

Novartis Research and Development

UNR844

Clinical Trial Protocol 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**

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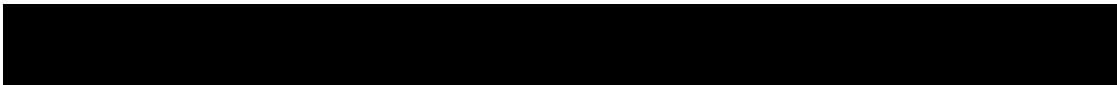


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### List of abbreviations

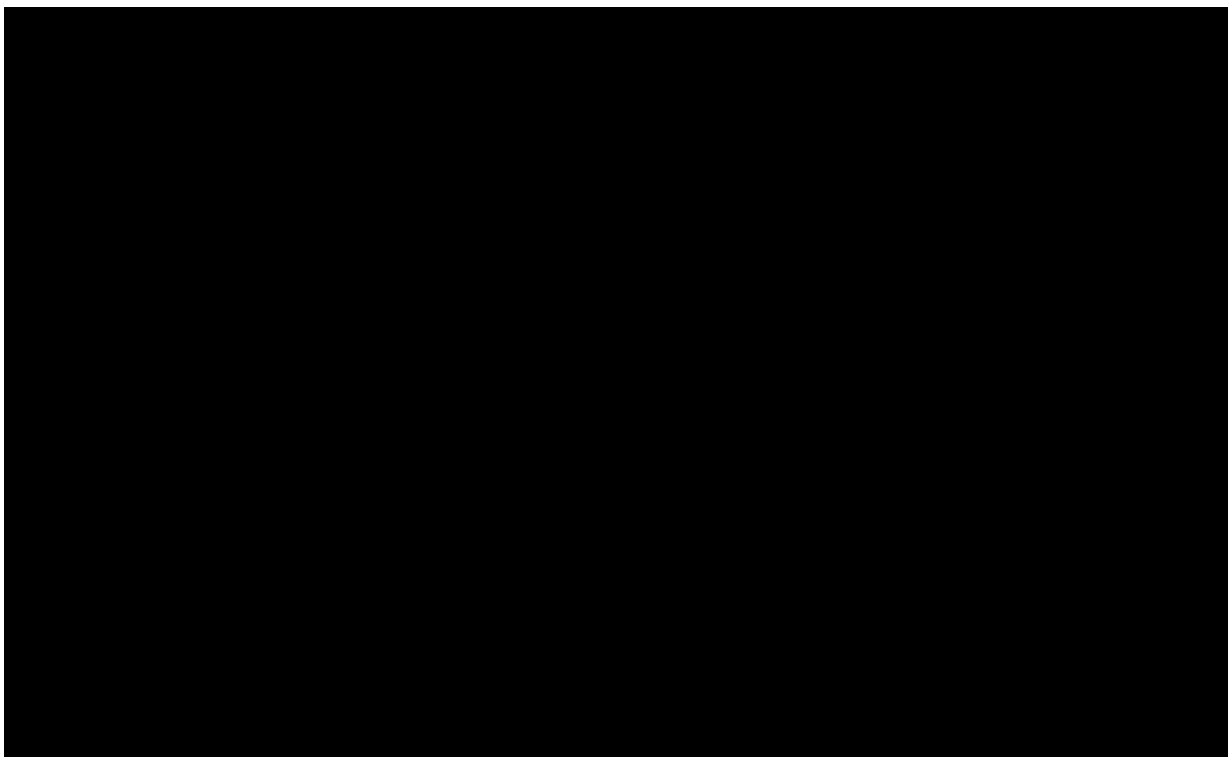
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCDVA	Best-corrected distance visual acuity
BP	Blood Pressure
CFR	Code of Federal Regulation
CIR	Copy Increment from Reference
Cl	Chloride
CRO	Contract Research Organization
DCNVA	Distance-corrected near visual acuity
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
IRT	Interactive Response Technology
LA	Lipoic Acid
LACE	Lipoic Acid Choline Ester
LDH	lactate dehydrogenase
MAR	Missing At Random
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed effect Model Repeat Measurement
No.	Number
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
WoC	Withdrawal of consent

## Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g., 100 mg once a day, 75 mg twice-daily)
EDC (electronic data capture)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source documents used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study Treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.

Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, <u>and</u> does not want any further visits or assessments, <u>and</u> does not want any further study related contact, <u>and</u> does not allow analysis of already obtained biologic material

## Amendment 01



### Changes to the protocol

1. Section [5.1 Inclusion criterion 3](#)

Less than 70 ETDRS letters at baseline and no more than 5 ETDRS letters difference between screening and baseline is changed to apply to binocular DCNVA only.

2. Section [8 Visit Schedule and assessments](#)

A sentence was added; “Screening visit assessments may be split on separate days as close as possible to each other, however all visual acuity and refraction assessments must be performed on the same day.”





4. [Table 8-2 Safety Assessments specifications](#)

Editorial correction of the sentence “Vital signs include blood pressure (BP) and heart rate measurements at screening” by deleting “at screening” since vital signs are performed at all visits as correctly displayed in [Table 8-1](#).

5. Section [6.3.1 Subject numbering](#)

Editorial correction removing “...by the Interactive Response Technology (IRT)”

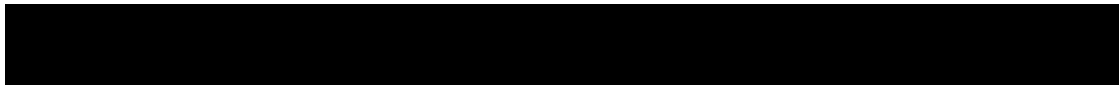
Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the trial specific model ICF.



## Protocol summary

<b>Protocol number</b>	CUNR844A2203
<b>Full Title</b>	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
<b>Brief title</b>	Study of safety and efficacy of UNR844-CI eye drops in subjects with presbyopia
<b>Sponsor and Clinical Phase</b>	Novartis Phase II study
<b>Investigation type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	To assess the effect of topical UNR844-CI (lipoic acid choline ester chloride) ophthalmic solution on near visual function in presbyopic subjects.
<b>Primary Objective</b>	The primary objective of this study is to assess the efficacy of topical lipoic acid choline ester chloride ophthalmic solution in presbyopic subjects aged 45 to 55 years by assessing the change in binocular distance-corrected near visual acuity from baseline when compared to placebo after 3 months of treatment.
<b>Secondary Objectives</b>	To assess the efficacy of topical lipoic acid choline ester chloride ophthalmic solution in presbyopic subjects aged 45 to 55 years by assessing the proportion of subjects achieving 75 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in binocular distance-corrected near visual acuity when compared to placebo after 3 months of treatment.  To assess the safety of topical lipoic acid choline ester chloride ophthalmic solution by comparing the frequency of treatment emergent adverse events and treatment emergent serious adverse event in all subjects treated with lipoic acid choline ester chloride and placebo over a treatment period of 3 months.
<b>Study design</b>	This is a randomized, double-masked, placebo-controlled, parallel-group study.  Eligible subjects will be randomized 1:1 to receive either topical lipoic acid choline ester chloride ophthalmic solution 1.5% or placebo, dosed one drop in each eye twice-daily for 3 months.
<b>Population</b>	Approximately 120 male or female subjects aged 45 to 65 years with presbyopia will be enrolled, of which approximately 72 subjects will be aged 45 to 55 years, and 48 subjects will be aged 56 to 65 years.
<b>Key Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Phakic presbyopic male or female subjects aged 45 to 65 years, inclusive</li> <li>• Distance-corrected near visual acuity at 40 cm of less than 70 ETDRS letters for each eye and for binocular vision</li> <li>• Need a minimum add of +1.00D or greater to achieve binocular distance-corrected near visual acuity at 40 cm of at least 85 ETDRS letters assessed by the investigator.</li> </ul>
<b>Key Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Best-corrected distance visual acuity at 4 m of less than 85 ETDRS letters in either eye</li> <li>• Spherical equivalent greater than +4.0D or less than -4.0D in either eye based on manifest refraction at screening or baseline visit</li> <li>• Any other clinically significant visual, ocular or systemic conditions</li> </ul>
<b>Study treatment</b>	Topical lipoic acid choline ester chloride ophthalmic solution (UNR844-CI) 1.5%, administered as one drop in each eye twice-daily for three months



