NOVARTIS

Clinical Development

UNR844

CUNR844A2203 / NCT03809611

A 3-month, randomized, placebo-controlled, double-masked, multi-center study to evaluate the safety and efficacy of topical ocular UNR844-CI in subjects with presbyopia

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
BCDVA	Best-corrected distance visual acuity
BP	Blood pressure
CIR	Copy Increment from Reference
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study report
DCNVA	Distance-corrected near visual acuity
FAS	Full Analysis Set
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
eCRF	Electronic Case Report Form
IRT	Interactive Response Technology
IVR	Interactive Voice Response
MAR	Missing At Random
[redacted]	[redacted]
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed effect Model Repeat Measurement
RAP	Report and Analysis Process
PD	Protocol Deviation
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

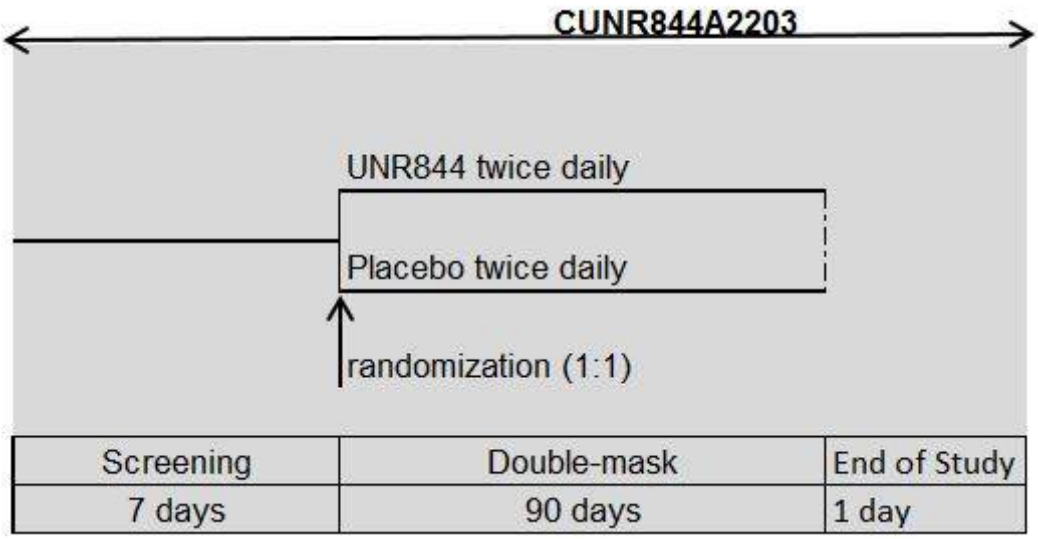
The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of statistical analysis planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study CUNR844A2203.

The analysis will be conducted on all subject data at the time the study ends.

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.

1.1 Study design

Figure 1-1 Study Design



This is a multi-center, double-masked, placebo-controlled, randomized, parallel-group study. The total duration of the study will be approximately 3 months (Figure 1-1). Approximately 120 presbyopic subjects will be enrolled into the study.

Screening and Baseline: Subjects will be screened for eligibility followed by a baseline visit after which they will be randomized to receive either lipoic acid choline ester chloride (UNR844-Cl) or placebo, dosed one drop in each eye twice-daily for 3 months.

Randomization will be stratified based on binocular distance-corrected near visual acuity (DCNVA) (59 Early Treatment Diabetic Retinopathy Study [ETDRS] letters or less; 60 ETDRS letters or more) and age (45 to 50 years, 51 to 55 years and 56 to 65 years) at baseline.

Subjects will be randomized 1:1 within each stratum to either UNR844-Cl or placebo.

Randomized subjects will attend the following study visits after baseline: at Week 2, Month 1, Month 2 and Month 3.

The primary objective of this study is to evaluate the efficacy of topical UNR844-Cl ophthalmic solution in presbyopic subjects aged 45 to 55 years by assessing the change in binocular DCNVA from baseline when compared to placebo after three months of treatment.

There is no interim analysis planned.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• Assess the efficacy of UNR844-Cl on binocular DCNVA in presbyopic subjects aged 45 to 55 years	• Change from baseline in binocular DCNVA in subjects aged 45 to 55 years at Month 3 after UNR844-Cl or placebo treatment
Secondary objectives	**Endpoints for secondary objectives**
• Assess the efficacy of UNR844-Cl on achieving 75 or more ETDRS letters in binocular DCNVA in presbyopic subjects aged 45 to 55 years	• Proportion of subjects aged 45 to 55 years achieving 75 or more ETDRS letters in binocular DCNVA at Month 3 after UNR844-Cl or placebo treatment
• Evaluate the safety of UNR844-Cl in presbyopic subjects	• Frequency of treatment-emergent adverse events and treatment-emergent serious adverse events in all subjects after UNR844-Cl or placebo treatment

[redacted]

2 Statistical methods

2.1 Data analysis general information

The analysis will be performed by the Biostatistics and statistical programming groups of Novartis, using SAS 9.4.

For categorical variables, frequencies and percentages will be computed. For continuous variables, descriptive statistics, including number of non-missing observations, mean, standard deviation, median, and range will be produced, where appropriate, point estimates and confidence intervals of treatment group differences will be provided.

These summary statistics will be presented by treatment group unless otherwise specified.

The randomization stratification factors in general 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

Any drug administered to the study participants as part of the required study procedures, including investigational drug and control, which are:

- Topical UNR844-Cl ophthalmic solution 1.5%, administered as one drop in each eye twice a day for three months
- Placebo (vehicle ophthalmic solution), administered as one drop in each eye twice a day for three months

2.1.1.2 Baseline and post-Baseline

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

All data collected after the first date of 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 randomization) + 1;

The *study day* for a scheduled or unscheduled visit before baseline is defined as

Study day = (Date of visit) – (Date of randomization).

