostatistics, will be designated within Novartis. The IS responsible for the Biostatistics, will be involved in the daily activities of the trial until the start

of the process at the beginning of the IA when another statistician within Novartis will assume the role of Trial Statistician until the end of the study.

The IP will be designated within Novartis and will not be involved in the daily activities of the trial or program other than those involved in preparing and providing information to the IAT. The IS and IP will have access to clinical data in the GPS restricted area and the randomization list including the treatment group description directly from the RO via WDCS II.

The Independent Statistician and Independent Programmer will receive unmasked treatment codes according to the applicable and documented Novartis procedures. Thus, all analyses outputs sent to the IAT will be unmasked. Independent Statistician will provide paper/electronic reports to the IAT, and then communicate with the IAT as needed.

The Independent Statistician will function independently of the investigators and CTT members, and will be responsible to the IAT for the conduct of all interim analyses of efficacy and safety data.

2.14.5.5 IRT Provider

The IRT provider Novartis IRT will release the randomization list to the Randomization Office and DI-C&S as soon as complete. No further approval by the RO is necessary.

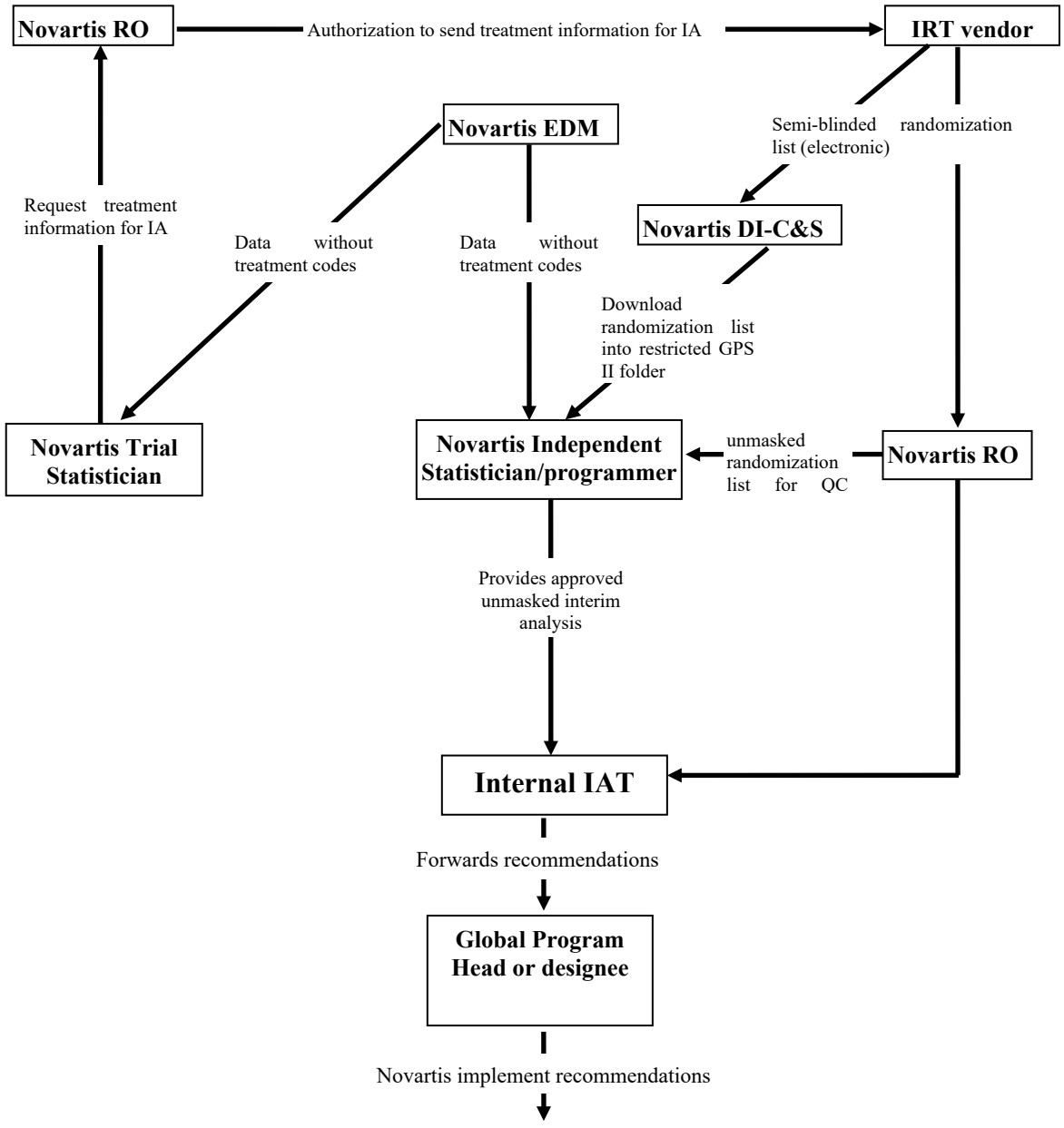
2.14.6 Confidentiality Agreement

Confidentiality agreements will be signed by all participants in the IAT who will see unmasked interim results. For IAT members this confidentiality agreement is part of their employee contract with the Global Program Head (GPH). For this trial, these agreements will have been signed by GPH, Global Clinical Program Head (GCPH), Clinical Development Director (CDD), Independent Statistician (IS), Independent Programmer (IP), and filed according to Novartis' SOPs. The confidentiality agreement is designed to ensure that the interim analysis results will not be shared with others inappropriately or without proper documentation before the final trial clinical database is locked and the final analysis is completed.

2.14.7 Organizational diagram

The organization diagram shown below shows the inter-relationship between the IAT and other functional areas involved in the trial.

Figure 2-3 Organization diagram



1. Before the interim analysis database lock:

- The Novartis Trial Statistician will request the Novartis Randomization Office (RO) to authorize DI-C&S to download the randomization list including the treatment group description into the restricted area in the Global Programming and Statistical Environment (GPS II). Only the Independent Statistician and Programmer will have access to the restricted area in GPS II.