	Placebo (vehicle ophthalmic solution), administered as one drop in each eye twice-daily for three months
<b>Efficacy assessments</b>	<ul style="list-style-type: none"> <li>Binocular distance-corrected near visual acuity at 40 cm</li> </ul>
<b>Key safety assessments</b>	<ul style="list-style-type: none"> <li>Adverse event monitoring</li> <li>Ophthalmic examinations</li> <li>Best-corrected distance visual acuity at 4 m, for each eye and for binocular vision</li> </ul>
<b>Other assessments</b>	
<b>Data analysis</b>	<p>The primary efficacy analysis will test the null hypothesis that there is no difference in the change from baseline in binocular distance-corrected near visual acuity for subjects aged 45 to 55 years between the treatment groups at three months, and the alternative hypothesis that this change from baseline is greater for the UNR844-CI group than for the placebo group. A mixed-effect model repeated measure model will be fitted and the comparison between the two treatment groups will be performed using a two-group t-test at a one-sided significance level of 5%.</p> <p>The secondary efficacy analysis will test the null hypothesis that there is no difference in the proportion of subjects aged 45 to 55 years achieving 75 or more ETDRS letters in binocular distance-corrected near visual acuity between the treatment groups at three months, and the alternative hypothesis that this proportion is greater for the UNR844-CI group than for the placebo group. The comparison between the two treatment groups will be performed using a stratified Cochran-Mantel-Haenszel test at a one-sided significance level of 5%.</p>
<b>Key words</b>	Presbyopia, near visual acuity, adults, randomized study, placebo



## 1 Introduction

### 1.1 Background

Presbyopia is a common age-related vision disorder characterized by a progressive inability to focus on near objects. Approximately 80% of people aged 40 years or older will likely develop presbyopia ([Holden et al 2008](#)). It is estimated that there were 1.8 billion people affected by presbyopia worldwide in 2015 and it is predicted that 1.9 billion people will be affected by 2050 ([Fricke et al 2018](#)).

Current management of presbyopia relies on optical correction (e.g., spectacles, contact lens) or surgical intervention (e.g., corneal inlay, corneal refractive procedures, and intraocular lens replacement). A pharmacological approach may offer an alternative therapeutic option that can have advantages in terms of improving patient convenience and satisfaction.

There are various etiologies proposed for the cause of presbyopia such as loss of ciliary muscle activity, geometric changes in the lens and hardening of the lens with increasing age ([Strenk et al 2005](#)). However, it is generally accepted that crystalline lens hardening leads to less accommodation in presbyopes. Recent research suggests that age-dependent increase in lens protein disulfides may be related to the loss of lens elasticity that contributes to presbyopia, and treatment with an antioxidant agent can restore lens elasticity ([Garner and Garner 2016](#)).

[REDACTED]

UNR844-CI 1.5% topical ophthalmic solution was evaluated in a randomized, double-masked, placebo-controlled clinical study with 75 subjects with presbyopia. Fifty subjects were treated with UNR844-CI 1.5% one drop to each eye twice a day for up to three months, while 25 subjects received placebo treatment. UNR844-CI was well tolerated and there were no safety issues identified. After three months, subjects treated with UNR844-CI had a mean improvement in distance-corrected near visual acuity (DCNVA) of 8.1 Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in their first treated eye, compared to a mean improvement of 4.3 ETDRS letter score in the placebo group.

The current study is designed to further evaluate the efficacy as observed in this previous study in terms of improvement in binocular DCNVA. [REDACTED]

[REDACTED] Distance-corrected near visual acuity is the measurement of near vision at 40 cm while subjects are wearing their prescription to correct their distance vision, if any (i.e.,

[REDACTED]

for myopia, hyperopia or astigmatism). Core score is a multi- factor combination visual score ranked in terms of difficulty to identify targets of varying contrast, size and presentation time.

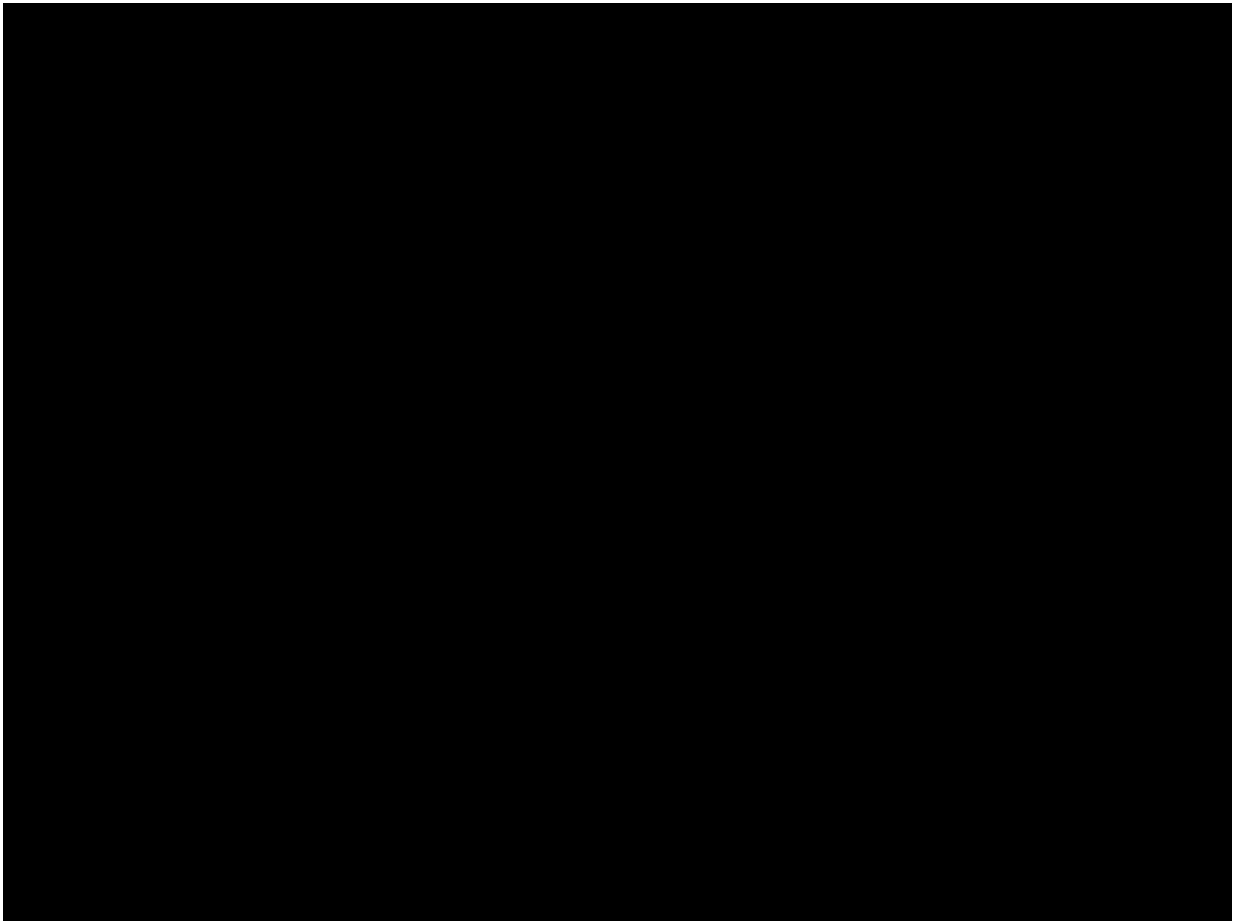
## 1.2 Purpose

The primary purpose of this study is to assess the safety and efficacy of UNR844-CI in presbyopic subjects aged 45 to 55 years, as measured by the improvement in DCNVA.