2.1.1.3 End of study/end of treatment/unscheduled visit day 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 of the last study treatment prior to/on the end of study date. For reporting data by visit in outputs, the end of study with discontinuation (Subject status from 'Study disposition' CRF NOT being 'Completed')/end of treatment with discontinuation (Subject status from 'Treatment disposition' CRF NOT being 'Completed')/unscheduled visit date will be allocated to the nearest planned main visit, by a 1/3 – 2/3 rule. To be more specific, suppose such a visit falls in two adjacent scheduled visits (e.g., visits A and B) of an assessment corresponding to visit days of 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, and to visit B otherwise. 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/unscheduled 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, 2 and 3.

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

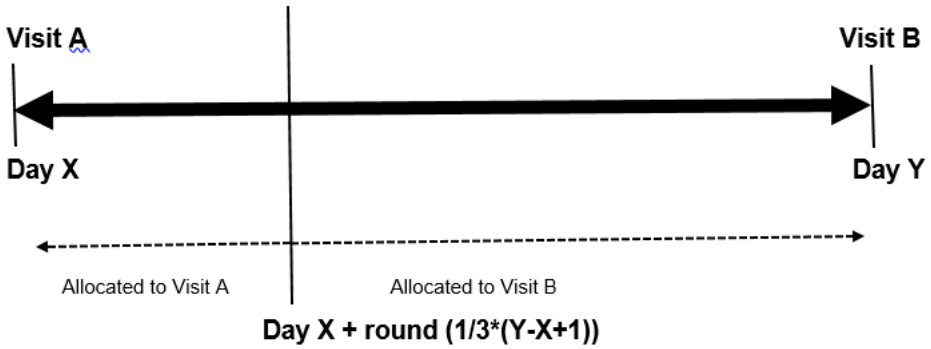


Table 2-1 Allocation of end of study/end of treatment/unscheduled visit for an assessment to be done at each scheduled visit

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 – 35	
M1.5	45	36 – 50	
M2	60	51 – 65	
M2.5	75	66 – 80	
M3	90	>= 81	

Table 2-2 Allocation of end of study/end of treatment/unscheduled visit for an assessment to be done at Baseline, Month 1, 2 and 3

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	

After allocation, if the nearest planned main visit already exists: for assessments with continuous scale, the mean value of all values from the scheduled planned main visit, and the end of study/end of treatment/unscheduled visit(s) allocated to that main visit will be used for tabulation or analyses by visit; for assessments with binary/categorical scale: data of the allocated value will only be used for tabulation and analyses by visit, if data of the corresponding scheduled visit is missing. If there are multiple entries of data for a scheduled visit of an assessment with binary/categorical scale, the last entry of the data will be used.

2.1.1.4 Unscheduled visits

For tabulation and analyses by visit, all data collected at the unscheduled visits will first be allocated to a nearest planned main visit, then taken into account as the data (or part of the data) for that visit (Section 2.1.1.3). For analyses showing abnormalities, data from unscheduled visits will be considered individually, without mapping to a main visit.

All data collected at unscheduled visits will be listed.

2.1.1.5 On-treatment period

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment, i.e., date of the last actual administration of any study treatment (from 'Study treatment' CRF) – date of first administration of study treatment (from 'Study treatment' CRF) +1 + 30.

2.1.1.6 Missing baseline data

Missing baseline data will not be imputed.

2.1.1.7 Missing post-baseline data

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

2.1.1.8 Better-seeing and worse-seeing eyes

The worse-seeing eye is defined as the eye that has the lower monocular DCNVA ETDRS letter score at baseline and the better-seeing eye is defined as the eye that has the higher ETDRS letter score. For subjects with identical monocular DCNVA ETDRS letter scores for both eyes at baseline, the right eye is defined as the worse-seeing eye.

2.2 Analysis sets

The **Full Analysis Set** (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. FAS will be used for all efficacy variables, unless otherwise stated.

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

Rules of exclusion criteria of analysis sets with protocol deviations and subject classification are specified in Appendix 5.3.

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

[redacted]

2.3 Subject 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 disease characteristics (including DCNVA, best-corrected distance visual acuity [BCDVA], [redacted]) will be listed and summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

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

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SAF will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

2.4.1 Study treatment / compliance

The duration of exposure in days to UNR844-Cl or placebo will be summarized by means of descriptive statistics. The duration of exposure in days to UNR844-Cl or placebo is defined as: date of the last actual administration of UNR844-Cl or placebo (from ‘Study treatment’ CRF) – date of first administration of UNR844-Cl 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 any treatment by treatment group. Reason of premature discontinuation from study treatment will also be summarized.

Total number of days with any treatment is calculated from 'Study treatment' CRF, by summing number of days 'Dose interrupted' and number of days from 'Dose permanently discontinued' to study end (the total number of days without treatment), then subtracted by duration of exposure. Suppose a subject has twice with 'Dose interrupted' and later 'Dose permanently discontinued' as recorded on 'Study treatment' CRF, then this subject's total number of days without treatment is: (Start date of dose after the first dose interruption – stop date of dose before the first dose interruption) + (Start date of dose after the second dose interruption – Stop date of dose before the second dose interruption) + (end of study date – stop date of dose when 'Dose permanently discontinued').

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as drugs taken and stopped prior to the first dose 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 and concomitant significant non-drug therapies will be summarized by treatment group (separately for ocular and non-ocular medications/therapies), presented in alphabetical order by ATC classification codes and preferred term. The tables will be presented with 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, all information will be listed including the reported name, laterality, and treatment start/end date, etc.