2. The RO will release a copy of the randomization list including the treatment group description to the Independent Statistician for QC purposes. After each interim analysis database lock:
   - The Independent Statistician and Programmer will produce an interim analysis report according to plan using the randomization list;
   - The Independent Statistician will send the interim analysis report to the IAT members.
3. After each IAT meeting where interim analysis are reviewed:
   - The IAT recommendation(s) will be provided in writing by the IAT Chair to the GPH or designee.

Novartis will review the IAT recommendations and take appropriate actions.

2.14.8 Data Review Meetings

Meetings are planned to take place two times in this study. At each meeting, the IAT will review cumulative patient safety data. The meeting will be limited to members of the IAT.

The first interim analysis meeting is planned for the IAT to review comparative data relating to treatment efficacy and patient safety.

The second interim meeting is planned for the IAT to review the data from FPFV up to 60% of the participants complete 6 months (i.e. Month 9) of treatment holiday period. The major objective of this interim analysis is to assess the retention of the treatment effect over the 9 months treatment holiday period.

2.14.9 Recommendations from the IAT

A summary (e.g. FIR slide deck) from the IAT Chair will be provided in writing to the GPH or designee. This summary may or may not provide any comparative information (e.g. if the IAT recommendation is to continue the trial without modification). The GPH or designee will communicate the IAT conclusions to Novartis management, investigators, and the Novartis clinical team as appropriate, depending upon the type of recommendation.

Any recommendations of the IAT involving an issue that poses a possible safety risk to patients will be handled by all parties in an expedited manner. In the event that there is a safety concern about trial continuation, or other recommendation to modify the trial, the IAT Chair should communicate this immediately to the GPH or designee, who will then inform the Global Head of Development at Novartis. Communication of concerns expressed by the IAT shall be restricted to the fewest number of individuals possible associated with the trial, or within Novartis. This will generally include the Global Head of Analytics (or designee) and the Head of DS&E. Other individuals will be brought into the discussions only as needed, i.e. if their input is needed to assist in reaching a final decision. Further communication by this small group with the IAT will take place as necessary. However, individuals directly involved in decision

making or conduct of the trial will not have access to this information until a final decision has been made.

