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Novartis Research and Development

UNR844

Clinical Trial Protocol CUNR844A2202 / NCT04806503

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

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification System
BAC	Benzalkonium chloride
BCDVA	Best-corrected distance visual acuity
BP	Blood Pressure
BSE	Better-seeing eye
CFR	Code of Federal Regulations
ClinRO	Clinician Reported Outcomes
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease - 19
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTT	Clinical Trial Team
DCNVA	Distance-corrected near visual acuity
DDE	Direct Data Entry
DLT	Dose Limiting Toxicity
ED50	Effective dose
EDC	Electronic Data Capture
EMA	European Medicines Agency
Emax	Maximum Effect
EOS	End of Study
[redacted]	[redacted]
eSource	Electronic Source
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full analysis set
GCP	Good Clinical Practice
GCS	Global Clinical Supply
HbA1C	Hemoglobin A1C
HPßCD	Hydroxypropyl ß cyclodextrin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDEEL	Impact of Dry Eye on Everyday Life
IEC	Independent Ethics Committee
IN	Investigator Notification
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology

[redacted]

IUD	Intrauterine device
IUS	Intrauterine system
LA	Lipoic Acid
LoA	Limits of Agreement
MAR	Missing at Random
MCP-Mod	Multiple Comparison Procedure - Modeling
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Multilevel Modelling for Repeated Measures
[redacted]	[redacted]
[redacted]	[redacted]
NCNVA	Near corrected near visual acuity
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ObsRO	Observer Reported Outcomes
OD	Oculus Dexter
OS	Oculus Sinister
OU	Oculus Uterque
[redacted]	[redacted]
PerfO	Performance Outcomes
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
[redacted]	[redacted]
QMS	Quality Management System
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQ	Standardized MedDRA Query
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
[redacted]	[redacted]
UI	Unmasked Individual
US	United States
VA	Visual Acuity
WHO	World Health Organization
WoC	Withdrawal of Consent
WSE	Worse-seeing eye

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	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 paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.

[redacted]

Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or 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 participant
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

[redacted]

Amendment v02 (03-Sep-2021)

Amendment rationale

[redacted] The 30 days phone call follow up and SAE reporting after end of study treatment is corrected to end of study visit. Further clarification for safety reporting is included for subjects who discontinue study treatment during the 3 month treatment period.

The amendment also includes correcting a typographical error in inclusion # 5. There are also typographical errors and clarifications provided on other minor aspects of the protocol.

Changes to the protocol

1. Section 5.1 Inclusion Criteria

   In inclusion criterion # 5, DCNVA is corrected to NCNVA since the VA is currently assessed using near correction at 40 cm. The same correction is made in the protocol summary.

2. Section 8-1 Assessment Schedule

   Safety lab data will be transferred to Novartis database. Therefore, footnote # 1, assessment to be recorded in the source documentation only, is deleted for Hematology, Clinical Chemistry, Urinalysis and Pregnancy test (serum).

   The assessment related to the Trial Feedback Questionnaire is removed from Table 8-1, since this is not a study assessment and will be used to collect overall experience with Novartis clinical trials.

3. Section 8.2 Participant demographics/other baseline characteristics

   Room illumination range for measuring non-dilated pupil size has been revised from 8-15 lux to 25-60 lux. This change has been made based on the calibration of the new light sensor on the electronic visual acuity system provide for use in the study.

   [redacted]

5. Section 8.4 Safety, Table 8-2 Safety Assessment Specification

   In the Refractive Status, Cyclopentolate 1% is now indicated as an example to give some flexibility to the sites.

6. Section 8.5.1 Clinical Outcome Assessments (COAs)

   [redacted]

[redacted]

[redacted]

8. Section 9.2 Study completion and post study treatment

   A correction was made to the treatment period, to reflect the correct length, which is 3 months. The clarification about safety follow up for discontinued participants has been moved to Section 9.1.1.

9. Section 10.1.1 Adverse events

   A phrase was added stating that investigational device would be monitored for AE temporal or causality along with the investigational drug. Another statement was added that risks associated with the investigational device can be found in a separate investigational brochure.

10. Section 10.1.3 SAE reporting

    Correction is made for the requirement of a 30 day safety follow up call after the last study visit instead of last study treatment. Additional clarification regarding urgency of SAE reporting is provided.

11. Section 12.4.3 Handling of remaining intercurrent events of primary estimand

    Clarification is provided regarding handling of primary estimand in case of multiple intercurrent events. 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 and Health Authority approval according to local regulations prior to implementation. The changes herein do NOT affect the trial-specific model ICF.

[redacted]

Amendment v01 (19-Jan-2021)

Amendment rationale

[redacted]

The amendment also corrects typographical errors and provides clarifications on certain minor aspects of the protocol.

Changes to the protocol

1. Section 6.1.1 Treatment Compliance

   Removed the statement that the frequency of artificial tears usage during the study will be captured in the e-diary as this will no longer be done.

[redacted]

3. Section 8.3.1 Distance-Corrected Near Visual Acuity using electronic system

   Two binocular DCNVA assessments will be done at all study visits and not in a few visits as in the previous protocol. This change is now aligned with the data flagging planned in the M&S technologies VA system and will help to keep the number of assessments same across visits to avoid any confusion to the sites. The following sentence is added to address this change 'At all study visits starting from Screening, for binocular Table 16-8 DCNVA (using letters) only, two assessments separated by at least 10 min will be done'.

[redacted]

The rest of the changes in Appendix 2 subsections were updated to align with the above-mentioned change.

[redacted]

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.

[redacted]

Protocol summary

Protocol number	CUNR844A2202
Full Title	A randomized, placebo-controlled, double-masked, multi-center, dose-ranging study to evaluate the safety, and efficacy of UNR844 in subjects with presbyopia
Brief title	Study of safety and efficacy of UNR844 in subjects with presbyopia
Sponsor and Clinical Phase	Novartis Phase IIb study
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the study is to determine the optimum dose of UNR844 treatment and duration of effect of UNR844 treatment for further development.
Primary Objective(s)	The primary objective of this study is to characterize the dose-response of UNR844 treatment with respect to change from baseline in binocular distance-corrected near visual acuity using letters, at Month 3.
Secondary Objectives	The secondary objectives includes, characterizing the dose-response of UNR844 based on monocular distance-corrected near visual acuity at Month 3 and to assess the duration of effect after stopping UNR844 treatment using change in binocular and monocular distance-corrected near visual acuity from Month 4 to Month 12. Additionally, the study will also evaluate the proportion of participants gaining at least 0.3 logMAR in binocular and monocular DCNVA from baseline at Month 3.
Study design	This is a randomized, placebo-controlled, double-masked, multi-arm, parallel-group, multi-center study. Eligible subjects will be randomized 1:1:1:1:1 to receive: UNR844 dose concentrations of 5 mg/mL, 13.3 mg/mL, 23 mg/mL and 30 mg/mL or placebo dosed one drop in each eye twice-daily for 3 months.
Study population	Approximately 225 male or female presbyopic participants aged 45 to 55 years will be enrolled
Key Inclusion criteria	• Phakic male or female participants aged 45 to 55 years, inclusive, at the Screening visit. • Monocular and binocular distance-corrected near visual acuity at 40 cm distance worse than 0.3 logMAR at the Screening and Baseline visits. • Binocular distance-corrected near visual acuity at baseline must not be different by more than 0.1 logMAR from the corresponding assessment at the Screening visit. • Need a minimum near addition prescription of +1.00 D or more to achieve binocular near-corrected near visual acuity (NCNVA) of at least 0.0 logMAR at 40 cm distance, as assessed by the Investigator, at the Screening visit.