Moreover, concomitant medications as well as significant non-drug therapies that are prohibited as per protocol (refer to Table 2-3 below) and given during the conduct of the study will be provided, separately for ocular and non-ocular medications/therapies. Summary tables on the start, stop or change dosing of the following treatments (Table 2-4) after the screening visit, unless as part of the study protocol will also be shown.

Table 2-3 Prohibited medications and therapies

Medication/therapy	Prohibition period	Action taken
Intraocular surgery or laser surgery of any kind in either eye, including cataract extraction	Any time after screening and throughout the study	Discontinue study treatment
[redacted]	[redacted]	[redacted]
Other investigational medicinal product or therapy	Any time after screening and throughout the study	Discontinue study treatment

Therapy for presbyopia other than optical correction (e.g., supplements, medications, training exercises, ciliary body electrostimulation, corneal implants, surgery)	Any time after screening and throughout the study	Discontinue study treatment

Table 2-4 Prohibited medication changes

Medication	Prohibition period	Action taken
Antipsychotics	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug
Antidepressants	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug
Anticholinergics	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug
Calcium channel blockers	Any time after screening and	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug
Glaucoma medications	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug
Psychostimulants	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug
Alpha-adrenergic agonists	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug
Any over-the counter or prescription ocular medications (except artificial tear products)	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug

Medication	Prohibition period	Action taken
Any other medications assessed by the investigator known to affect accommodation, pupil size or near vision	Any time after screening and throughout the study	Record changes in the concomitant medication eCRF and report this protocol violation; subject can stay on study drug

2.5 Analysis of the primary objective

The primary objective of the study is to assess the efficacy of UNR844-Cl on binocular DCNVA in presbyopic subjects aged 45 to 55 years.

2.5.1 Primary endpoint

The primary estimand is defined as follows:

- Population - subjects aged 45 to 55 years in the FAS with at least one post-baseline binocular DCNVA assessment
- Variable - change in ETDRS letter score from baseline in binocular DCNVA
- Intercurrent events - data collected after any use of prohibited medications or therapies (Table 2-3), after prohibited medication changes (Table 2-4) or after discontinuation of study treatment will not be included in the estimand and will be treated as missing and imputed as described in Section 2.5.3.
- Population level summary - difference in variable means between treatment conditions at Month 3.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy endpoint, change from baseline in binocular DCNVA, will be analyzed at Month 3 based on the data observed in the FAS population, according to the treatment group subjects were randomized to and the strata that were assigned at randomization. The strata information will be based on the data obtained from Interactive Response Technology (IRT) that was utilized for randomization. The comparison between the two treatment groups will be performed using a two group t-test at one-sided 5% level of significance.

Assuming general linear model for change from baseline in binocular DCNVA, the following hypotheses will be tested:

H_0: $\delta_1 = 0$ vs. H_a: $\delta_1 > 0$

where δ_1 is the difference of change from baseline in numbers of letters read correctly between the UNR844-Cl and placebo at Month 3.

A mixed effect model repeat measurement (MMRM) model with the change from baseline in binocular DCNVA will be fitted. The model will include the change from baseline in binocular DCNVA as the dependent variable, binocular DCNVA at baseline (on its original continuous scale) as the covariate, treatment group and age group stratum at randomization, assessment visit, interaction of treatment group and assessment visit as the fixed effects and subject 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 for the primary endpoint analysis and one of the supportive analysis (Section 2.5.3).

The p-value will be adjusted to one-sided, and is calculated as follows:

- 0.5*(original two-sided p-value) if the least squares mean difference of UNR844 versus placebo is greater than 0
- 1-0.5*(original two-sided p-value) if the least squares mean difference of UNR844 versus placebo is smaller than or equal to 0.

2.5.3 Handling of missing values/ multiple values/ censoring/ discontinuations

The details of data handling for the primary efficacy endpoint are described below.

If more than one DCNVA score is recorded for each eye or both eyes at a scheduled visit, this will be handled as follows:

- Any score of "100" will be ignored;
- Of the remaining scores, the one that was entered last will be used.

For subjects who either (1) fulfilled the protocol definition of having taken prohibited medications or therapy, or made prohibited medication changes (Section 2.4.2), or (2) discontinued study treatment permanently, the data collected following either scenario (1) or (2) will be excluded and treated as missing and imputed as follows.

- For scenario (1) and (2) with reason for discontinuation being either adverse event or unsatisfactory therapeutic effect, Copy Increment from Reference (CIR) method will be used for imputation.
- For all others, the Missing at Random (MAR) imputation approach with the Five Macros (Carpenter et al. 2013) will be used for imputation.

The prohibited medications and therapies, as well as prohibited medication changes will be identified through PDs. Data after (identified through PD start date) the use of prohibited medications or therapies will be excluded. Also, data after the prohibited medication change (identified through PD start date of a new PD for the changed prohibited medication) will be excluded.

2.5.4 Supportive analyses

There will be two supportive analyses

Supportive analysis #1:

The efficacy endpoint for Supportive analysis #1 is change from baseline in binocular DCNVA at Month 3 regardless of whether or not the intercurrent events occurred. The only difference between this analysis and the primary efficacy analysis is the inclusion of the data points after use of prohibited medications or therapy, prohibited medication changes or treatment discontinuation.

All data collected will be included in this analysis and the same imputation methods as those for the primary efficacy endpoint will be used to impute the time points that the data was truly missing.

Supportive analysis #2:

The efficacy endpoint for Supportive analysis #2 is change from baseline in binocular DCNVA at the end of treatment, i.e., the time when last study treatment is administered, which is always observed. There is no missing data imputation for the efficacy endpoint of this supportive analysis.