## 2 Objectives and endpoints

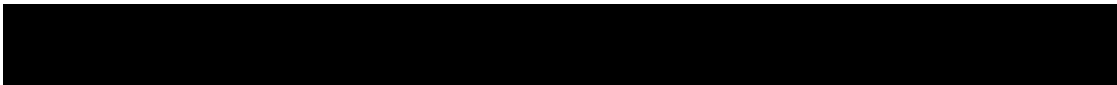
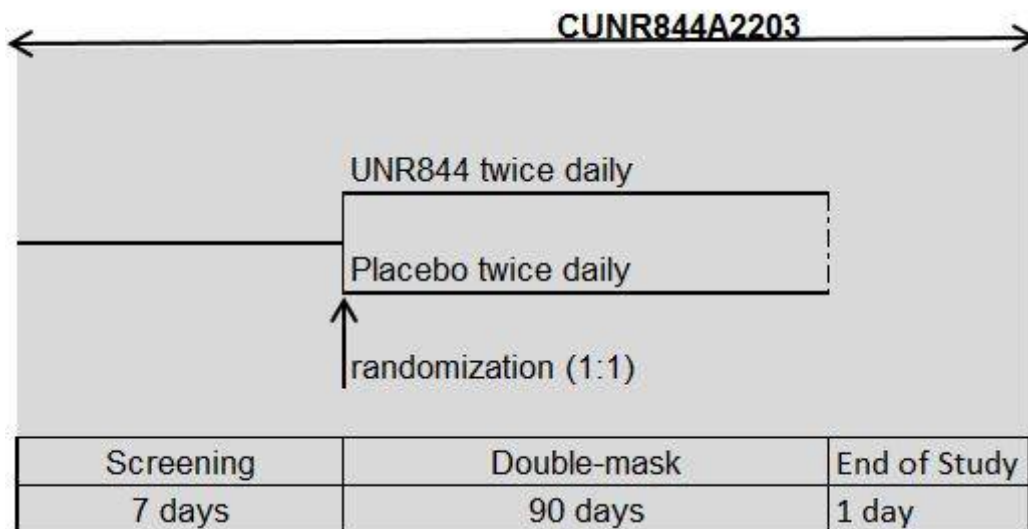
**Table 2-1 Objectives and related endpoints**

<b>Objective(s)</b>	<b>Endpoint(s)</b>
<b>Primary objective(s)</b>	<b>Endpoint(s) for primary objective(s)</b>
<ul style="list-style-type: none"><li>Assess the efficacy of UNR844-CI on binocular DCNVA in presbyopic subjects aged 45 to 55 years</li></ul>	<ul style="list-style-type: none"><li>Change from baseline in binocular DCNVA in subjects aged 45 to 55 years at Month 3 after UNR844-CI or placebo treatment</li></ul>
<b>Secondary objective(s)</b>	<b>Endpoint(s) for secondary objective(s)</b>
<ul style="list-style-type: none"><li>Assess the efficacy of UNR844-CI on achieving 75 or more ETDRS letters in binocular DCNVA in presbyopic subjects aged 45 to 55 years</li><li>Assess the safety of UNR844-CI in presbyopic subjects</li></ul>	<ul style="list-style-type: none"><li>Proportion of subjects aged 45 to 55 years achieving 75 or more ETDRS letters in binocular DCNVA at Month 3 after UNR844-CI or placebo treatment</li><li>Frequency of treatment emergent adverse events and treatment emergent serious adverse events in all subjects after UNR844-CI or placebo treatment</li></ul>



### 3 Study design

Figure 3-1 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 3-1). 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 UNR844-Cl or placebo, dosed one drop in each eye twice-daily, for 3 months.

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

## **4 Rationale**

### **4.1 Rationale for study design**

The rationale for this study is to further evaluate the efficacy as observed in the previous study with UNR844-Cl. This will be a randomized, double-masked, multi-center, placebo-controlled study.

#### **Age group**

Presbyopic subjects aged 45 to 55 years will be the primary age group in this study as in the previous clinical study with UNR844-Cl. [REDACTED]

#### **Number of arms and dosing**

One concentration of UNR844-Cl was evaluated in a prior clinical study. Since this study is to evaluate the efficacy observed earlier, the same UNR844-Cl 1.5% concentration [REDACTED] will be evaluated and subjects will be dosed twice-daily with either UNR844-Cl or placebo (two arms).

#### **Duration of treatment**

[REDACTED]  
Therefore, the total treatment duration in this study will be three months.

##### **4.1.1 Rationale for choice of background therapy**

Currently, there are no pharmacological therapies approved for presbyopia. Subjects will be able to wear their optical correction, if needed, when not undergoing study assessments. Subjects will be instructed not to wear contact lenses prior to completing the study assessments on the day of the study visits.

##### **4.2 Rationale for dose/regimen and duration of treatment**

[REDACTED]

[REDACTED]

[REDACTED], subjects will receive twice-daily UNR844-Cl treatment, one drop in each eye, for three months.

#### **4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs**

The control in this study is placebo, which comprise the formulation vehicle of UNR844-Cl (all inactive ingredients except the active drug substance UNR844-Cl). There are no approved pharmacological treatment for presbyopia. The aim of this study is evaluate the impact of UNR844-Cl on near visual function and therefore placebo (vehicle) is an appropriate comparator.

#### **4.4 Purpose and timing of interim analyses/design adaptations**

Not applicable.

#### **4.5 Risks and benefits**

In a prior clinical study with UNR844-Cl, there were no safety concerns identified. There were no serious adverse events (SAEs) and no subjects discontinued from the study because of an adverse event (AE).

The most commonly reported AEs were:

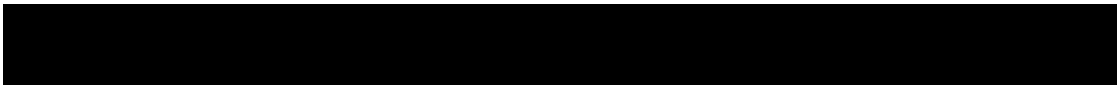
- Nasopharyngitis (16% UNR844-Cl subjects, 8% placebo subjects)
- Dysgeusia (14% UNR844-Cl subjects, 0% placebo subjects)
- Upper respiratory tract infection (2% UNR844-Cl subjects, 8% placebo subjects)
- Headache (8% UNR844-Cl subjects, 0% placebo subjects)

The most commonly reported AEs in the "eye disorders" system organ class were:

- Eye irritation (6% UNR844-Cl subjects, 0% placebo subjects)
- Asthenopia (4% UNR844-Cl subjects, 0% placebo subjects)
- Conjunctival hyperemia (0% UNR844-Cl subjects, 8% placebo subjects)
- Eye pruritus (4% UNR844-Cl subjects, 0% placebo subjects)
- Foreign body sensation in eyes (4% UNR844-Cl subjects, 0% placebo subjects)
- Ocular hyperemia (4% UNR844-Cl subjects, 0% placebo subjects)

The risk to subjects in this study will be minimized by compliance with the eligibility criteria and study procedures, as well as periodic monitoring of safety data.

The effects of UNR844-Cl ophthalmic solution on fertility, pregnancy and lactation have not been studied. No safety concerns are expected based on the nature of UNR844-Cl. However, women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criterion. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.





Although UNR844-C1 exhibited a beneficial effect with respect to DCNVA in presbyopic subjects in a prior clinical study, it cannot be guaranteed that a similar effect would be observed in this study.

## 5 Population

Approximately 120 male or female presbyopic subjects aged 45 to 65 years will be enrolled, of which approximately 72 subjects will be aged 45 to 55 years and approximately 48 subjects will be aged 56 to 65 years.

With an estimated 10% drop-out rate, this would mean approximately 66 subjects are anticipated to complete the study in the 45 to 55 years age group and 44 subjects in the 56 to 65 years age group.