Key Exclusion criteria	• Best-corrected distance visual acuity worse than 0.0 logMAR at 4 m distance in either eye at the Screening visit. • Spherical equivalent greater than +4.0 D or less than -4.0 D, based on manifest refraction, in either eye at the Screening visit. • Astigmatism of greater than 1.25 D, based on manifest refraction, in either eye at the Screening visit. • Difference in manifest refraction spherical equivalent of greater than 0.75 D between eyes at the Screening visit. • 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
Study treatment	Participants will be randomized equally to one of five treatment arms, consisting of: • Placebo eye drops, twice-a-day for three months • UNR844 5 mg/mL eye drops, twice-a-day for three months • UNR844 13.3 mg/mL eye drops, twice-a-day for three months • UNR844 23 mg/mL eye drops, twice-a-day for three months • UNR844 30 mg/mL eye drops, twice-a-day for three months
Key Efficacy assessments	• Binocular distance-corrected near visual acuity at 40 cm
Key safety assessments	• Adverse event monitoring • Ophthalmic examinations [redacted] • Refractive status for each eye
Other assessments	• Distance-corrected near visual acuity using letters at 40 cm for each eye [redacted]
Data analysis	The primary objective of the study is to characterize the dose response relationship among UNR844 doses 0 mg/mL, 5 mg/mL, 13.3 mg/mL, 23 mg/mL and 30 mg/mL dosed twice-daily at Month 3. This will be evaluated by measuring the binocular DCNVA (letters) in logMAR using the electronic visual acuity system. The null hypothesis of flat dose-response relationship for change from baseline in binocular DCNVA at Month 3 as compared to placebo will be tested at a one-sided significance level of 2.5% against the alternative hypothesis of a monotonic decreasing dose response relationship. MCP-Mod methodology is utilized to test for a dose-response signal and estimate the dose-response relationship. One of the secondary objectives is to characterize the dose response relationship among various UNR844 doses at Month 3, with change from baseline in monocular DCNVA at Month 3 for the worse-seeing eye (WSE) and better-seeing eye (BSE) as the endpoints. The same null and alternative

[redacted]

	hypotheses as the primary will be considered, by utilizing the MCP-Mod to test for a dose-response signal and estimate the dose-response relationship. The other secondary objective is to evaluate the efficacy of improving DCNVA in presbyopic participants, with the corresponding endpoints gaining at least 3 lines (change from baseline of </= - 0.3 logMAR) in binocular, worse-seeing eye and better-seeing eye, respectively at Month 3. No formal testing will be done for the objective. A logistic regression model, by adjusting for baseline DCNVA and age (grouped as 45 to 50 years and 51 to 55 years), will be fitted to obtain pairwise comparison of each dose versus placebo. The third secondary objective is to assess the duration of effect using change in DCNVA after Month 3 with various dose concentrations of UNR844. The corresponding endpoint is DCNVA during treatment and treatment holiday, i.e., from baseline till Month 12. No formal hypothesis testing will be undertaken. An individualized nonlinear mixed effect model will be fitted to assess the effect over time.
Key words	Presbyopia, near visual acuity, adults, randomized study, placebo

[redacted]

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.

Alpha-R-lipoic acid choline ester eye drops solution (Novartis product code UNR844, formerly known as EV06), is being developed as a topical pharmacological treatment for presbyopia. UNR844's active ingredient, a salt of alpha-R-lipoic acid choline ester, has been shown to improve the topical ocular delivery of arlipoic acid (lipoic acid or LA) to the aqueous humor Garner and Garner 2016. Arlipoic acid is thought to be further metabolized in the lens fiber cells to dihydrolipoic acid that may act to reduce age-related disulfide bonds between lens proteins, restoring lens elasticity. Similarly, UNR844 is also expected to be metabolized in other ocular tissues such as cornea, iris and conjunctiva, with no known adverse effects Khan et al 2011.

UNR844 1.3% (13.3 mg/mL) eye drops solution was evaluated in a randomized, double-masked, placebo-controlled clinical study with 75 participants with presbyopia in Study EV-C-002 (Novartis study code: CUNR844A2201). Fifty participants were treated with UNR844 one drop to each eye twice a day for up to three months, while 25 participants received placebo treatment. UNR844 was well tolerated and there were no safety issues identified. After three months, participants treated with UNR844 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. Of those participants who were followed up for seven months after completing the treatment, the mean improvement in DCNVA largely persisted throughout this period in Study EV-C-003 (Novartis study code: CUNR844A2201E1). Another study using UNR844 1.3% in 124 presbyopic participants of age 45 to 65 years was also completed (CUNR844A2203). No safety concerns were identified and the results supported further evaluation of the compound.

The previous studies evaluated the chloride salt of UNR844, and the tosylate form of UNR844 will be evaluated in the current study (CUNR844A2202) for dose-finding purposes.

[redacted]

1.2 Purpose

The purpose of the study is to determine the optimum dose of UNR844 tosylate treatment and duration of effect of UNR844 treatment for further development.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Characterize dose-response of UNR844 for change from baseline in binocular DCNVA at Month 3.	• Change from baseline in binocular DCNVA assessed using letters at Month 3
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Characterize dose response of UNR844 as measured by change from baseline in monocular DCNVA at Month 3	• Change from baseline in monocular DCNVA, assessed using letters (i.e., worse-seeing eye and better-seeing eye) at Month 3
• Assess the duration of effect using change in DCNVA after Month 3 with various dose concentrations of UNR844	• Binocular and monocular DCNVA assessed using letters, over time after Month 3 (i.e., Month 4 to Month 12)
• Evaluate the efficacy of improving DCNVA in presbyopic participants, as measured by proportion of participants gaining at least 0.3 logMAR DCNVA at Month 3	• Proportion of participants gaining at least 0.3 logMAR in binocular and monocular (worse-seeing eye and better-seeing eye) DCNVA assessed using letters (without near correction) from baseline at Month 3
[redacted]	

2.1 Primary estimands

The clinical question of interest is:

What is the efficacy attributable to different doses of UNR844 received after 3 months of treatment, taking into account any unfavorable effect of the drug such as discontinuation due to unsatisfactory therapeutic effect or AE?

The primary estimand is described by the following attributes:

1. Population: Participants aged 45 to 55 years with presbyopia. Further details about the population are provided in Section 5.
2. Primary variable: Change from baseline in binocular DCNVA at Month 3
3. Treatment of interest: the randomized treatment (different doses) of the investigational treatment UNR844 administered or the placebo treatment) taken up to Month 3, assuming no further benefit after data collection for participants who discontinue treatment due to adverse events or unsatisfactory therapeutic events.

Handling of remaining intercurrent events, with the corresponding assumption that these intercurrent events had not occurred:

- Use of prohibited medications or therapy, or changes in prohibited medication (hypothetical strategy)
- Study treatment discontinuation due to other reasons (hypothetical strategy)

The summary measure: difference in variable means between treatments.

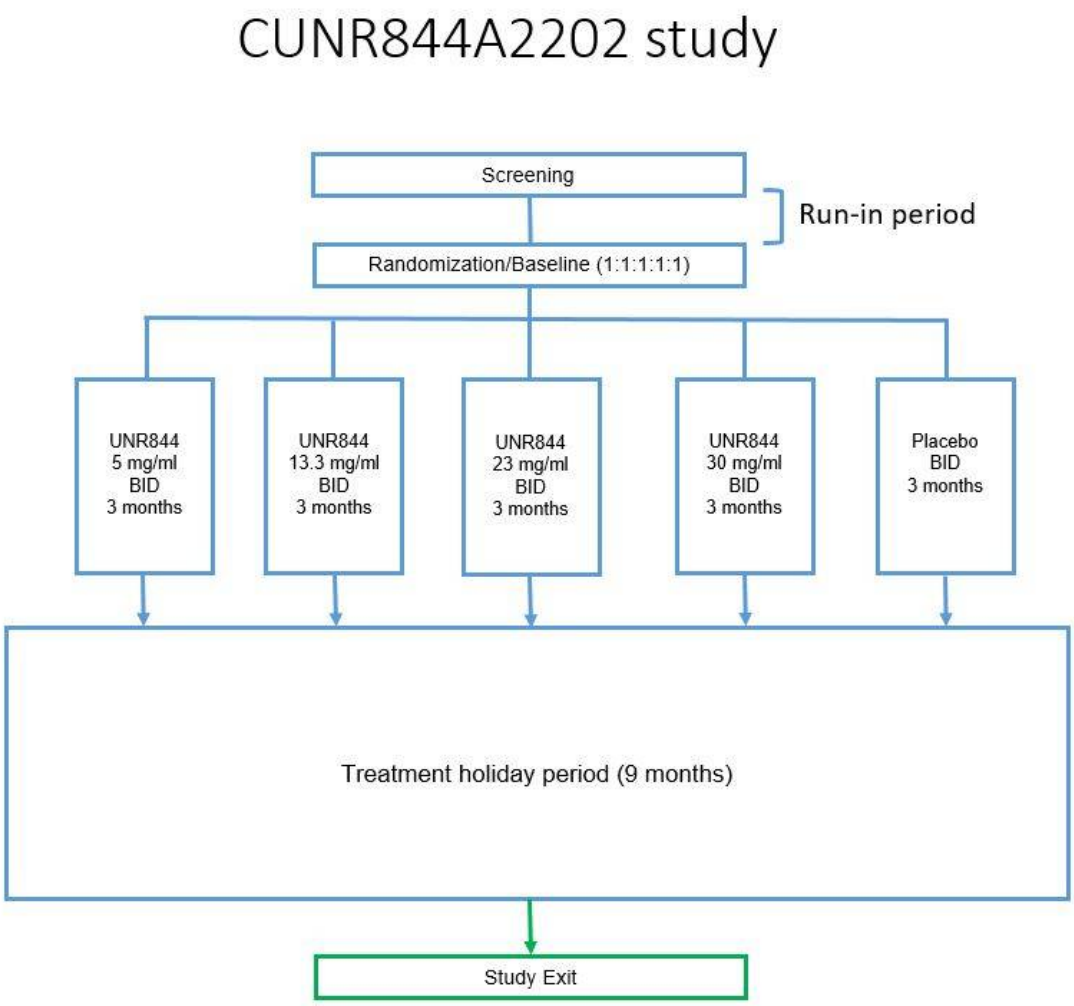
2.2 Secondary estimands

Not applicable.