2.6 Analysis of the key secondary objective

There is no key secondary objective for the study.

2.7 Analysis of secondary efficacy objectives

The secondary endpoint for efficacy is the proportion of subjects aged 45 to 55 years achieving 75 or more ETDRS letters in binocular DCNVA at Month 3 after UNR844-Cl or placebo treatment.

2.7.1 Secondary endpoints

The secondary efficacy endpoint is the proportion of subjects aged 45 to 55 years achieving 75 or more ETDRS letters in binocular DCNVA at Month 3.

2.7.2 Statistical hypothesis, model, and method of analysis

The analysis of the secondary efficacy endpoint is based on the data observed in the FAS population, according to the treatment group subjects was randomized and the DCNVA stratum that was assigned at randomization. The comparison between the two treatment groups will be performed using stratified Cochran-Mantel-Haenszel (CMH) test at one-sided 5% level of significance, with stratified baseline DCNVA and age group as the stratification factors. Alternatively, if the cell count for any of the strata is too small (e.g., <5), the analysis will be done separately for each of the two stratification factors.

Assuming the following hypotheses will be tested:

H_0: $\delta_2 = 0$ vs. H_a: $\delta_2 > 0$

where δ_2 is the difference of proportion of subjects achieving 75 or more ETDRS letters in binocular DCNVA between the UNR844-Cl and placebo at Month 3.

2.7.3 Handling of missing values/censoring/discontinuations

The estimand for the secondary efficacy endpoint is closely related to the estimand for the primary efficacy endpoint (refer to Section 2.5.3). For subjects who has a DCNVA assessment at Month 3 and do not have intercurrent event (as defined in Section 2.5.1), the observed letter score will be used to derive the endpoint of achieving 75 or more ETDRS letters or not. For subjects who has no DCNVA assessment at Month 3 or have intercurrent event (Section 2.5.1), the predicted value of the estimand for the primary efficacy endpoint will be used to derive the endpoint of achieving 75 or more ETDRS letters or not.

2.8 Safety analyses

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

2.8.1 Adverse events (AEs)

Summary tables for AEs and SAEs will summarize only on-treatment events, with a start date during the on-treatment period (TEAEs and TESAEs, respectively). The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment (Section 2.1.1.5).

The secondary endpoint for safety is the frequency of TEAEs and TESAEs in all subjects.

The number (and proportion) of subjects with TEAE will be summarized for ocular and non-ocular AEs separately, by treatment group and overall in the following ways:

- Overall summary of subjects with any TEAE, any severe TEAE, any study drug related TEAE, any TEAE leading to study drug discontinuation, any TESAE, any study drug related TESAE
- TEAE by primary system organ class and preferred term
- TEAE by primary system organ class, preferred term and maximum severity
- TESAE by primary system organ class and preferred term
- Study drug related TESAE by system organ class and preferred term
- TEAE leading to study drug discontinuation by primary system organ class and preferred term
- TEAE leading to study drug interruption by primary system organ class and preferred term

Except for the first table, all the above AE summaries will be provided by descending frequency in the UNR844-Cl group. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Any other AEs or SAEs will be listed.
All these analyses will be based on the most updated MedDRA version available prior to the database lock.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

Death will not be individually listed, or tabulated, but will be included as part of the AE analyses.

2.8.3 Laboratory data

It is not applicable, as data will only be recorded in the source document.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

It is not applicable, as data will only be recorded in the source document.

2.8.4.2 Vital signs

All vital signs data (including systolic/diastolic blood pressure (BP), and heart rate measurements) will be listed by treatment group, subject, and visit/time. Summary statistics (n, mean, median, standard deviation, min, max) for the absolute value and the change from baseline will be provided by treatment and visit/time.