3 Sample size calculation

3.1 Primary endpoint(s)

A total sample size of 210 randomized participants (in 1:1:1:1:1 allocation ratios corresponding to five UNR844 dosing regimens [placebo, 5 mg/mL, 13.3 mg/mL, 23 mg/mL, 30 mg/mL, respectively, treated twice-daily for 3 months]) is required to ensure an average power of 86% to detect the presence of dose response under the set of candidate models considered in MCP-Mod, assuming a maximum effect for mean binocular change from baseline in logMAR over placebo of -0.08 (SD = 0.14) for a UNR844 arm. To allow for a ~5% drop-out rate during the treatment period (i.e. 3 months), 225 participants (45 in each of the 5 treatment groups) will be randomized. The power calculations leading to the sample size determination were based on simulations using all five candidate models considered in MCP-Mod. The maximum t-statistic contrast test was applied to each of the simulated data sets to assess the presence of a dose response signal. It is the average power of this test that is ensured to be 86% under two of the candidate models (the most likely and the worst case) considered for the sample size of 225 participants.

If participants dropping out due to COVID-19 leads to power reduction to be below 82% based on the above assumptions, additional participants will be recruited to ensure adequate power.

4 Change to protocol specified analyses

In protocol Section 12.5.1, it is stated: gain of 3 lines (change from baseline of ≤ - 0.3 logMAR) in binocular, worse-seeing eye and better-seeing eye, respectively at Month 3. Now the team has updated the success criteria to: gain of 3 lines (change from baseline of ≤ - 0.30 logMAR and < + 0.10 logMAR in BCDVA) in binocular and monocular DCNVA at Month 3.

In protocol Section 12.6.1, it is stated: summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. In order to get summary level information also on the post-treatment AEs, it is decided to show the t AEs and SAEs from the first date of treatment to the end of study in the summary tables. In addition, summary tables for AEs related to study treatment will also be provided, as stated in the corresponding section of the SAP.

Due to the early termination of the study, all analysis has been simplified and some of them have been limited to descriptive statistics.

The analysis of exploratory variables will be performed for variables which will provide information for future trials within the UNR844 program, hence the following exploratory endpoints for final analysis are removed:

[redacted]

[redacted]

The second planned interim analysis is removed.

[redacted]

Concomitant medications as well as significant non-drug therapies that are prohibited will not be provided. The start, stop or change in dosing after the screening visit will not be provided either.

5 Appendix

Statistical methods are described in the main part of the clinical study report. This appendix provides further details on missing data imputation, statistical methods and the statistical derivation.

5.1 Imputation rules of missing dates

The general approach to handling partial dates is shown below for dates of AEs, medical history diagnosis, and concomitant treatment. The imputation of missing dates for surgery or procedures will use the same rules as for concomitant treatment.

The detailed algorithms will appear in Programming Dataset Specifications.

For the purpose of date imputation, the treatment follow up period date is defined as the last available visit date.

5.1.1 AE partial date imputation

5.1.1.1 Adverse event end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death, cut-off date if available).

2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (the last visit date, last day of the month, date of death, cut-off date if available).

3. If AE year is missing or AE is ongoing, the end date will not be imputed.

4. In case the imputed AE end date is before AE start date, then use AE start date as imputed AE end date.

5.1.1.2 Adverse event start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY	(1)	(1)	(1)	(1)
MISSING	No convention	No convention	No convention	No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date.

Impute AE start date:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE day and month are missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. If AE month is missing but day is not missing, the observed start date will be used with month imputed as JulYYYY.
    c. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE day and month are missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. If AE month is missing but day is not missing, the observed start date will be used with month imputed as JulYYYY.
    c. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:

a. And the AE day and month are missing the imputed AE start date is set to the AE reference start date + 1 day.
b. If AE month is missing and day is not missing, the observed start date will be used with month imputed as the reference start month.
c. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
d. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication partial date imputation

5.1.2.1 Concomitant treatment end date imputation

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of last visit date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of last visit date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.
4. If imputed CM end date is greater than date of death, date of cutoff, or the last visit date, then use the minimum of date of death, date of cutoff, and the last visit date as the imputed CM end date.

5.1.2.2 Concomitant treatment start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain
YYYY < TRTY	**(2.a)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start
YYYY = TRTY	**(4.a)** Uncertain	**(4.b)** Before Treatment Start	**(4.a)** Uncertain	**(4.c)** After Treatment Start
YYYY > TRTY	**(3.a)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM day and month are missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. If CM month is missing but day is not missing, the observed start date will be used with month imputed as JulYYYY.
    c. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM day and month are missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. If CM month is missing but day is not missing, the observed start date will be used with month imputed as JanYYYY.
    c. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM day and CM month are missing or the CM day is missing and CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).
5. If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.2.3 Medical history partial date of diagnosis imputation

No applicable.