[redacted]

3 Study design

Figure 3-1 Study design



This is a randomized, placebo-controlled, double-masked, multi-arm, parallel-group, multi-center study.

The 13-month study will consist of:

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

[redacted]

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

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

Participants will undergo a 1 week run-in period where they will be assessed for entry criteria during the Screening visit. During the run-in period, participants will administer 1 drop of artificial tears twice-a-day (1 drop in the morning and 1 drop in the evening) in each eye at home. This run-in period is designed to help minimize any potential variability in DCNVA caused due to initial ocular surface issues and help to establish an accurate baseline prior to randomization. The run-in period will help to exclude participants with a change in DCNVA of 0.1 logMAR difference between Screening and Baseline.

Participants will be dosed with the various concentrations of UNR844 in both eyes for 3 months. An interim analysis will be performed on the 3-month safety and efficacy results. This analysis will be performed by a separate unmasked study team that will have no other involvement in the study. The results of this interim analysis will be used to select the optimum dose concentration.

The duration of effect of UNR844 (i.e., how long does the improvement in DCNVA last) with respect to DCNVA will be evaluated during the 9-month treatment holiday period.

4 Rationale

4.1 Rationale for study design

The study is designed as a randomized, parallel group, placebo-controlled, double-masked, multi-center study. Double-masking and randomization are used to minimize any bias associated with treatment knowledge. Randomization ratio is 1:1:1:1:1 to the five treatment arms, and randomization will be stratified by baseline binocular DCNVA to account for different near visual acuity starting levels, region to account for possible regional differences and age group 45 to 50 years and 51 to 55 years.

After the treatment course, participants will be followed for nine months. This duration is based on results from the previous CUNR844A2201E1 study, where the improvement in DCNVA due to UNR844 treatment persisted largely for approximately seven months on average.

4.1.1 Rationale for choice of background therapy

Currently, there are no pharmacological therapies approved for presbyopia. Participants will be able to use optical correction (i.e., spectacles), if needed, after completing study assessments.

Upon signing the informed consent form, participants who currently wear contact lenses (including multifocal contact lenses) will then be instructed to stop wearing soft contact lenses approximately 1 week prior to Screening visit and in the case of hard or toric contact lenses

[redacted]

approximately 2 weeks prior to Screening visit. Participants will be provided with spectacles to wear at home during the entire study period to replace their habitual contact lenses.

4.2 Rationale for dose/regimen and duration of treatment

The study will evaluate UNR844 dose concentrations of 5 mg/mL, 13.3 mg/mL, 23 mg/mL and 30 mg/mL. The 5mg/mL is the lowest concentration tested in ocular nonclinical PK studies that showed adequate exposure, the 13.3 mg/mL concentration is equivalent in free base UNR844 concentration to that previously assessed in the CUNR844A2201 and CUNR844A2203 clinical studies, and the 30 mg/mL concentration is the maximum feasible concentration of UNR844. The range of concentrations are expected to provide sufficient data to help model the dose-response relationship of UNR844.

Twice-a-day administration will be evaluated in this study. This is a common dose frequency with ocular eye drops, and is in part based on rabbit pharmacokinetic studies which measured time dependent concentrations of UNR844 in the anterior chamber. More frequent dosing is associated with increased user inconvenience.

Treatment duration of three months will be evaluated. Results from previous clinical studies using UNR844 suggested that efficacy is achieved by a 3-month treatment course.

The selected dose regimens are supported by non-clinical toxicity study results in the rabbit and the dog species of up to 40 mg/mL, administered three times-a-day over three months.

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

The control in this study is placebo eye drops, which comprise of the inactive ingredients in the UNR844 eye drop except hydroxypropyl-beta-cyclodextrin (HPβCD). The placebo also includes preservative benzalkonium chloride (BAC).

The aim of the study is to evaluate the safety and efficacy of UNR844 in presbyopia, hence placebo is an appropriate comparator in this non-serious condition with no approved pharmacological therapies.

4.4 Purpose of Interim Analysis

There are two interim analyses planned in the study. The objective of the first interim analysis is to determine whether the overall null hypothesis of a flat dose response can be rejected and will be done when all participants complete the Month 3 visit. The second interim analysis will be performed to assess the retention of the treatment effect over the 9 months treatment holiday period. Additional details are provided in Section 12.7.

4.5 Risks and benefits

In two previous clinical studies (CUNR844A2201 and CUNR844A2203), there were no safety concerns identified. There were no serious adverse events (SAEs) and no participants discontinued from the study because of an adverse event (AE). Please refer to the Investigator's Brochure for details on the reported AEs.

[redacted]

Non-clinical studies with UNR844, which will be evaluated in this study, did not show any safety or tolerability concerns. Safety of UNR844 is also being evaluated in a study in healthy participants and information from this study will be provided in an update to the Investigator's Brochure prior to the start of the CUNR844A2202 study.

The risk to participants 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 eye drops solution on fertility, pregnancy and lactation have not been studied. No safety concerns are expected based on the nature of UNR844. 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 exhibited a beneficial effect with respect to near visual acuity in presbyopic participants in a prior clinical study, it cannot be guaranteed that a similar effect would be observed in this study.

5 Study Population

Approximately 225 male or female presbyopic participants aged 45 to 55 years will be enrolled.

With an estimated 5% drop-out rate during the treatment period (i.e., 3 months) this would mean approximately 210 participants would complete 3 months of treatment period. All efforts would be taken to minimize/maintain the drop-out rate during the 9 months treatment holiday period. If the power of the study drops below 82%, additional participants will be enrolled to replace drop outs due to COVID-19.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Phakic male or female participants aged 45 to 55 years, inclusive, at the Screening visit.
3. Monocular and binocular distance-corrected near visual acuity at 40 cm distance worse than 0.3 logMAR at the Screening and Baseline visits.
4. Binocular distance-corrected near visual acuity at baseline must not be different by more than 0.1 logMAR from the corresponding assessment at the Screening visit.
5. Need a minimum near addition prescription of +1.00 D or more to achieve binocular near corrected near visual acuity (NCNVA) of at least 0.0 logMAR at 40 cm distance, as assessed by the Investigator, at the Screening visit.

[redacted]

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Best-corrected distance visual acuity worse than 0.0 logMAR at 4 m distance in either eye at the Screening visit.
2. Spherical equivalent greater than +4.0 D or less than -4.0 D, based on manifest refraction, in either eye at the Screening visit.
3. Astigmatism of greater than 1.25 D, based on manifest refraction, in either eye at the Screening visit.
4. Difference of greater than 0.50D between manifest refraction spherical equivalent and the cycloplegic refraction spherical equivalent.
5. Difference in manifest refraction spherical equivalent of greater than 0.75 D between eyes at the Screening visit.
6. Unequal pupil diameters with a difference of greater than 1 mm between eyes.
7. Non-circular pupil assessed by the Investigator to be related to a pathologic cause.
8. Contraindication to pupil dilation in either eye or a history of untreated narrow angles or currently occludable angles in either eye.
9. Insufficient pupillary dilation that precludes observation of the fundus or lens in either eye, in the opinion of the investigator.
10. Contact lens wear within 1 week for soft lenses and 2 weeks for hard or toric lenses, prior to Screening visit and for the duration of the study.
11. Prior history or current diagnosis of accommodative spasm, accommodative insufficiencies or other accommodative issues, except age-related accommodative issues related to presbyopia.
12. 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.
13. Secondary cause of presbyopia in either eye (e.g., damage to lens, zonules or ciliary muscle, multiple sclerosis, and myasthenia gravis).
14. Any active ocular infection (i.e., bacterial, viral, parasitic or fungal), or inflammation, or a history of herpetic ocular infection in either eye at the Screening or Baseline visit.
15. History of idiopathic or auto-immune uveitis in either eye.
16. Ocular surface disease with a IDEEL blurry vision score greater than "slightly" AND corneal staining in the central zone greater than grade 1 at Screening visit.
17. History or current diagnosis of treated or untreated glaucoma of any type.
18. History of penetrating ocular trauma, significant blunt ocular trauma or uveitis in either eye.
19. Prior intraocular/extraocular surgery or laser surgery of any kind in either eye, including cataract surgery in either eye during the study period.
20. History of hypersensitivity to any of the study treatments (including placebo) or its inactive ingredients or to active ingredients of similar chemical classes.
21. Change in dose of any medication known to affect accommodation, pupil size or intraocular pressure during the study, as listed in Table 6-3. Participants who have been on

[redacted]

stable dose of such medications for at least three months before the Screening visit and who are not expected to change the dose/ regimen or discontinue the medication are eligible for the study.