2.9 Pharmacokinetic endpoints

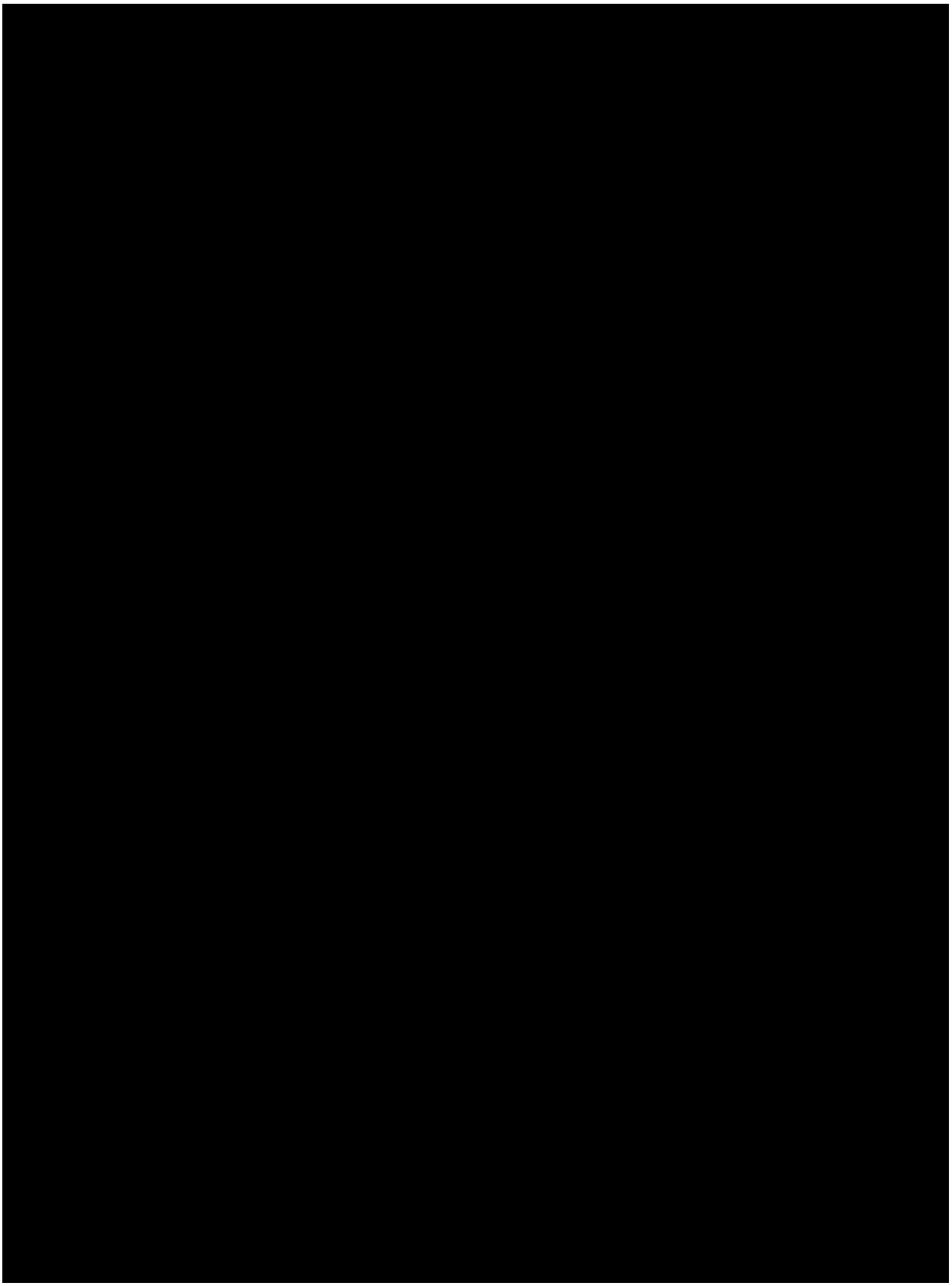
Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Biomarkers

Not applicable.



2.13 Interim analysis

Not applicable.

3 Sample size calculation

3.1.1 Primary endpoint

Assuming a mean difference of 4.9 ETDRS letters with a common standard deviation of 6.02 ETDRS letters in change from baseline in binocular DCNVA at 3 months between UNR844 and placebo, based on the results of the prior study in presbyopic subjects, 66 subjects (33 in each arm) aged 45 to 55 years are required to complete the study to achieve an approximate power of 94% at 5% (one-sided) significance level. Assuming about 90% subjects will complete the study, a total of 72 subjects for the primary efficacy endpoint will be enrolled.

3.1.2 Secondary endpoints

Assuming the proportion of subjects achieving 75 or more ETDRS letters in binocular DCNVA at Month 3 are 40.5% and 10.5% for UNR844-Cl and placebo, respectively, based on the results of the prior study in presbyopic subjects, 66 subjects (33 in each arm) aged 45 to 55 years are required to be completed to achieve an approximate power of 82% at 5% (one-sided) significance level.

[redacted]

4 Change to protocol specified analyses

Not applicable.

5 Appendix

Statistical methods are described in the main part of the clinical study report. This appendix provides further details on the statistical derivation and practical implementation.

5.1 Imputation rules of missing dates

The general approach to handling missing 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 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 MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.c) Before Treatment Start	(2.c) Before Treatment Start	(2.c) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.c) Before Treatment Start	(4.d) Uncertain	(4.d) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.c) After Treatment Start	(3.c) After Treatment Start	(3.c) 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 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 treatment end 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 treatment end date and the end of the year (31DECYYYY).
3. Only include if ongoing records will have an imputed CM end date. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.
5. 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.c) Before Treatment Start	(2.c) Before Treatment Start	(2.c) 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.c) After Treatment Start	(3.c) After Treatment Start	(3.c) 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).

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.

5.2 Statistical models

5.2.1 Primary analysis and supportive analyses

The multiple imputation for the primary analysis and the supportive analyses will be done using the Five Macros (Carpenter et al. 2013). The code of the Mixed Model with Repeated Measures

(MMRM) is included in macro 'part3_55' for the primary analysis and the supportive analyses. To get the 90% confidence intervals, the default of 'Alpha' as an input parameter of the macro 'part3_55' can be changed to 0.1:

```
%part3(Jobname=<XXX>
,anref=0
,alpha=0.1

,Label=<YYY>);
```

The model fitting part included in the macro is essentially equivalent to fitting the MMRM model to each individually imputed data set using the following SAS code:

Change from baseline in binocular DCNVA = intercept + treatment + baseline binocular DCNVA + visit + age group + treatment*visit + error.

The following SAS code can be used to perform these analyses:

```
PROC MIXED DATA=<Dataset> order=Internal;
   CLASS USUBJID <Treatment> <VISIT> <AGE GROUP>;
   MODEL <Chg_DCNVA> = <Treatment> <VISIIT> <VISIT by Treatment>
                       <Baseline binocular DCNVA> <Age group> /
DDFM=KENWARDROGER
                       ALPHA=0.05;
   REPEATED <VISIT>/type=UN subject=USUBJID;
   LSMEANS  <VISIT>*<Treatment> / DIFF CL ALPHA = 0.05;
   ODS OUTPUT LSMEANS=outLsm
              DIFFS=Diffs;
RUN;
```

The terms in the brackets are to be adjusted according to the real data set and variable names.

Names of the output data sets from the Five Macros are: &jobname._datafinal (final multiply imputed data sets) and &jobname._out (model fitting statistics of the multiply imputed data sets). The two-sided p-value provided by the ESTIMATE statement will be converted to one-sided p-value as follows:

- If the mean difference is ≥ 0, the one-sided p-value = two-sided p-value/2;
- If the mean difference is < 0, the one-sided p-value = 1 – two-sided p-value/2.