### 5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria at the screening visit unless specified otherwise:


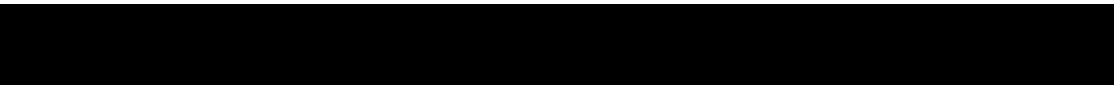
1. Written informed consent must be obtained before any assessment is performed.
2. Phakic presbyopic male or female subjects aged 45 to 65 years, inclusive.
3. DCNVA of each eye, as well as for binocular vision, less than 70 ETDRS letters at 40 cm distance at the screening visit.
  - In addition, DCNVA for binocular vision at baseline must also be less than 70 ETDRS letters at this visit and not more than 5 ETDRS letters different from the corresponding assessment at the screening visit.
4. Subjects who need a minimum add of +1.00D or greater to achieve binocular DCNVA of at least 85 ETDRS letters at 40 cm distance, as assessed by the investigator.

### 5.2 Exclusion criteria

Subjects meeting any of the following criteria at the screening visit (or unless specified otherwise) are not eligible for inclusion into this study.

1. Best-corrected distance visual acuity (BCDVA) less than 85 ETDRS letters at 4 m distance in either eye.
2. Spherical equivalent greater than +4.0D or less than -4.0D, based on manifest refraction, in either eye at the screening or baseline visit.
3. Astigmatism of greater than 1.25D, based on manifest refraction, in either eye at the screening or baseline visit.
4. Difference of greater than 0.50D between manifest refraction spherical equivalent and the cycloplegic refraction spherical equivalent.
5. Anisometropia of spherical equivalent of greater than 0.75D at the screening or baseline visit.
6. Any clinically significant congenital malformation or acquired changes to the lens or iris in either eye that might have an impact on visual acuity (e.g., clinically significant cataractous lens changes) or clinically significant phacodonesis.

7. Undilated pupillary diameter of less than 2.5 mm in either eye measured at an ambient light level of 8 to 15 lux.
8. Unequal pupil diameters with a difference of greater than 1 mm between eyes.
9. Non-circular pupil assessed by the investigator to be related to a pathological cause.
10. Contraindication to pupil dilation in either eye or a history of untreated narrow angles or currently occludable angles in either eye.
11. Prior history or current diagnosis of accommodative spasm, accommodative insufficiencies, or other accommodative issues that would preclude accurate measurement of lens accommodation (except accommodative issues related to presbyopia).
12. Secondary cause of presbyopia in either eye (e.g., damage to lens, zonules or ciliary muscle, multiple sclerosis, cardiovascular accidents, vascular insufficiency, myasthenia gravis, anemia, influenza, measles).
13. Any active ocular infection (i.e., bacterial, viral, parasitic or fungal), or inflammation, or a history of herpetic ocular infection in either eye at screening or baseline.
14. History of idiopathic or autoimmune uveitis in either eye.
15. Ocular surface disease from any cause (e.g., dry eye, blepharitis, exposure) in either eye at the screening visit that is greater than mild in severity and is not controlled by use of over-the-counter artificial tear products.
16. History or current diagnosis of treated or untreated glaucoma of any type.
17. History of penetrating ocular trauma, significant blunt ocular trauma in either eye.
18. Prior intraocular surgery or laser surgery of any kind in either eye, including prior cataract extraction.
19. Planned intraocular or extra-ocular surgery (e.g., cataract extraction or refractive surgery) in either eye during the study period.

- 
21. Prior participation in the EV-C-002 study or prior use of UNR844-C1.
  22. History of hypersensitivity to any of the study drugs or its inactive ingredients or to active ingredients of similar chemical classes.
  23. Use of any medication known to affect accommodation, pupil size or intraocular pressure during the study, as listed in [Table 6-3](#). Subjects who have been on a stable dose of such medication for at least 3 months prior to the screening visit and who are not expected to change the dose/regimen or discontinue the medication are eligible for the study.
  24. Use of other investigational drugs within five half-lives or within 30 days of the screening visit (until the expected pharmacodynamic effect has returned to baseline, whichever is longer).
  25. Prior therapy for presbyopia other than optical correction (e.g., supplements, medications, training exercises, ciliary body electrostimulation, corneal implants, surgery).
  26. History of clinically significant cardiac abnormality.
  27. History of diabetes mellitus.
  28. History of malignancy of any organ system (other than localized squamous cell or basal cell carcinoma of the skin or *in situ* cervical cancer) within six months of the screening visit.
- 

29. Any ocular or systemic condition that, in the opinion of the investigator, would jeopardize subject safety, has an impact on visual acuity, affects study assessments or validity of study results.
30. Pregnant or nursing (lactating) women at screening.
31. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during the course of the study. Basic contraception methods include:
- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male sterilization (at least six months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
  - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps).
  - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device or intrauterine system

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

32. Subjects in a dependent or unequal relationship with the Sponsor or study site staff (e.g., employees of the Sponsor, employees or students under the direct supervision of the study site staff, immediate relatives of the study site staff)

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

## **6 Treatment**

### **6.1 Study treatment**

Subjects will be randomized 1:1 to either UNR844-C1 or vehicle (placebo) dosed twice-daily for three months.

### 6.1.1 Investigational and control drugs

**Table 6-1** Investigational and control drugs

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
UNR844-CI 1.5%	Ophthalmic Solution	Topical ocular	Opaque plastic bottle	Novartis global
Placebo	Ophthalmic Solution	Topical ocular	Opaque plastic bottle	Novartis global

### 6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial.

### 6.1.3 Treatment arms/group

Subjects will be assigned at the baseline visit to one of the following two treatment arms in a 1:1 ratio.

- UNR844-CI 1.5% ophthalmic solution - one drop in each eye twice-daily
- Placebo ophthalmic solution - one drop in each eye twice-daily

### 6.1.4 Treatment duration

The planned treatment duration is three months.

## 6.2 Other treatment(s)

Not applicable.

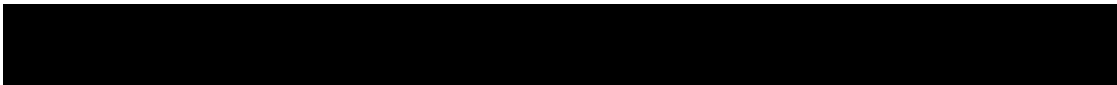
### 6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies or procedures electronic Case Report Form (eCRF) pages.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already randomized, contact Novartis to determine if the subject should continue participation in the study.

### 6.2.2 Prohibited medication

Use of the medications and therapies described in [Table 6-2](#) are not allowed after screening.



**Table 6-2 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

Subjects are not allowed to start, stop or change dosing of the following treatments after the screening visit, unless as part of the study protocol ([Table 6-3](#)).

**Table 6-3 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 throughout the study	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



<b>Medication</b>	<b>Prohibition period</b>	<b>Action taken</b>
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
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

Subjects who have prohibited medication/therapy or have prohibited medication changes during the study can continue in the study and their data will be handled as detailed in [Section 12.4.3](#).

## **6.3 Subject numbering, treatment assignment, randomization**

### **6.3.1 Subject numbering**

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the study. The Subject No. consists of the Center Number (Center No.) (made of 4 numbers as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it (made of 3 numbers), so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available.

### **6.3.2 Treatment assignment, randomization**

At baseline visit, all eligible subjects will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis

Global Clinical Supplies using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified based on binocular DCNVA (59 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-CI or placebo.

## **6.4 Treatment blinding**

Subjects, investigator staff, those performing the assessments, and the Novartis study team will remain masked to the identity of the treatment from the time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unmasking, and will not be accessible by anyone else involved in the study
2. The identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, labeling and schedule of administration.

Unmasking will occur in the case of subject emergencies and at the conclusion of the study.

## **6.5 Dose escalation and dose modification**

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

### **6.5.1 Dose modifications**

Dose modifications are not allowed in this study. For subjects who do not tolerate the protocol-specified dosing schedule, study treatment should be discontinued and, if possible, the subject is continued to be monitored in the study ([Section 9.1.1](#)).