22. Use of other investigational drugs within 5 half-lives or within 30 days of the Screening visit, until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
23. Prior therapy for presbyopia other than physical optical correction (e.g., supplements, medications, training exercises, ciliary body electrostimulation, corneal implants surgery).
24. History of clinically significant cardiac abnormalities or cerebrovascular conditions.
25. Suboptimally controlled diabetes mellitus (i.e., HbA1c 7% or more at the Screening visit) or history of insulin autoimmune disease.
26. History of or current use of arlipoic acid or dihydrolipoic acid oral supplements or eye drops.
27. Prior participation in a clinical study evaluating UNR844 or EV06.
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
31. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. 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 bilateral 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 6 months prior to screening). For female participants 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). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository
    - 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 (IUD) or intrauterine system (IUS)

[redacted]

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.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF

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 bilateral 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. Participants 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).

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
UNR844 5 mg/mL	Eye drops solution	Topical ocular	Opaque plastic bottle	Novartis global
UNR844 13.3 mg/mL	Eye drops solution	Topical ocular	Opaque plastic bottle	Novartis global
UNR844 23 mg/mL	Eye drops solution	Topical ocular	Opaque plastic bottle	Novartis global
UNR844 30 mg/mL	Eye drops solution	Topical ocular	Opaque plastic bottle	Novartis global
Placebo	Eye drops solution	Topical ocular	Opaque plastic bottle	Novartis global

6.1.2 Additional study treatments

Novartis will provide artificial tears to the participants for administration of one-drop twice-dailybetween screening and the baseline visits at home.

Artificial tears will also be administered to participants prior to any visual acuity assessments during the study visit days in the clinic. Instill one drop of artificial tears in each eye at least 30 minutes before starting visual acuity assessments. Novartis will provide Investigators with artificial tears for such use at the site. These should be stored according to the manufacturer's instructions.

[redacted]

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

6.1.3 Treatment arms/group

Participants will be assigned at the Baseline visit to one of the following five treatment arms in a ratio of 1:1:1:1:1.

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

6.1.4 Treatment duration

The planned treatment duration is three months.

6.2 Other treatment(s)

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 enrolled, contact Novartis/sponsor 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 and for the entire duration of the study.

Table 6-2 Prohibited medications and therapies

Medication/therapy	Prohibition period	Action taken after baseline visit
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 (see Section 9.1.1)
Arlipoic acid or dihydrolipoic acid oral supplements or eye drops (other than study treatment)	Any time after screening and throughout the study	Discontinue study treatment (see Section 9.1.1)

[redacted]

Medication/therapy	Prohibition period	Action taken after baseline visit
Other investigational medicinal product or therapy	Any time after screening and throughout the study	Discontinue study treatment (see Section 9.1.1)
Therapy for presbyopia other than physical 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 (see Section 9.1.1)

Participants are not allowed to start, stop or change dosing of the following treatments after the screening visit and for the entire duration of the study, 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
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

[redacted]

Medication	Prohibition period	Action taken
Any over-the counter or prescription ocular medications (except artificial tear products	Any time after screening and throughout the study No change in the brand and regimen of the artificial tears during 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

Participants who use their own artificial tears during the study after Baseline visit must wait at least 10-15 minutes after dosing study treatment, to avoid any washout of study drug. Participants 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 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available. In situations where a participant is re-screened, a new Participant No. will be assigned.

6.3.2 Treatment assignment, randomization

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

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant 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 Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

[redacted]

Randomization will be stratified based on binocular DCNVA (0.5 logMAR or less; 0.52 logMAR or more) and age (45 to 50 years and 51 to 55 years) at baseline, and region.

Participants will be randomized 1:1:1:1:1 within each stratum to either treatment arm. The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Participants, investigator and site staff, persons performing the assessments, and monitors 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 unmasked 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 treatment that are all identical in packaging, labeling, schedule of administration and appearance.

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

Table 6-4 Masked and unmasked plan

	Time or Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**Interim Analysis**
Participants	M	M	M	M
Site staff	M	M	M*	M
Global Clinical Supply and Randomization Office	M	M	M	M
Unmasked sponsor staff e.g. for study treatment re-supply, unmasked monitor(s), sample analyst(s)	M	UI	UI	UI
Unmasked Pharmacovigilance sponsor staff	M	M	UI	M
Statistician/statistical programmer/ data analysts	M	M	M	UI
All other sponsor staff not identified above	M	M	M	M

Key:
UI: Allowed to be unmasked on individual participant level
M: Remains masked
*Investigator will be unmasked in case of emergency breaking of treatment code (Section 6.6.2)

[redacted]

6.5 Dose escalation and dose modification

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

For participants who do not tolerate the protocol-specified dosing regimen, study treatment should be discontinued and, if possible, the subject is continued to be monitored in the study (Section 9.1.1).

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Participants will be instructed at each on-therapy study visit to take the study treatment exactly as prescribed.

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. Participants will be provided with an ediary to complete every day after they administer study drug. Compliance will be assessed by the investigator and/or study personnel at each visit. Participants 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 and ediary data. 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 participant safely. Masked codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. However, participants can continue to participate in the study (Section 9.1.1). Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant 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
- participant number

[redacted]

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unmasking 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 participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document. Study medication will be dispensed to the patient at the clinic as outlined in table of assessments in Section 8. In the event of COVID-19 pandemic it may be necessary to make alternative arrangements (e.g., curb-side pickup or home delivery) for the participant to obtain study medication at the designated study visit as allowed by local regulations, site capabilities and participant's comfort level.

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 label.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant 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. Participants 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.

[redacted]

6.7.1.2 Handling of additional treatment

Artificial tears will be provided to the participants for use at home between the Screening and Baseline visits. Participants will return artificial tears at the Baseline visit.

6.7.2 Instruction for prescribing and taking study treatment

Participants should take the study treatment at approximately the same time each day, twice-a-day. For example, morning dose at approximately 8 am and evening dose at approximately 8 pm. If a dose is missed and it has been more than six hours from the approximate usual time of dosing, participants 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 participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant 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 participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH 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/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant 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 participant.

The following informed consents are included in this study:

- Main study consent
- As applicable, Pregnancy Outcomes Reporting Consent for female Participants.
- [redacted]

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.

[redacted]

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants 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. Missed or rescheduled visits should not lead to automatic discontinuation. Participants 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 the adverse event and concomitant medications recorded on the CRF.

Assessments assigned to the screening visit can be conducted on separate days as close to each other as possible. Visual acuity and refraction assessments must be performed on the same day.

According to evaluation performed for this study all visits must be performed at site. No evaluation at home is possible with the exception of the [redacted], in case of COVID pandemic.

If the COVID-19 pandemic limits or prevents on-site study visits and other study assessments may not be performed, alternative methods of safety monitoring may be implemented. Depending on local regulations, site capabilities and participant's visit status in the study, phone calls or virtual contacts (e.g., teleconsult) can be performed for safety follow-up for the duration of the pandemic, until it is safe for the participant to visit the site again.

If a participant is unable to attend the scheduled baseline visit due to illness, the run-in period could be extended up to 2 weeks from the Screening visit. During this extended run-in period, participants will continue to administer the Sponsor provided artificial tears as directed.