The summary statistics of the primary variable based on the multiply imputed data sets can be obtained using the following SAS macro:

```
%macro prim_sum(datain,Visit,Trt,Resp,Imput,dataout) ;
PROC SORT DATA=&datain;
BY &Visit &Imput &Trt;
RUN;

ODS OUTPUT ConfLimits=SUM;
PROC TTEST DATA = &datain;
BY &Visit &Imput;
CLASS &Trt;
```

```
VAR &Resp;
RUN;

DATA SUM;
SET SUM;
BY &Visit &Imput;
where method^="Satterthwaite";
keep &Visit &Imput Class Mean StdDev;
RUN;

PROC SORT data=SUM;
BY &Visit Class &Imput;
RUN;

PROC MIANALYZE data=SUM alpha=0.1; *for the 90% confidence intervals;
BY &Visit Class;
ODS OUTPUT PARAMETERESTIMATES=&dataout;
MODELEFFECTS Mean;
STDERR StdDev;
RUN;
%mend  ;
```

To call the above macro, &datain should be &jobname._datafinal, &visit is the variable used to indicate different visits <Visit>, &trt is the variable indicating treatment arms <Treatment>, &Resp is the response variable < Chg_DCNVA>, &imput is the variable indicating sets of different imputed data. If only data at Month 3 needs to be presented, shown by stratum, the <Visit> variable can be supplied by stratification variable when calling the macro.

5.2.2 Secondary analysis

The secondary analysis results can be performed by running the following SAS macro (Ratitch et al. 2013):