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The below severity grade will be used in this study:

- Mild: usually transient in nature and generally not interfering with normal activities
- Moderate: sufficiently discomforting to interfere with normal activities
- Severe: prevents normal activities

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

Multiple comparison procedures-modeling approach (MCP-Mod) was qualified by CHMP as "an efficient statistical methodology for model-based design and analysis of Phase II dose-finding studies under model uncertainty" *(*EMA 2014*)*. This methodology allows both the statistical testing of evidence of dose response (PoC), as well as the estimation of target doses to be used in confirmatory studies.

Generalized MCP-Mod *(*Pinheiro, Bornkamp et al. 2014) will be applied based on the output from a Multilevel Modelling for Repeated Measurements (MMRM). The model will include the change from baseline in binocular DCNVA (mean of the two assessments) as the dependent variable, binocular DCNVA at the baseline as the covariate, region, dose, age group, assessment visit, interaction of dose and assessment visit as the fixed effect and participant as a random effect. For subjects who do not have a binocular DCNVA assessment at Month 3, the predicted values of the individual subject based on the multiple imputation will be used as dependent variable.

To perform generalized MCP-Mod the least square mean per dose and associated covariance matrix will be obtained from the MMRM.

Five candidate models to describe the potential dose-response shape (defined in terms of change from baseline in binocular DCNVA at Month 3 as compared to placebo) were selected

1. E_{max} model: $f(d,\theta) = E_0 + E_{max} \times d/(d + ED_{50})$
   - E_{max} model 1: ED_{50} = 0.079%
   - E_{max} model 2: ED_{50} = 0.375%
2. Sigmoid E_{max} model: $f(d,\theta) = E_0 + E_{max} \times d^h/(d^h + {ED_{50}}^h)$ with fixed hill parameter
   - Sigmoid-E_{max} model 1 : ED_{50} = 1.500% and h = 4.301
   - Sigmoid-E_{max} model 2 : ED_{50} = 1.089% and h = 2.643
3. Exponential model: $f(d,\theta) = E_0 + E_1 \times exp(d/\delta - 1)$
   - Exponential model 1 : δ =1.770

where E_0 is the expected placebo effect, E_{max} is the maximum change in effect over placebo, ED_{50} is the dose at with which 50% of Emax is achieved, h is Hill parameter, E_1 is the slope parameter, δ is controlling the convexity of the model, d is total daily dose and θ refers to the vector of model parameters.

Bootstrap model averaging will be used to estimate the dose-response curve, the target dose and to derive confidence intervals. Parametric bootstrap simulation will be performed using the least-squares dose group estimates based on their multivariate normal distribution.

The main steps for the parametric bootstrap are showed below:

1. Simulate a set of dose response according to the least square mean per dose obtained from MMRM.
2. For each set of simulated dose response fit E_{max}, Sigmoid E_{max}, and Exponential model by minimizing the generalized least-squares.
3. Select the best dose-response model (e.g. model with the lowest least squares).
4. Save inferences based on the selected model (e.g. dose-response predictions or dose predictions).

The multiple imputation for different estimand frameworks will be done using the "Five Macros", which fit a Bayesian Normal RM model and then impute post withdrawal data under a series of possible post-withdrawal profiles including J2R, CIR, and CR as described by Carpenter et al (Carpenter et al. 2013).

In "Five Macros", all intermediate missing values will be imputed assuming MAR and the MNAR part of the model is restricted to patterns that are monotone. That means control-based imputations method is only applicable to monotone missing pattern, therefore we need to prepare the data in several tweaks in order to use "Five Macros".

1. Prepare the data <in_data>: <in_data> stores the change from baseline in DCNVA where the structure is one record per subject per analysis visit. If a subject experiences IEs stated in SAP. Define a new variable <Method_var> and assign value according to different estimand framework.
2. Part1A declares the parameter estimation model and checks consistency with the dataset.

```
%part1A(Jobname=UNR,Data=<in_data>,Subject=<SUBJID>,
        Response=<CHG_DCNVA>,Time=<VISIT>,Treat=<Treatment>,
        Catcov=<Region> <Age group>,Cov=<Baseline DCNVA>,
        Covgroup=<Treatment>);
```