[redacted]

Table 8-1 Assessment Schedule

Period	Run-in	Treatment					Treatment holiday period								
Visit Name	**Screening**	**Baseline**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12/EOS**
Days	**-7**	**1**	**14**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**
Informed consent	X														
Demography	X														
Medical history/current medical conditions	X														
Prior medications	X	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion criteria	X	X													
Vital Signs	X	X				X			X			X			X
Physical Examination[1]	X														X
[redacted]															
Distance-corrected near visual acuity (letters)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Period	Run-in	Treatment					Treatment holiday period								
Visit Name	Screening	Baseline	W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12/EOS
Days	-7	1	14	30	60	90	120	150	180	210	240	270	300	330	360
[redacted]															
IDEEL blurry vision question[1]	X														
Cycloplegic refraction	X														
Pupil size (non-dilated)	X														
Slit lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Corneal Staining	X	X	X			X						X			X
Intraocular Pressure (IOP)	X	X	X	X	X	X	X		X			X			X
Dilated fundus exam	X					X									X
Hematology	X					X									
Clinical Chemistry	X					X									
Urinalysis	X					X									
Pregnancy Test (serum)	X														
Pregnancy Test (urine)[1]						X									X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispensation		X		X	X										
Study completion information															X
eDiary compliance assessment		X	X	X	X	X									

[redacted]

Period	Run-in	Treatment					Treatment holiday period								
Visit Name	Screening	Baseline	W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12/EOS
Days	-7	1	14	30	60	90	120	150	180	210	240	270	300	330	360

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[1] Assessment to be recorded in the source documentation only

[redacted]

[3] Duplicate binocular DCNVA assessments will be completed at all visits

[redacted]

[redacted]

[redacted]

8.1 Screening

Screening

If a participant is unable to attend the baseline visit after the extended run-in period due to prolonged recovery from an illness, the participant can be re-screened once at a later time after discussion with the Sponsor.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail, that the participant was not randomized.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Subject demographic and baseline characteristic data to be collected on all participants 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 CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Participants will provide their response to the blurry vision question from the IDEEL symptom bother questionnaire at Screening visit. Non-dilated pupil size will be assessed in a room illumination of 25 to 60 lux at Screening visit for eligibility.

Baseline ocular characteristics, including DCNVA, [redacted] will be collected.

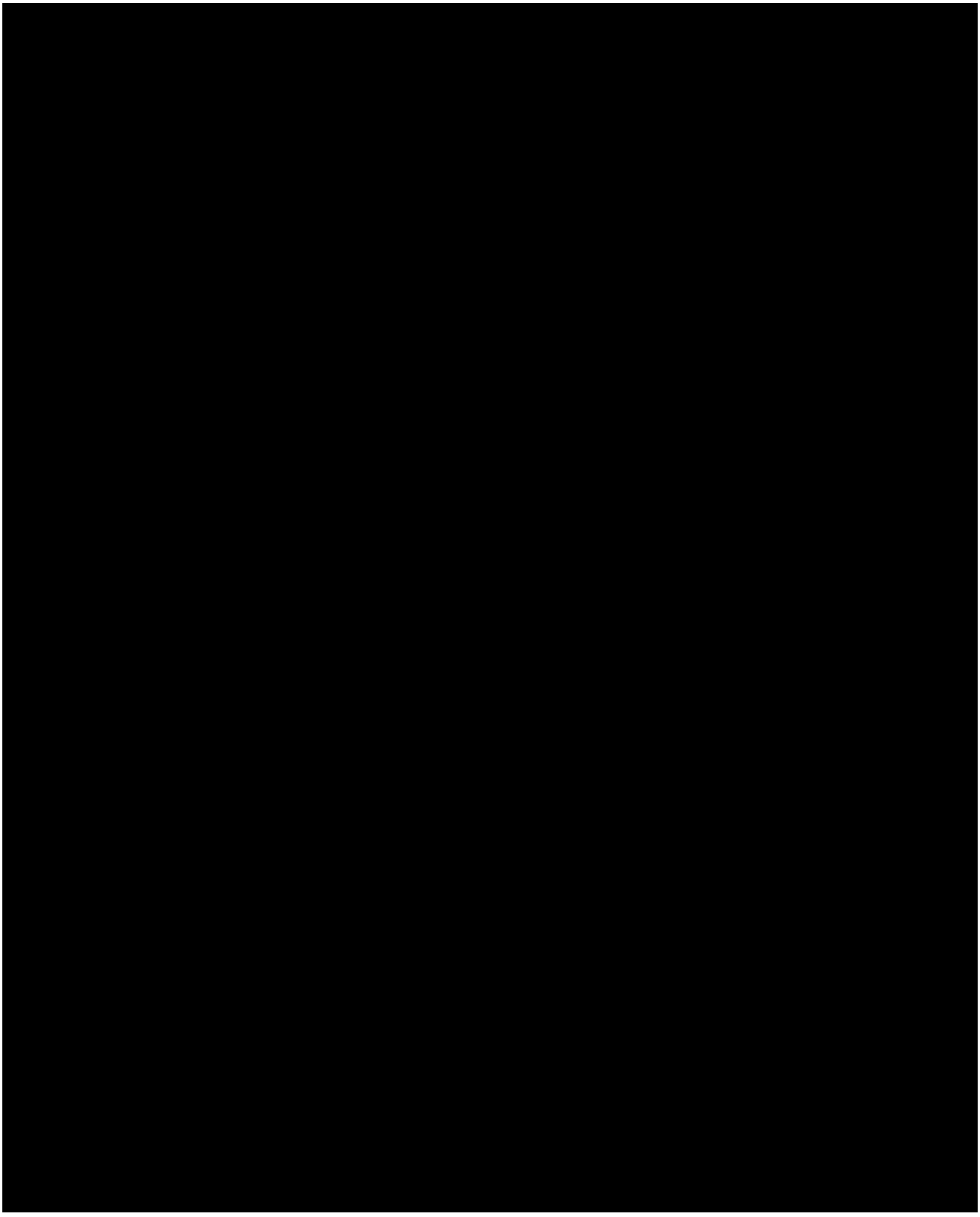
8.3 Efficacy

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

At the clinic during the scheduled study visits, instill one drop of Novartis provided artificial tear product in each eye at least 30 minutes prior to starting visual acuity assessments. The time of artificial tears administration should be recorded in the source. Participants are encouraged not to engage in near work such as reading books or continuous use of mobile phone for texting or browsing while waiting at the site for study assessments. Participants should minimize the

[redacted]

use of their near correction (i.e., multifocal spectacles or reading glasses), prior to all study assessments during their clinic visits, including Screening visit.



[redacted]

8.3.3 Appropriateness of efficacy assessments

Presbyopia manifests as difficulty with near vision tasks, such as reading. Hence the use of DCNVA is an appropriate measure to evaluate if UNR844 can benefit participants with presbyopia.

Similarly, currently optical correction is used to improve near vision in presbyopia. [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.

For details on AE collection and reporting, refer to Section 10.1.

Table 8-2 Safety assessment specification

Assessment	Specification
Physical examination	A routine physical examination will be performed at the screening visit and at Month 12 and will include an evaluation of the general appearance (e.g., skin, peripheral blood perfusion, extremities, lymph nodes). 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 signs	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

[redacted]

Assessment	Specification
	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.

[redacted]

Assessment	Specification
[redacted]	
Ophthalmic Examination	The following ocular assessments will be performed as per the schedule assessment: 1. Slit-lamp biomicroscopy include evaluation of the lids/lashes, conjunctiva, cornea (including corneal staining using the grading scale below), 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 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. 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. 3. Dilated fundus examination will be performed in both eyes. Any clinically significant findings must be documented in the eCRF.

8.4.1 Corneal fluorescein staining

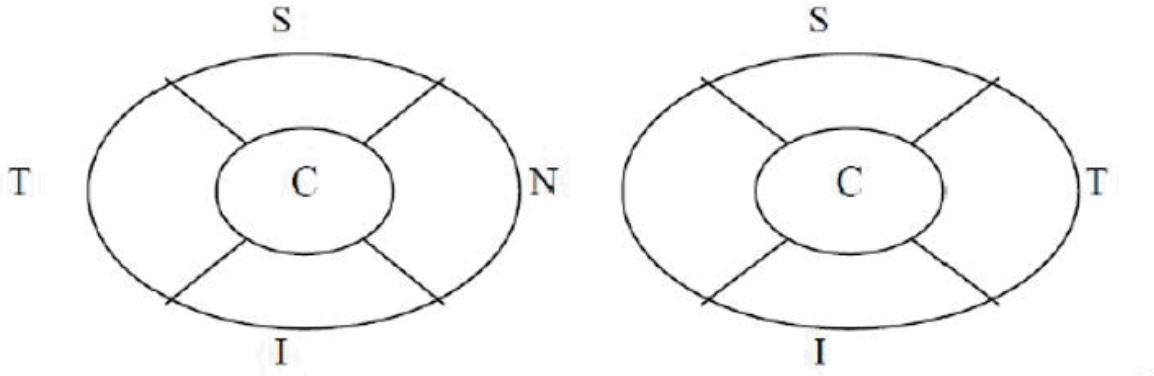
Corneal fluorescein staining will be determined on a scale of 0 - 3 as the average from each of 5 zones (central plus 4 quadrants). Results will be recorded for each zone. This test will be performed using 5 µL of non-preserved 2% sodium fluorescein or equivalent per country instilled into the lower palpebral conjunctiva of both eyes.