### **6.5.2 Follow-up for toxicities**

Not applicable.

## **6.6 Additional treatment guidance**

Not applicable.

### **6.6.1 Treatment compliance**

Subjects will be instructed at each on-therapy study visit to take the study treatment exactly as prescribed. Subjects will also be instructed to bring used/unused medication bottles to the study visits and the site staff will check compliance based on the number of bottles used.

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

## **6.6.2 Emergency breaking of assigned treatment code**

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- Protocol number
- Subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

## **6.7 Preparation and dispensation**

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

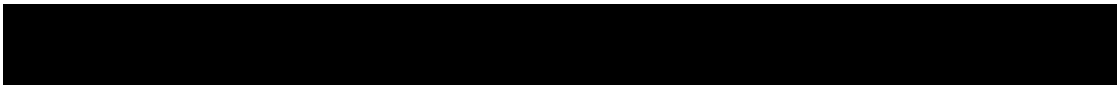
A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study drug has a 2-part label (base plus tear-off or peel-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

### **6.7.1 Handling of study treatment and additional treatment**

#### **6.7.1.1 Handling of study treatment**

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure (IB). Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with local legal requirements. They will include storage conditions for the study treatment but no information about the subject except for the medication number.





The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

### 6.7.1.2 Handling of additional treatment

Artificial tears are administered to subjects prior to certain visual function assessments in this study. Novartis will provide investigators with artificial tears for such use. These should be stored according to the manufacturers' instructions.

At the conclusion of the study, unused product can be disposed of by the investigator according to local practice.

## 6.7.2 Instruction for prescribing and taking study treatment

**Table 6-4 Dose and treatment schedule**

Investigational/Control Drug (UNR844-CI/ Placebo)	Dose	Frequency and/or Regimen
UNR844-CI 1.5%	One drop in each eye	Twice-daily
Placebo	One drop in each eye	Twice-daily

Subjects should take the study treatment at approximately the same time each day twice-daily. For example, morning dose at approximately 8AM and evening dose at approximately 8PM. Contact lenses must be removed prior to administering the study treatment. Contact lenses may be worn approximately 15 minutes after administering the study treatment. If a dose is missed and it has been more than 6 hours from the approximate usual time of dosing, subjects should continue with the next scheduled dose.

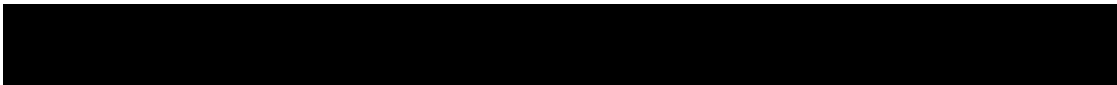
All kits of study treatment assigned by the IRT will be recorded in the IRT system.

## 7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation) institutional review board (IRB) approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.



Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis after IRB approval.

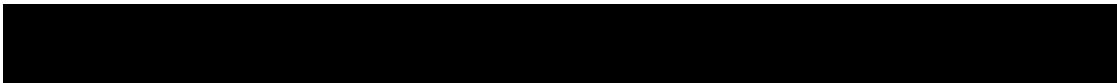


## 8 Visit schedule and assessments

The assessment schedule ([Table 8-1](#)) lists all of the assessments and indicates with an “X” the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

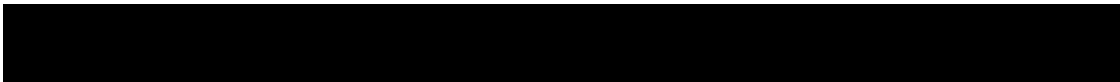
Subjects should be seen for all visits/assessments as outlined in the assessment schedule ([Table 8-1](#)) or as close to the designated day/time as possible. Screening visit assessments may be split on separate days as close as possible to each other, however all visual acuity and refraction assessments must be performed on the same day. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and any adverse event and concomitant medications recorded on the eCRF.

All randomized and/or treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment ([Section 9.2](#)).



**Table 8-1 Assessment Schedule**

<b>Period</b>	<b>Screening</b>	<b>Treatment</b>						
<b>Visit Name</b>	<b>Screening</b>	<b>Baseline</b>	<b>W2</b>	<b>M1</b>	<b>M1.5</b>	<b>M2</b>	<b>M2.5</b>	<b>M3/EOS</b>
<b>Days</b>	<b>-7</b>	<b>1</b>	<b>14</b>	<b>30</b>	<b>45</b>	<b>60</b>	<b>75</b>	<b>90</b>
Informed consent	X							
Demography	X							
Study completion information								X
Medical history/current medical conditions	X							
Inclusion/Exclusion criteria	X	X						
Vital Signs	X	X	X	X		X		X
Physical Examination		X						
Electrocardiogram (ECG)	X							
Hematology	X							
Clinical Chemistry	X							
Urinalysis	X							
Best-corrected distance visual acuity	X	X	X	X		X		X
Distance-corrected near visual acuity	X	X	X	X		X		X
Pregnancy Test (serum)	X							
Pregnancy Test (urine)								X
Slit lamp biomicroscopy	X	X	X	X		X		X
Intraocular Pressure (IOP)	X	X	X	X		X		X
Dilated fundus exam	X							X
Adverse Events	X	X	X	X		X		X



<b>Period</b>	<b>Screening</b>	<b>Treatment</b>						
<b>Visit Name</b>	<b>Screening</b>	<b>Baseline</b>	<b>W2</b>	<b>M1</b>	<b>M1.5</b>	<b>M2</b>	<b>M2.5</b>	<b>M3/EOS</b>
<b>Days</b>	<b>-7</b>	<b>1</b>	<b>14</b>	<b>30</b>	<b>45</b>	<b>60</b>	<b>75</b>	<b>90</b>
Concomitant medications	X	X	X	X		X		X
Drug dispensation		X		X		X		



## 8.1 Screening

### Screening

Re-screening is allowed once for those subjects who screen failed under the original Protocol v00 due to Inclusion criterion 3. All screening and baseline assessments must be repeated and Inclusion/Exclusion criteria as per amended Protocol v01 must be met for subjects who screen failed under original protocol. No other re-screenings are allowed.

#### 8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for not starting on treatment will be entered on the screening phase disposition eCRF page. The demographic information, informed consent, and Inclusion/Exclusion eCRF pages must also be completed for screen failed patients. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a SAE during the screening phase (see Serious Adverse Events [Section 10.1.3](#) for reporting details). If the subject fails to be randomized, the IRT must be notified within two days of the screen fail that the subject was not randomized.

## 8.2 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all subjects include: age, sex, race, ethnicity, relevant medical history/current medical condition (diagnosis and not symptoms will be recorded).

Investigators will have the discretion to record abnormal test findings on the Medical History eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Baseline ocular characteristics include BCDVA, DCNVA, [REDACTED] anterior and posterior eye segment health.

## 8.3 Efficacy

Efficacy assessments will be performed at the visits as specified in the assessment schedule ([Table 8-1](#)).

Instill one drop of artificial tear product in each eye approximately 5 minutes prior to starting visual acuity assessments. Additional drops may be used as needed. A period of approximately 3 minutes should be observed between instillation of drops and restarting any visual assessments.

#### 8.3.1 Distance-corrected near visual acuity

Distance-corrected near visual acuity at 40 cm at 100% contrast is measured binocularly and monocularly using an electronic near visual acuity testing system (M&S technologies Clinical Trial Suite). This assessment must be performed with subjects corrected for any distance



refractive errors. The system will provide the subject's DCNVA in ETDRS letter numerical score.

Novartis will provide the M&S Technologies Clinical Trial Suite system and training and certification on the system prior to the start of the study.

[REDACTED]

[REDACTED]

#### 8.4 Safety

Safety assessments are specified below ([Table 8-2](#)) with the assessment schedule ([Table 8-1](#)) detailing when each assessment is to be performed. A detailed description about how to perform the assessments will be provided in the site operations manual.