3. Part1B fits the parameter estimation model using the MCMC procedure and draws a pseudo-independent sample from the joint posterior distribution for the linear predictor parameters and the covariance parameters.

```
%part1B(Jobname=UNR,Ndraws=1000,thin=100,seed=20220810);
```

4. Part2A calculates the predicted mean under MAR, and under MNAR for each subject based on their withdrawal pattern once for each draw of the linear predictor parameter estimates. The choice of MNAR is controlled by the method used, which may vary from subject to subject.

```
%part2A(Jobname=UNR,methodV=<Method_var>,ref=<PLACEBO>);
```

<PLACEBO>is the treatment level used as the reference arm for every record

5. Part2B imputes the intermediate missing values using MAR and the trailing missing values using MNAR, by deriving the conditional distribution for the missing values conditional on the observed values and covariates, using the appropriate sampled covariance parameter estimates.

```
%part2B(Jobname=UNR,seed=20220824);
```

6. Carry out MMRM analysis as stated in Section 5.4.1 per imputation for <Dataset>. Then combine the least-squares means, and treatment differences using the PROC MIANALYZE procedure to provide the final results.

In Five Macros, the imputation method per subject should be unique for monotone missing pattern, which means it cannot handle the scenario when one subject has different imputation methods for the monotone missing records. In supportive estimand 3, when the treatment discontinuation due to lack of efficacy or AEs happens first, and infection by COVID-19 infection occurs later, the imputation methods could be different in such case (e.g. CIR first and then MAR). In order to deal with this scenario with Five Macros, we will first impute the missing data with CIR and manually set the records that are supposed to be imputed as MAR to missing in all imputed data sets. Then use Five Macros again to impute the missing data as MAR for each of the imputed data sets.

5.4.2 Secondary analysis

Logistic regression

The change of DCNVA from baseline will be dichotomized to generate the endpoints of gaining of 3 lines in both eyes, worse-seeing eye and better-seeing eye, respectively at Month 3. Then a logistic regression model, by adjusting for baseline DCNVA and age.

Odds ratios will be computed for comparisons of UNR844 versus placebo utilizing the logistic regression model fitted.

If the proportions of 3-lines gain are 0% or 100% in one of the treatment groups odds ratio estimate and p-values will not be displayed in outputs, but "-" will be shown.

The odds ratio will be calculated such that an odds ratio >1 is favorable for UNR844. Using PROC GENMOD to calculate the confidence interval for the odds ratios assumes asymptotic normality of the Wald estimate for the regression coefficient. The 95% confidence interval for the regression parameter of the active treatment effect relative to control(s) will be calculated using an exponential transformation to create the confidence interval for the odds ratio.

All p-values reported on linear hypotheses about regression coefficients will be based on the Wald tests, and converted to one-sided, based on the formula below:

- If the point estimate of the odds ratio is ≥ 1, the one-sided p-value = two-sided p-value/2;
- If the point estimate of the odds ratio is < 1, the one-sided p-value = 1 – two-sided p-value/2.

The SAS procedure PROC GENMOD will be used for logistic regression model by adding the model options: DIST=BIN, and LINK=LOGIT. The following SAS code will be used to fit the logistic regression model to each of the multiply imputed data set, and combine the results:

```
PROC GENMOD DATA = <Dataset>;
      CLASS <Treatment> <Age group>
      MODEL <CAT_DCNVA> = <Baseline DCNVA> <Age group>
                          <Treatment>/DIST = BIN LINK = LOGIT;
      LSMEAN <Treatment> / DIFF cl;
      BY _IMPUTATION_;
      OUTPUT DIFFS = diff;
```

```
RUN;

PROC MIANALYZE parms= diff;
      CLASS <Treatment>;
      modeleffects <Treatment>;
      ods output PARAMETERESTIMATES=outDIFF;
RUN;
```

5.5 Rule of exclusion criteria of analysis sets

The below classification of non-PDs will be used for the analysis sets.

Table 5-1 Subject Classification

Analysis Set	Non-PD criteria that cause participants to be excluded
Full Analysis Set	Not randomized, or mistakenly randomized.
Safety Set	Did not receive any dose of the study treatment

6 Reference

EMA (2014). "Qualification Opinion on MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty."

Pinheiro, J., B. Bornkamp, E. Glimm and F. Bretz (2014). "Model-based dose finding under model uncertainty using general parametric models." Statistics in Medicine **33**(10): 1646-1661.

Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat; 23(6):1352-71.