[redacted]

Table 8-3 Corneal staining scale

OD		OS
Degree of Staining	**Region**	**Degree of Staining**
0....1....2....3	C-Central	0....1....2....3
0....1....2....3	S-Superior	0....1....2....3
0....1....2....3	T-Temporal	0....1....2....3
0....1....2....3	N-Nasal	0....1....2....3
0....1....2....3	I-Inferior	0....1....2....3

Figure 8-1 Corneal staining scale



Grade 0 = Normal → No staining

Grade 1 = Mild → Superficial stippling micropunctate staining

Grade 2 = Moderate → Macropunctate staining with some coalescent areas

Grade 3 = Severe → Numerous coalescent macropunctate areas and/or patches

8.4.2 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. All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met.

[redacted]

Table 8-4 Laboratory evaluations

Test Category	Test Name
Hematology	Hemoglobin, platelets, white blood cells, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, and other)
Chemistry	Albumin, alkaline phosphatase, serum alanine aminotransferase, serum aspartate aminotransferase, lactate dehydrogenase, calcium, magnesium, phosphorus, sodium, potassium, creatinine, direct bilirubin, total bilirubin, urea, uric acid, amylase, lipase, glucose (non-fasting), and glycated hemoglobin (HbA1c).
Urinalysis	Macroscopic (Dipstick) panel - color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen Microscopic panel - red blood cells, white blood cells, casts, crystals, bacteria and epithelial cells. Microscopic analysis is only required if any parameter of the macroscopic panel is abnormal.
Pregnancy Test	serum pregnancy test at screening/ urine pregnancy test will be done at the other required time points.

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 urine pregnancy test is sufficient at other timepoints. However, a positive urinary pregnancy test needs to be confirmed with a serum pregnancy test.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Appropriateness of safety measurements

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

[redacted]

8.5 Additional assessments

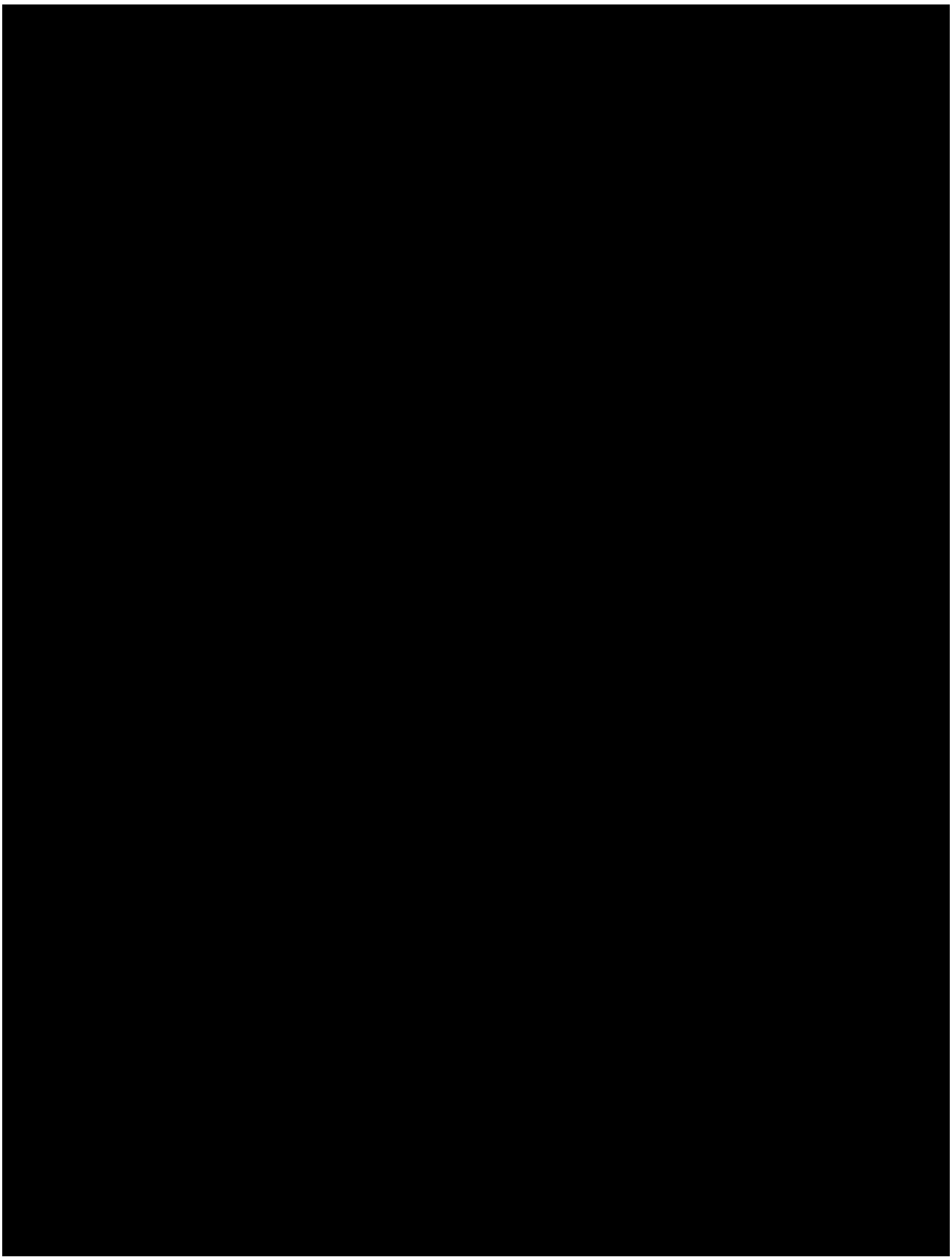
8.5.1 Clinical Outcome Assessments (COAs)

Clinician Reported Outcomes (ClinRO)

Not applicable.

[redacted]

[redacted]



[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Unsatisfactory therapeutic effect
- Use of prohibited treatment as per recommendations in Section 6.2.2
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unmasking

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

Participants 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, letter) should be made to contact the participant/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 participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. 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
- Adverse Events / Serious Adverse Events

[redacted]

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

If discontinuation occurs because treatment code has been broken, please refer to Section 6.6.2.

All randomized and/or treated participants who discontinued the study during the 3 month treatment period 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.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments 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 participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

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 participants 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 participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

[redacted]

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, Participants must be seen as soon as possible 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 local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant 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.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a 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 or an investigational device [redacted]

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

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

The occurrence of adverse events 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 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):

[redacted]

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 the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy are not caused by the trial drug, they happen in spite of its administration and/or lack of efficacy 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

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 interventions required to treat it, and the outcome.

[redacted]

Abnormal laboratory values or test results constitute adverse events 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 subject with the underlying condition.

[redacted]

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(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 participant 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 participant'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, e.g. defined as an event that jeopardizes the participant 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 participant 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 (please refer to the ICH E2D Guidelines).

All new 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 serious adverse event irrespective if a clinical event has occurred. (Section 10.1.5)

[redacted]

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit 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 folder provided to each site.

Information about all SAEs is collected and recorded on the appropriate eSAE CRF pages. In the event that the eSAE CRF pages are not available (after last study visit), SAEs must be reported using the paper SAE Report Form. All applicable sections of the form must be completed in order to provide a clinically thorough report.

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 immediately, without undue delay, and under **no circumstances later than 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 Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) 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 in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported by the investigator to Novartis Safety **within 24 hours** of learning of its occurrence, including pregnancies where the participant was exposed to placebo. 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. Standard Novartis Safety follow-ups are conducted for reports of pregnancy and data on health of newborns are collected for one year after delivery. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug should be reported.

[redacted]

Information on whether the baby was breast fed should be included where appropriate. 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 recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to 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 Dosing CRF (Yes/No)	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.

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 Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the 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.

[redacted]

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, 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 participant data for archiving at the investigational site.

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

[redacted]

11.2 Database management and quality control

Novartis personnel (or designated 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 (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (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 the clinical team and monitor. 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**. 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. eSource DDE or 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 participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, 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

[redacted]

performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & 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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The final analysis for the primary efficacy endpoint will be performed when at least 225 randomized participants have completed all assessments of the treatment period at Month 3 visit or discontinued from the study.

Additional analysis may be also conducted to evaluate the impact of COVID-19 pandemic.

Further technical details and discussions of the statistical considerations will be provided in the SAP.

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 Participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, Participants will be analyzed according to the treatment and strata (if applicable) they have been assigned to during the randomization procedure. FAS will be used for all efficacy variables, unless otherwise stated.