Instill one drop of artificial tear product in each eye approximately 5 minutes prior to starting visual acuity assessments. Additional drops may be used as needed. A period of approximately 3 minutes should be observed between instillation of drops and restarting any visual assessments.

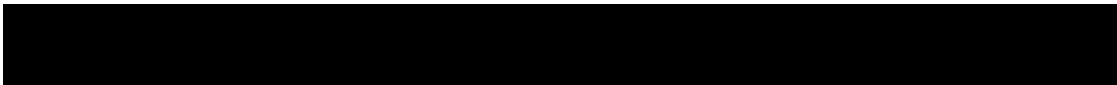
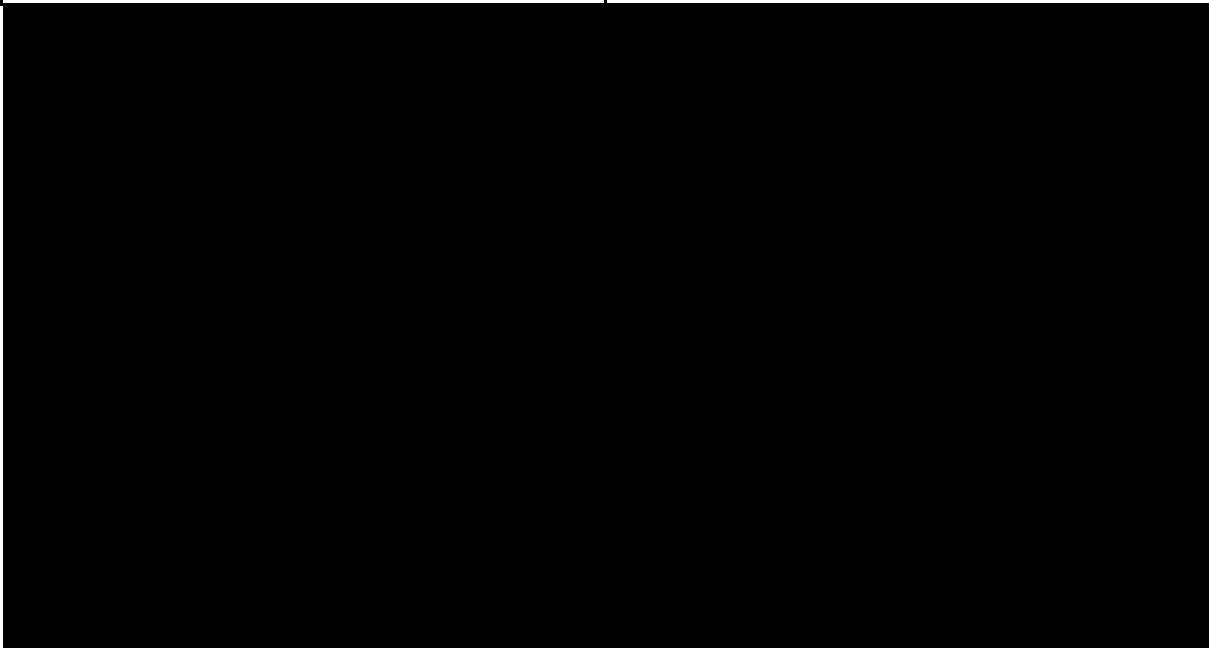
For details on AE collection and reporting, refer to Adverse Events [Section 10.1](#).

**Table 8-2 Safety assessment specifications**

Assessment	Specification
Physical examination	A routine physical examination will be performed at the baseline visit and will include an evaluation of the general appearance (e.g., skin, peripheral blood perfusion, extremities, lymph nodes).

[REDACTED]

<b>Assessment</b>	<b>Specification</b>
	Information for all physical examinations should be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after first administration of investigational drug that meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.
Vital sign	Vital signs include blood pressure (BP) and heart rate measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic BPs will be measured once using an automated validated device (e.g., OMRON) with an appropriately sized cuff. If the investigator has any concerns with the single measurement, BP measurements should then be repeated after at least 10 minutes from the first measurement. All individual measurements should be entered in the source document. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Best-corrected distance visual acuity (BCDVA)	BCDVA will be measured binocularly and monocularly at 100% contrast at 4 m at the visits as detailed in the assessment schedule. An electronic visual acuity testing system will be used for this assessment.



Assessment	Specification
Ophthalmic Examination	The following ocular assessments will be performed as per the schedule assessment: <ol style="list-style-type: none"><li>1. Slit-lamp examination include evaluation of the lids/lashes, conjunctiva, cornea, anterior chambers aqueous reactions (cells and flare), iris, lens and anterior part of the vitreous body and assessment of phacodonesis in both eyes. Slit-lamp examination will be performed before study treatment and throughout the study. Phacodonesis should be assessed after dilation at Screening and Month 3 visits. The results will be recorded in the source documents only and any clinically significant findings must be documented in the eCRF.</li><li>2. Intraocular pressure will be assessed in both eyes with Goldmann applanation tonometer or Tonopen. This assessment must be performed after any visual acuity assessments.</li><li>3. Dilated fundus examination will be performed in both eyes. Any clinically significant findings must be documented in the eCRF.</li></ol>

#### 8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected.

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF page.

Clinically significant abnormalities at screening must be recorded as medical history/current medical conditions.

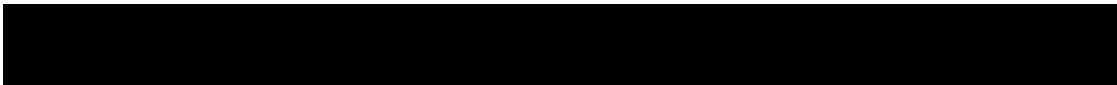
Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

##### 8.4.1.1 Hematology

Hemoglobin, platelets, white blood cells, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, other)

##### 8.4.1.2 Clinical chemistry

Albumin, alkaline phosphatase, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), lactate dehydrogenase (LDH), calcium, magnesium, phosphorus, sodium, potassium, creatinine, direct bilirubin, total bilirubin, urea, uric acid, amylase, lipase, glucose (non-fasting).





### **8.4.1.3 Urinalysis**

Macroscopic (Dipstick) panel - color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen

Microscopic panel - red blood cells, white blood cells, casts, crystals, bacteria and epithelial cells.

### **8.4.2 Electrocardiogram (ECG)**

Electrocardiograms must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula should be used for clinical decisions.

A single 12-lead ECG is collected. The original ECGs on non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site. If a patient had an ECG performed within 6 months of screening, the results of this ECG can be used in lieu of performing the screening ECG. A copy of the historical ECG will be retained in the patient's source documentation.

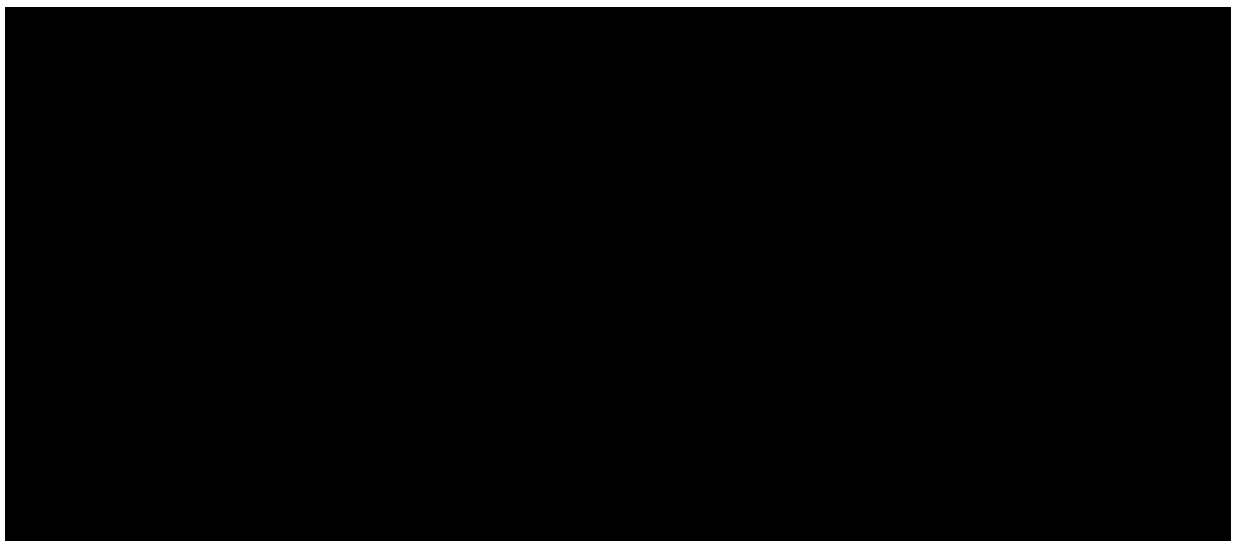
Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

### **8.4.3 Pregnancy and assessments of fertility**

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. A serum pregnancy test is performed at screening and a urinary pregnancy test is sufficient at the end of study visit.