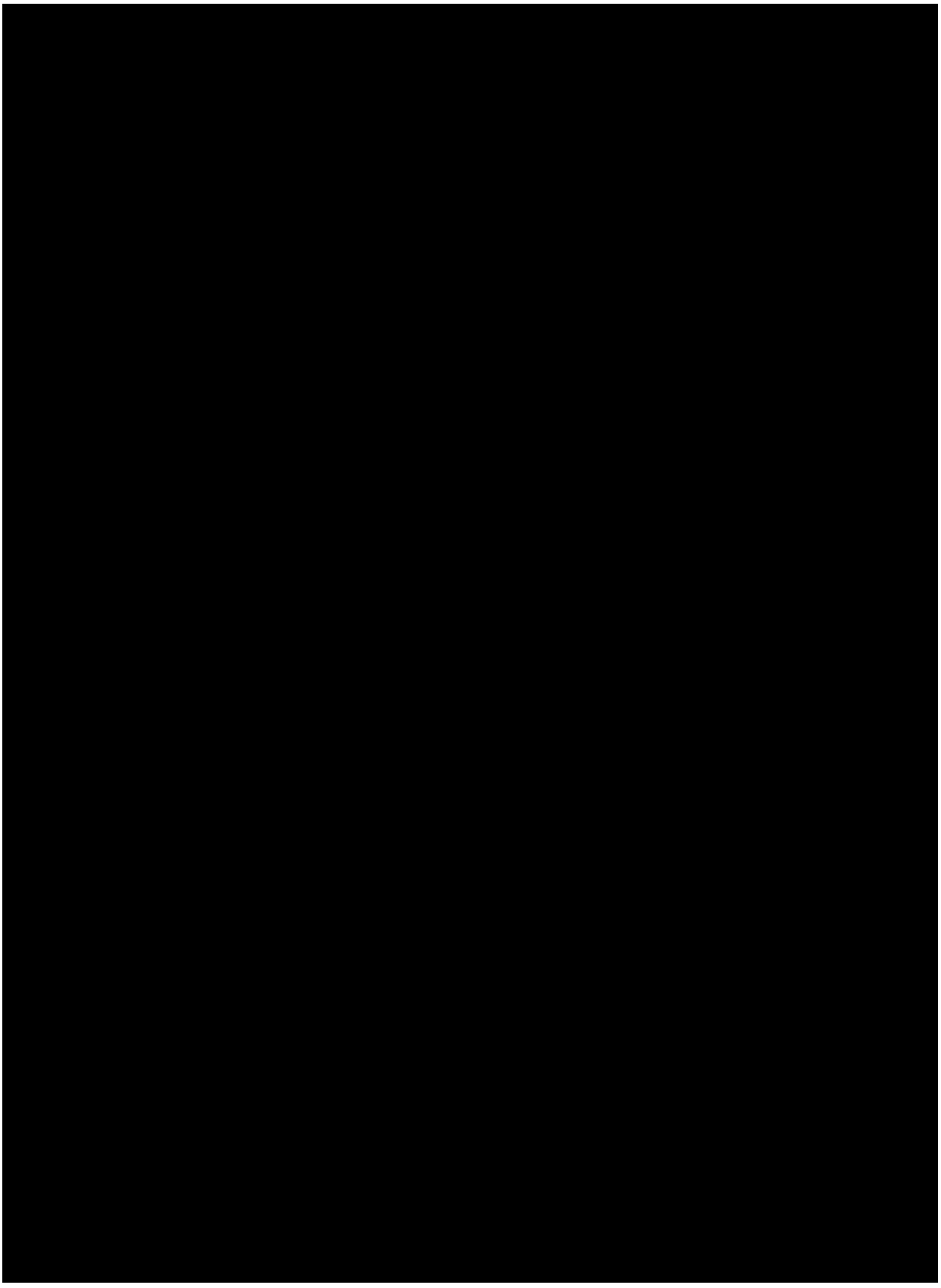
```
/*This macro performs all needed secondary analyses for UNR844A2203 study*/
%macro secondary(datain,Trt,Visit,Imput,Strata,Resp,method,dataout_sum,dataout_cmh,dataout_p) ;

PROC SORT data=&datain;
BY &Visit &Trt &Imput;
RUN;

/*************************************************************************
**************Summary statistics of secondary endpoint at M3*************
*************************************************************************/
/*Estimate proportions of responders in each arm*/
```

```
PROC FREQ DATA=&datain;
TABLES Resp_MA / cl binomial(level=2);
BY &Visit &Trt &Imput;
ODS OUTPUT BINOMIAL=prop;
RUN;
run;

*** From ODS output dataset BINOMIAL, create a dataset
containing estimated proportion of responders in each
treatment arm and their standard errors;
DATA prop_trt;
MERGE
prop(WHERE=(Label1="Proportion")
KEEP=&Imput &Visit &Trt nValue1 Label1
RENAME=(nValue1=prop))
prop(WHERE=(Label1="ASE")
KEEP=&Imput &Visit &Trt nValue1 Label1
RENAME=(nValue1=prop_se));
BY &Visit &Trt &Imput;
RUN;

*** Combine proportion estimates;
PROC SORT DATA=prop_trt; BY &Visit &Trt &Imput; RUN;
PROC MIANALYZE DATA=prop_trt alpha=0.1;
MODELEFFECTS prop;
STDERR prop_se;
BY &Visit &Trt;
ODS OUTPUT PARAMETERESTIMATES=&dataout_sum;
RUN;

/*********************************************************************
*****************Perform CMH test************************************
*********************************************************************/
*** Step I: Obtain Mantel-Haenszel estimate of the common odds ratio adjusted for
&Strata ***;
PROC SORT DATA=&datain;
by &Visit &Imput;
RUN;

PROC FREQ DATA=&datain;
TABLES &Strata*&Trt*&Resp / CMH;
ODS OUTPUT COMMONRELRISKS=comrrout;
BY &Visit &Imput;
RUN;

*** Log-transform odds ratio estimates
and obtain standard error from confidence intervals ***;
DATA ormh_t; SET comrrout(WHERE=(StudyType="Case-Control"));
log_or_mh_value=log(VALUE);
log_or_mh_se=(log(UPPERCL)-log(LOWERCL))/(2*quantile('Normal',.975));
RUN;

*** Combine proportion estimates;
PROC SORT DATA=ormh_t; BY &Visit &Imput; RUN;
```

```
PROC MIANALYZE DATA=ormh_t alpha=0.1;
MODELEFFECTS log_or_mh_value;
STDERR log_or_mh_se;
BY &Visit;
ODS OUTPUT PARAMETERESTIMATES=log_cmh;
RUN;

data &dataout_cmh ;
set log_cmh ;
Common_or = exp(Estimate);
*Or_upper = exp(Estimate+quantile('Normal',.95)*StdErr);
*Or_lower = exp(Estimate-quantile('Normal',.95)*StdErr);
e_lcl = exp(LCLMean);
e_ucl = exp(UCLmean);
Keep &Visit Common_or e_lcl e_ucl;
run;

PROC FREQ DATA=&datain;
TABLES &Strata*&Trt*&Resp / CMH;
ODS OUTPUT CMH=cmh;
BY &Visit &Imput;
RUN;

%if &method=1 %then %do;
/******Step II/Option 1: To obtain p-values, perform CMH test
by applying Wilson-Hilferty transformation to the CMH statistic*******/
*** Apply Wilson-Hilferty transformation to the CMH statistic and
standardize the resulting normal variable;
DATA cmh_wh; SET cmh(WHERE=(AltHypothesis="General Association"));
cmh_value_wh=((VALUE/DF)**(1/3) - (1-2/(9*DF)))/SQRT(2/(9*DF));
cmh_sterr_wh = 1.0;
RUN;
*** Combine results;
PROC MIANALYZE DATA=cmh_wh;
by &Visit;
ODS OUTPUT PARAMETERESTIMATES=mian_cmh_wh;
MODELEFFECTS cmh_value_wh;
STDERR cmh_sterr_wh;
RUN;
*** Compute one-sided p-value;
DATA &dataout_p; SET mian_cmh_wh;
IF tValue > 0 THEN Probt_WH = Probt/2;
ELSE Probt_WH = 1-Probt/2;
KEEP &Visit Probt_WH;
RUN;
%end;

%if &method=2 %then %do;
/******Step II/Option 2: To obtain p-values, perform CMH test
by applying Rubin & Li et al's transformation to the CMH statistic*******/
DATA cmh_rub; SET cmh(WHERE=(AltHypothesis="General Association"));
KEEP &Visit &Imput DF Value;
RUN;

PROC SORT DATA=cmh_rub ;
```

```
BY &Visit &Imput;
RUN;

*** Implement pooling procedure described in equations (3) and (4);
PROC IML;
USE cmh_rub ;
READ ALL VAR {Value} INTO chval;
READ ALL VAR {&Visit} INTO vis;
Read ALL VAR "DF";
close;
uvis=unique(vis);
n_vis=ncol(uvis);
df=unique(df);
n=nrow(chval);
m=n/n_vis;
Prob_Rub={};
VisitN={};
do i=1 to n_vis;
VisitN=VisitN//uvis[1,i];
st=(i-1)*m+1;
  en=i*m;
cvalroot_m = sum(chval[st:en]##0.5)/m;
  cval_m = sum(chval[st:en])/m;
  a=(chval[st:en]##0.5-j(m,1,1)*cvalroot_m)##2;
  rx = sum(a)*(1+1/m)/(m-1);
  Dx=(cval_m/df - (m+1)/(m-1)*rx)/(1+rx);
  df_den=(df**(-3/m))*(m-1)*(1+1/rx)**2;
  Pval1=1-CDF("F",Dx,df,df_den);
  Prob_Rub=Prob_Rub//Pval1;
end; *endc;
create &dataout_p var {Prob_rub VisitN} ;
APPEND;
close &dataout_p;
RUN; QUIT;

%end;
%mend  ;
```