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

[redacted]

12.2 Participant 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, 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 Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

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

12.4.1 Definition of primary endpoint(s)/estimand(s)

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

12.4.2 Statistical model, hypothesis, and method of analysis

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

Testing an overall dose-response signal

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

Five candidate models to describe the potential dose-response shape (defined in terms of change from baseline in binocular DCNVA at Month 3 as compared to placebo) were selected (see Figure 12-1 of the plot of the candidate models)

[redacted]

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

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

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

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

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

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

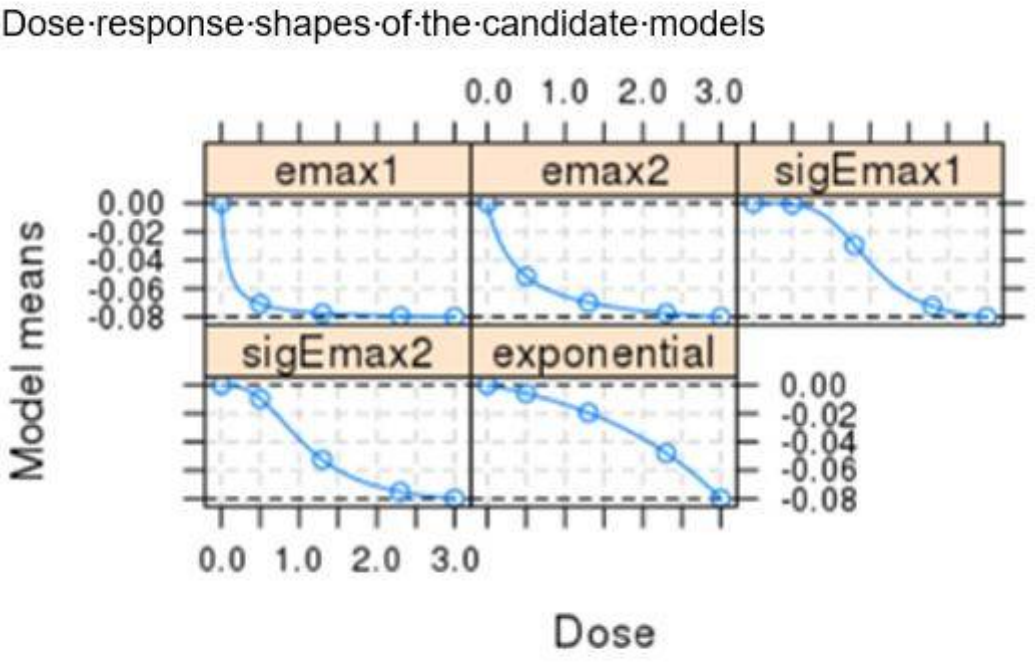
Bootstrap model averaging will be used to estimate the dose-response curve, the target dose and to derive confidence intervals. Parametric bootstrap simulation will be performed using the least-squares dose group estimates based on their multivariate normal distribution.

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

In addition to the information collected during the 3 months treatment period for MCP-Mod analysis, the information collected during the 9 months treatment free period for the estimation of duration of effect will be taken into consideration for the selection of dose for future studies.

[redacted]

Figure 12-1 Dose-response shapes of the candidate models



The primary, sensitivity and two supportive estimands are noted in the table below together with their key attributes. The estimands outlined will be discussed in further detail in the SAP.

[redacted]

Table 12-1 Primary, sensitivity, and supportive estimands

	Primary Estimand	Supportive Estimand 1	Supportive Estimand 2
Question	What is the efficacy attributable to different doses of UNR844 received after 3 months of treatment, taking into account any unfavorable effect of the drug such as discontinuation due to unsatisfactory therapeutic effect or AE?	What is the true efficacy of different doses of UNR844, when administered as planned for 3 months, in Participants who had no relevant intercurrent events such as discontinuation or use of prohibited medications?	What is the efficacy attributable to the randomly assigned doses of UNR844 after 3 months of treatment, considering the impact of any intercurrent events as inherent part of the assign treatment?
Estimand Definition	Dose-specific difference in mean change from baseline in DCNVA at Month 3 attributable to the initially randomized medication accounting for beneficial and detrimental effect of the drug	Dose-specific difference in mean change from baseline in DCNVA at Month 3 attributable to the study treatment received, excluding the effect of intercurrent events such as discontinuation or use of prohibited medications	Dose-specific difference in mean change from baseline in DCNVA at Month 3 attributable to randomized treatment
Discontinuation due to unsatisfactory therapeutic effect or AE	Primary: Include data collected post discontinuation if available. If not available, impute assuming no further benefit Sensitivity: Exclude data collected post discontinuation and impute assuming no further benefit	Exclude data collected post discontinuation; treat as missing and impute assuming missing at random	Include data collected post discontinuation, if available. If not available, impute assuming no further benefit
Discontinuation due to other reasons	Exclude data collected post discontinuation; treat as missing and impute assuming missing at random	Exclude data collected post discontinuation; treat as missing and impute assuming missing at random	Include data collected post discontinuation, if available. If not available, impute assuming no further benefit
Use of Prohibited medication or therapy, or changes in prohibited medication – Potentially affect efficacy	Exclude data collected post-use of prohibited medication; treat as missing and impute assuming missing at random	Exclude data collected post-use of prohibited medication; treat as missing and impute assuming missing at random	Include data collected post-use of prohibited medication, if available. If not available, impute assuming no further benefit

12.4.3 Handling of remaining intercurrent events of primary estimand

For participants who discontinued study treatment permanently with reason for discontinuation being either adverse event or unsatisfactory therapeutic event, the data collected post discontinuation will be included, if available. If not available, impute assuming no further benefit. For all other intercurrent events, data collected post intercurrent events will be removed; treat as missing and impute assuming missing at random.

If a subject has multiple intercurrent events, treatment discontinuation due to unsatisfactory therapeutic effect or AE will be considered as the priority intercurrent event, and data handling

[redacted]

following this intercurrent event will be according to what's specified above, by ignoring the other intercurrent event(s) of the same subject. If only the other (non-priority) two intercurrent events happen to the same subject, the earliest event will be considered. Data handling following this first intercurrent event will be according to what's specified above.

12.4.4 Handling of missing values not related to intercurrent event

In the case of missing data occurring in other scenarios, i.e., independent of intercurrent events related to response to study treatment, the estimand based on MAR approach will be considered specifically for each treatment arm the participants are assigned. This will result in a reasonable estimate of the true outcome based on the treatment effect observed at 7 months after study treatment discontinuation in CUNR844A2201E1 study.

12.4.5 Sensitivity analyses for primary endpoint/estimand

There will be one sensitivity analysis:

The efficacy endpoint is the same as the primary efficacy analysis, with the only change to exclude data collected post discontinuation and impute assuming no further benefit.

12.4.6 Supplementary analysis

Not applicable.

12.4.7 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. The only difference between this analysis and the primary efficacy analysis is the exclusion of the data collected post discontinuation or post-use of prohibited medications; treat as missing and impute assuming missing at random.

Supportive analysis #2

The efficacy endpoint for Supportive analysis #2 is change from baseline in binocular DCNVA at Month 3. The only difference between this analysis and the Supportive analysis #1 is the inclusion of data collected post discontinuation or post-use of prohibited medication, if available. If not available, impute assuming no further benefit.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

There are three secondary endpoints:

1. Change from baseline in monocular DCNVA (i.e., worse-seeing eye and better-seeing eye) at Month 3;

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- MCP-Mod as described in Section 12.4.2 will be applied to change from baseline in monocular DCNVA at Month 3 for the worse-seeing eye (WSE) and better-seeing eye (BSE), with intercurrent events and missing data handled in the same way as the for the primary estimand and supportive estimand 2 (Section 12.4)

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2. Gain of 3 lines (change from baseline of </= - 0.3 logMAR) in binocular, worse-seeing eye and better-seeing eye respectively at Month 3;
   - For monocular DCNVA, gaining of 3 lines is defined as change from baseline ≤ - 0.3 logMAR in DCNVA and < + 0.1 logMAR in BCDVA.
   - For the endpoints of gaining of 3 lines (change from baseline of 0.3 logMAR) in binocular, worse-seeing eye and better-seeing eye respectively at Month 3, missing data imputation will be done in the same way as for the primary endpoint (Section 12.4), defined for the primary estimand, based on their corresponding continuous endpoints, i.e., binocular and monocular DCNVA. After the imputation, these endpoints will be dichotomized to generate the endpoints of gaining of 3 lines in both eyes, worse-seeing eye and better-seeing eye, respectively at Month 3. Then a logistic regression model, by adjusting for baseline DCNVA and age (grouped as 45 to 50 years and 51 to 55 years), will be fitted to each imputed data set for each of the three endpoints. By applying Rubin's rule to combine results of these individual data sets, pairwise comparison of each dose versus placebo will be obtained for each of the three endpoints.
3. Change from Month 3 in binocular and monocular (worse-seeing and better-seeing eyes) DCNVA over time after Month 3 (i.e., Month 4 to Month 12).

For binocular, worse-seeing and better-seeing eyes, DCNVA over time after Month 3 will be summarized by treatment group and scheduled visits.