### **8.4.4 Appropriateness of safety measurements**

The safety assessments selected are appropriate evaluations of ocular and systemic health in presbyopic subjects administered UNR844-CI ophthalmic solution.



## 9 Study discontinuation and completion

### 9.1 Discontinuation

#### 9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject decision
- Pregnancy
- Use of prohibited medications or therapies as described in [Table 6-2](#)
- Unsatisfactory therapeutic effect
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unmasking

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 9.1.2](#)). **Where possible, they should return for the assessments indicated in the assessment schedule.** If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, or letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New/concomitant treatments
- AEs/SAEs

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section ([Section 6.6.2](#)).

### **9.1.2 Withdrawal of informed consent**

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, AND
- Does not allow further collection of personal data, AND
- Does not want any further study-related contacts

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table ([Table 8-1](#)).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

### **9.1.3 Lost to follow-up**

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject (e.g., dates of telephone calls, registered letters). A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

### **9.1.4 Early study termination by the sponsor**

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the

subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs of the early termination of the trial.

## **9.2 Study completion and post-study treatment**

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All randomized and/or treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in [Section 10.1.3](#). Documentation of attempts to contact the subject should be recorded in the source documentation.

## **10 Safety monitoring and reporting**

### **10.1 Definition of adverse events and reporting requirements**

#### **10.1.1 Adverse events**

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of AE must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to [Section 10.1.2](#)):

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

2. Its relationship to the study treatment
  - If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see [Section 10.1.2](#) for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
  - dose not changed
  - drug interrupted/withdrawn
6. Its outcome (i.e., its recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days (or end of study visit, whichever is longer) following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

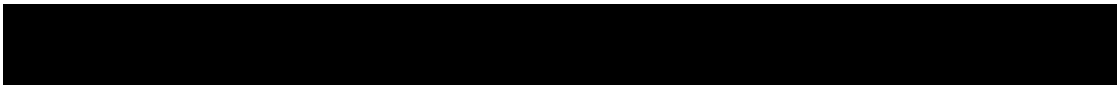
Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- They induce clinical signs or symptoms
- They are considered clinically significant
- They require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered to be non-typical in subjects with the underlying disease.

### **10.1.2 Serious adverse events**

A SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical condition(s) which meets any one of the following criteria:



- Fatal
- Life-threatening
  - Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the subject's general condition
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Is medically significant (i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above)

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant”. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

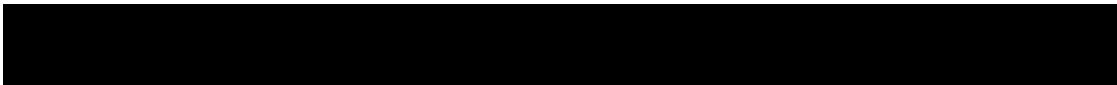
All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective if a clinical event has occurred ([Section 10.1.5](#)).

### **10.1.3 SAE reporting**

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis Safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator site file provided to each site.



All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB (i.e., a new occurrence) and is thought to be related to the study treatment, a Novartis Safety Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

#### **10.1.4 Pregnancy reporting**

##### **Pregnancies**

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

#### **10.1.5 Reporting of study treatment errors including misuse/abuse**

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the "Study treatment (Summary)" eCRF irrespective of whether or not associated with an AE/SAE and reported to Novartis Safety only if associated with an SAE. Misuse or abuse will

be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator’s awareness.

**Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse**

Treatment error type	Document in Study treatment (Summary) eCRF	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections ([Section 10.1.1](#), [Section 10.1.2](#) and [Section 10.1.3](#)).

## 10.2 Additional Safety Monitoring

Not applicable.

## 11 Data Collection and Database management

### 11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulation (CFR) Part 11 requirements. Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into the eCRF is complete and accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

### 11.2 Database management and quality control

Novartis personnel or designated contract research organization (CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator



site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) dispensed to the subject will be tracked using IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to Novartis personnel. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unmasked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

### **11.3 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture/data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by Novartis or designated CRO. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

## **12 Data analysis and statistical methods**

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

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

### **12.1 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 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.

### **12.2 Subject demographics and other baseline characteristics**

Demographic and other baseline data including disease characteristics 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 and preferred term, by treatment group.

### **12.3 Treatments**

The Safety Set 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.

The duration of exposure in days to UNR844-Cl or placebo will be summarized by means of descriptive statistics using the Safety Set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system, by treatment group.

### **12.4 Analysis of the primary endpoint(s)**

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.

#### **12.4.1 Definition of primary endpoint(s)**

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 6-2), after prohibited medication changes (Table 6-3) 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 12.4.3
- Population level summary - difference in variable means between treatment conditions at Month 3

#### 12.4.2 Statistical model, hypothesis, 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 and the strata that were assigned at randomization. The strata information will be based on the data obtained from 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:

$$H_0: \delta_1 = 0 \text{ vs. } H_a: \delta_1 > 0$$

where  $\delta_1$  is the difference of change from baseline in numbers of letters read correctly between the UNR844-C1 and placebo at Month 3.

The model will include the change from baseline in binocular DCNVA at Month 3 as the dependent variable, binocular DCNVA at baseline as the covariate and treatment group and age group stratum at randomization as factors.

#### 12.4.3 Handling of missing values/censoring/discontinuations

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 as the covariate, treatment group and age group, assessment visit, interaction of treatment group and assessment visit as the fixed effect 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.

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

For subjects who either (1) fulfilled the protocol definition of having taken prohibited medications or therapy, or made prohibited medication changes (Section 6.2.2), 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, Missing at Random (MAR) method will be used for imputation.

#### **12.4.4 Sensitivity and 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, which is always observed. There is no missing data imputation for the efficacy endpoint of this supportive analysis.

#### **12.5 Analysis of secondary endpoints**

There are two secondary endpoints, one for efficacy and one for safety.

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-C1 or placebo treatment.

The secondary endpoint for safety is the frequency of treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs) in all subjects after UNR844-C1 or placebo treatment.

##### **12.5.1 Efficacy endpoint**

The secondary efficacy endpoint, the proportion of subjects aged 45 to 55 years achieving 75 or more ETDRS letters in binocular DCNVA at Month 3, is based on the data observed in the FAS population, according to the treatment group patients 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 test at one-sided 5% level of significance.

Assuming the following hypotheses will be tested:

$$H_0: \delta_2 = 0 \text{ vs. } H_a: \delta_2 > 0$$

where  $\delta_2$  is the difference of proportion of subjects achieving 75 or more ETDRS letters in binocular DCNVA between the UNR844-C1 and placebo at Month 3.

The estimand for the secondary efficacy endpoint is closely related to the estimand for the primary efficacy endpoint. For subjects who has a DCNVA assessment at Month 3, 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, 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.

### **12.5.2 Safety endpoints**

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

Summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (TEAEs). 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.