Before calling the above macro, first create a ‘Strata’ variable for the interaction term of stratified baseline binocular DCNVA and age group <Stratified baseline binocular DCNVA by age group interaction>, which will result in four strata/levels. The response variable should be dichotomized based on the multiply imputed data set created by the Five Macros &jobname._datafinal. Set ‘method=2’ as Rubin and Li et al.’s approach will be used. The macro contains three output data sets: &dataout_sum contains summary statistics of the binary variable; &dataout_cmh contains point estimate(s) and standard error(s) of the combined CMH test; &dataout_p includes the corrected p-value(s) after combining CMH statistics from the multiply imputed data sets.



5.3 Rule of exclusion criteria of analysis sets

The following table provides the definitions of the protocol deviations of the study, together with the exclusion rules.

Table 1 Protocol Deviations

PD ID	Deviation Text	Data exclusion
INCL01	Informed consent not obtained	Exclude from all analysis sets

PD ID	Deviation Text	Data exclusion
INCL02	Phakic presbyopic male or female subjects aged 45 to 65 years at baseline	Include in all analysis sets
INCL03	DCNVA at 40 cms less than 70 ETDRS letters	Include in all analysis sets
INCL04	Near add of +1.00D or greater	Include in all analysis sets
EXCL01	Distance visual acuity of less than 85 ETDRS letters at 4m	Include in all analysis sets
EXCL02	Distance refractive error spherical equivalent greater than +4.0D or less than -4.0D	Include in all analysis sets
EXCL03	Astigmatism of greater than 1.25D	Include in all analysis sets
EXCL04	Difference of greater than 0.50D between manifest and cycloplegic refraction spherical equivalent	Include in all analysis sets
EXCL05	Anisometropia of greater than 0.75D	Include in all analysis sets
EXCL06	Clinically significant congenital or acquired changes to the lens or iris in either eye or clinically significant phacodonesis.	Include in all analysis sets
EXCL07	Undilated pupillary diameter of less than 2.5 mm in either eye	Include in all analysis sets
EXCL08	Unequal pupil diameters with a difference of greater than 1 mm between eyes	Include in all analysis sets
EXCL09	Non-circular pupil assessed related to a pathological cause	Include in all analysis sets
EXCL10	Contraindication to pupil dilation	Include in all analysis sets
EXCL11	Prior history or current diagnosis of any accommodative issues	Include in all analysis sets
EXCL12	Secondary cause of presbyopia in either eye	Include in all analysis sets
EXCL13	Any active ocular infection in either eye at screening or baseline.	Include in all analysis sets
EXCL14	History of idiopathic or autoimmune uveitis in either eye.	Include in all analysis sets
EXCL15	Ocular surface disease from any cause that is greater than mild in severity and is not controlled by OTC artificial tears	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
EXCL16	History or current diagnosis of treated or untreated glaucoma of any type.	Include in all analysis sets
EXCL17	History of ocular trauma in either eye.	Include in all analysis sets
EXCL18	Prior intraocular surgery or laser surgery including prior cataract extraction.	Include in all analysis sets
EXCL19	Planned intraocular or extra-ocular surgery (e.g., cataract extraction or refractive surgery) in either eye during the study period.	Include in all analysis sets
EXCL20	History of or current use of [redacted]	Include in all analysis sets
EXCL21	Prior participation in the EV-C-002 study or prior use of UNR844-Cl.	Include in all analysis sets
EXCL22	Hypersensitivity to any of the study drugs or its inactive ingredients	Include in all analysis sets
EXCL23	Use of any medication known to affect accommodation, pupils or intraocular pressure	Include in all analysis sets
EXCL24	Use of other investigational drugs within five half-lives or within 30 days of the screening visit	Include in all analysis sets
EXCL25	Prior therapy for presbyopia other than optical correction	Include in all analysis sets
EXCL26	History of clinically significant cardiac abnormality	Include in all analysis sets
EXCL27	History of diabetes mellitus	Include in all analysis sets
EXCL28	History of malignancy of any organ system within 6 months of screening	Include in all analysis sets
EXCL29	Any ocular or systemic condition that, in the opinion of the investigator, would jeopardize subject safety	Include in all analysis sets
EXCL30	Pregnant or nursing (lactating) women at screening	Include in all analysis sets
EXCL31	Women of child-bearing potential,unless they are using basic methods of contraception during the course of the study	Include in all analysis sets
EXCL32	Subjects in a dependent or unequal relationship with the Sponsor or study site staff	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
TRT01	Randomized but wrong IP administered during the study	Include in all analysis sets
TRT02	Investigational or other study treatment dose adjustments and/or interruptions made	Include in all analysis sets
TRT03	Subject missed a visit not allowed in the study	Include in all analysis sets
OTH01	Any other protocol deviation without impact on the safety of the patient	Include in all analysis sets
COMD01	Prohibited medication and/or procedure as per protocol	Include in all analysis sets
COMD02	Prohibited medication change as per protocol	Include in all analysis sets
WITH01	Subject withdrew consent but continue to receive study medication.	Include in all analysis sets
WITH02	Subject not tolerating the protocol prescribed dosing schedule but not withdrawn from the study.	Include in all analysis sets

6 Reference

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

Ratitch B, Lipkovich I, and O'Kelly M (2013). Combining analysis resutls from multiply imputed categorical data. PharmaSUG 2013: Paper SP03.