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 in the following ways:

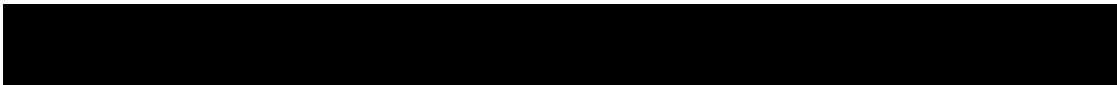
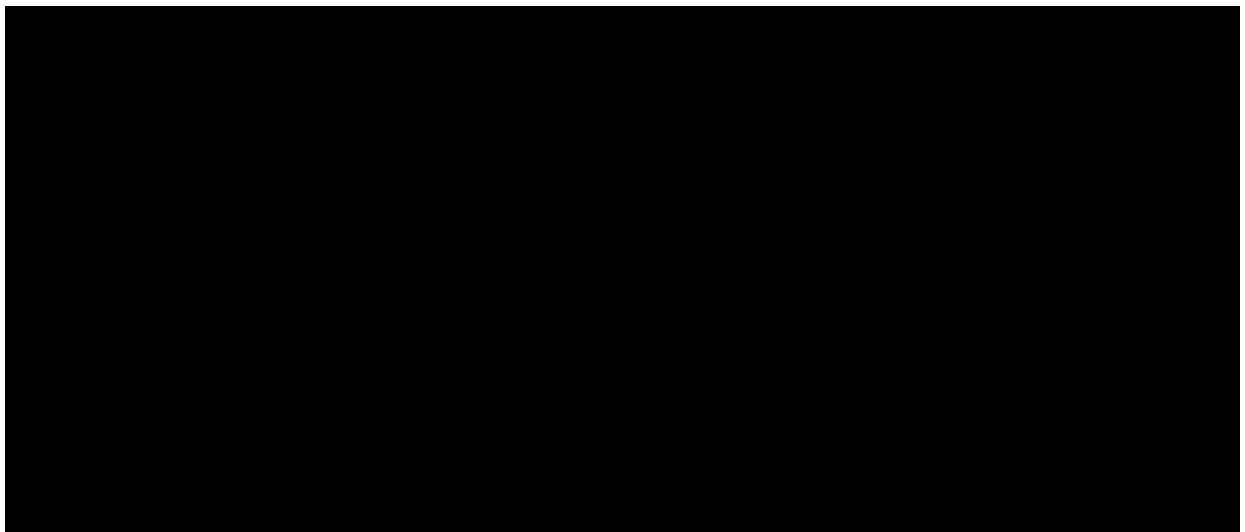
- Overall summary of subjects with any TEAE, any severe TEAE, any study drug related TEAE, any TEAE leading to study drug discontinuation, any TESAE, any study drug related TESAE
- TEAE by primary system organ class and preferred term
- TEAE by descending frequency and preferred term for ocular and non-ocular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

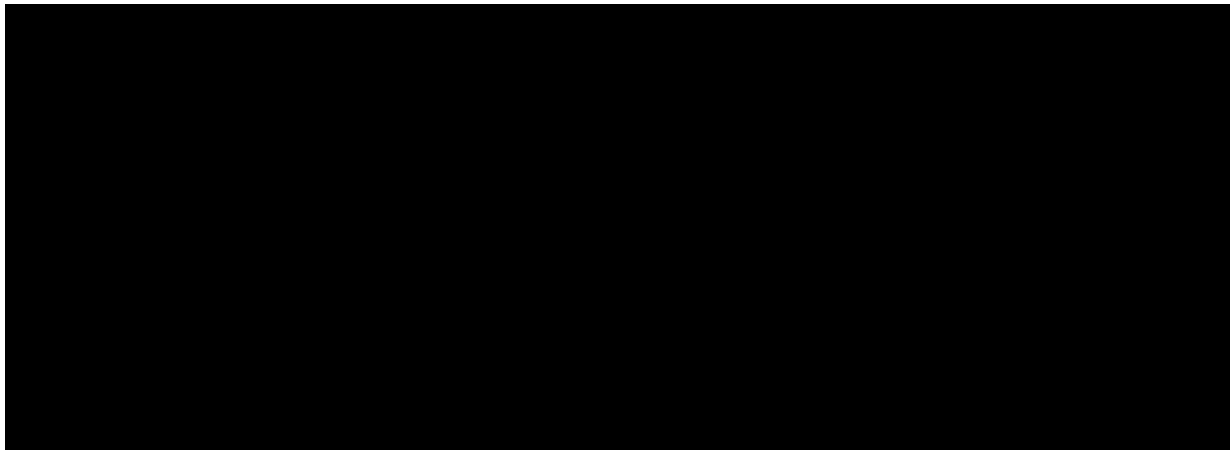
Any other AEs or SAEs will be listed.

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.

### **Vital signs**

All vital signs data will be listed by treatment group, subject, and visit/time. Summary statistics will be provided by treatment and visit/time.





## **12.7 Interim analyses**

Not applicable.

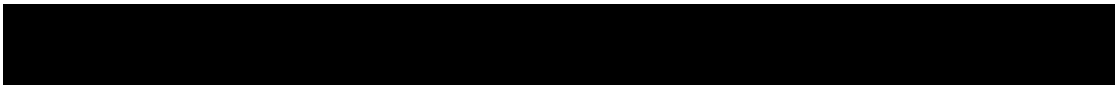
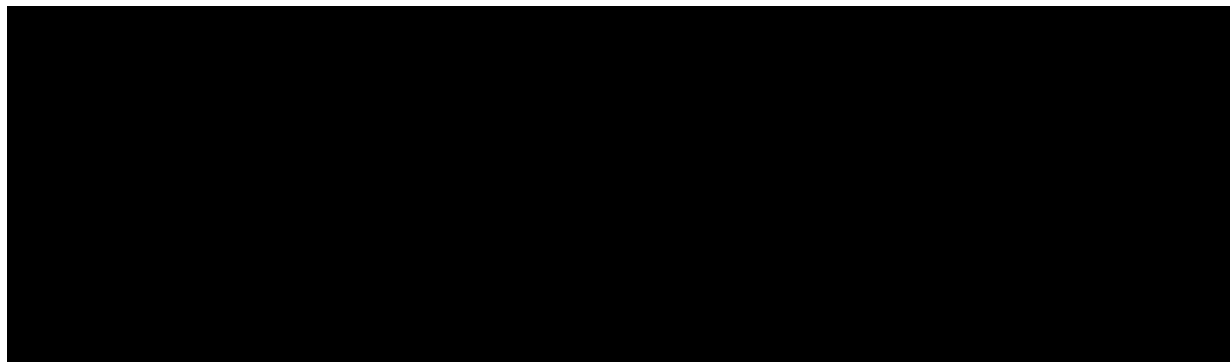
## **12.8 Sample size calculation**

### **12.8.1 Primary endpoint(s)**

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.

### **12.8.2 Secondary endpoint(s)**

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-CI 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.



## **13 Ethical considerations and administrative procedures**

### **13.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

### **13.2 Responsibilities of the investigator and IRB/IEC**

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

### **13.3 Publication of study protocol and results**

The protocol will be registered in a publicly accessible database such as *clinicaltrials.gov*. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., *clinicaltrials.gov*).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that are provided prior to study start.

### **13.4 Quality Control and Quality Assurance**

Novartis maintains a robust Quality Management System that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures, and are performed according to written Novartis processes.

## **14 Protocol adherence**

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be

administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

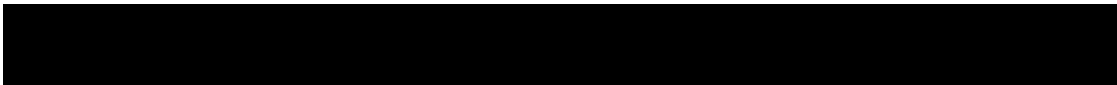
Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB and health authorities, where required, it cannot be implemented.

#### **14.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB at the study site should be informed according to local regulations.





## 15 References

References are available upon request

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **16 Appendices**

Not applicable.