For DCNVA data (during treatment and treatment holiday), an individualized nonlinear mixed effect model will be used to describe the data and results will be provided in a separate modeling analysis report and not in the study CSR.

12.5.2 Safety endpoints

Not applicable.

12.5.3 Patient reported outcomes

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

Two interim analyses will be planned for the study:

The first interim analysis will be performed when all patients complete (or discontinue prior to) the Month 3 visit as described in Section 12.4. The major objective of this interim analysis is to determine if the overall null hypothesis of a flat dose-response curve can be rejected.

The second interim analysis will be performed when 60% of the participants complete 6 months (i.e., Month 9) of treatment holiday period. The major objective of this interim analysis is to assess the retention of the treatment effect over the 9 months treatment holiday period.

[redacted]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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

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

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 Harmonized Tripartite Guidelines for Good Clinical Practice, 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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/IECs, 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 and as required in EudraCT. In addition, after study completion and finalization of the study report

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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, EudraCT etc.)

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) 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 SOPs, 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 participants 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/IEC 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/IEC prior to implementation.

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

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Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant 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/IEC at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request

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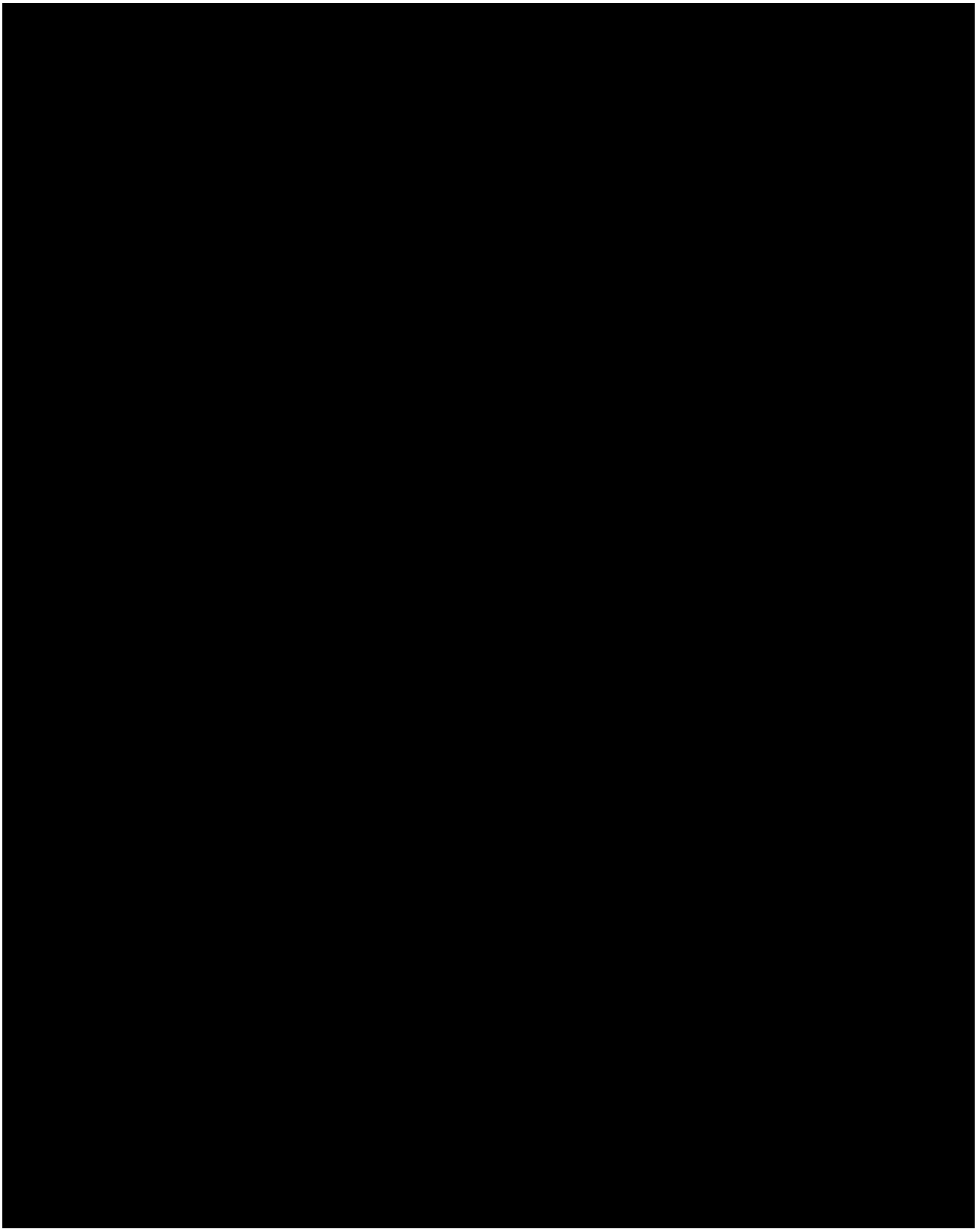

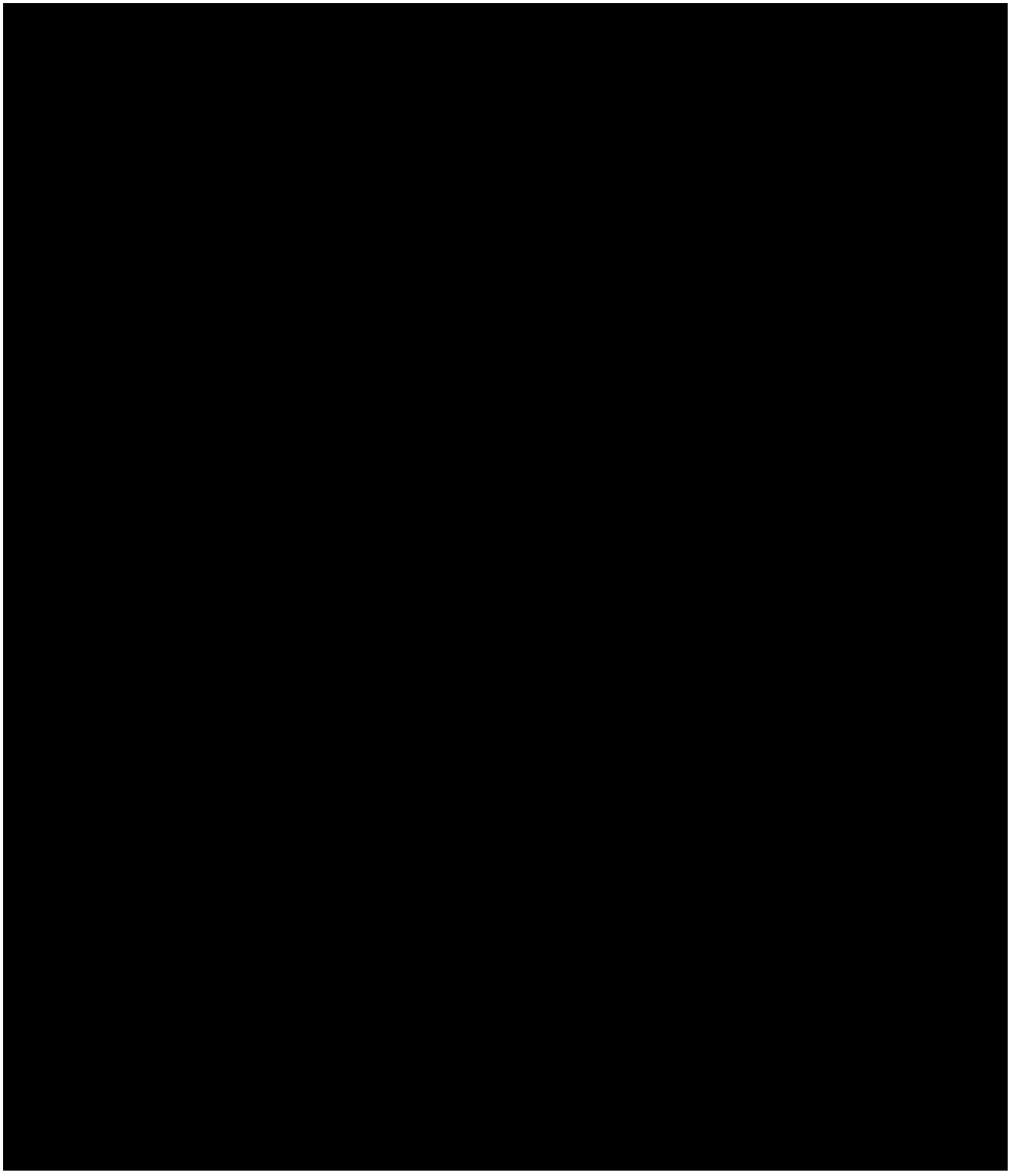

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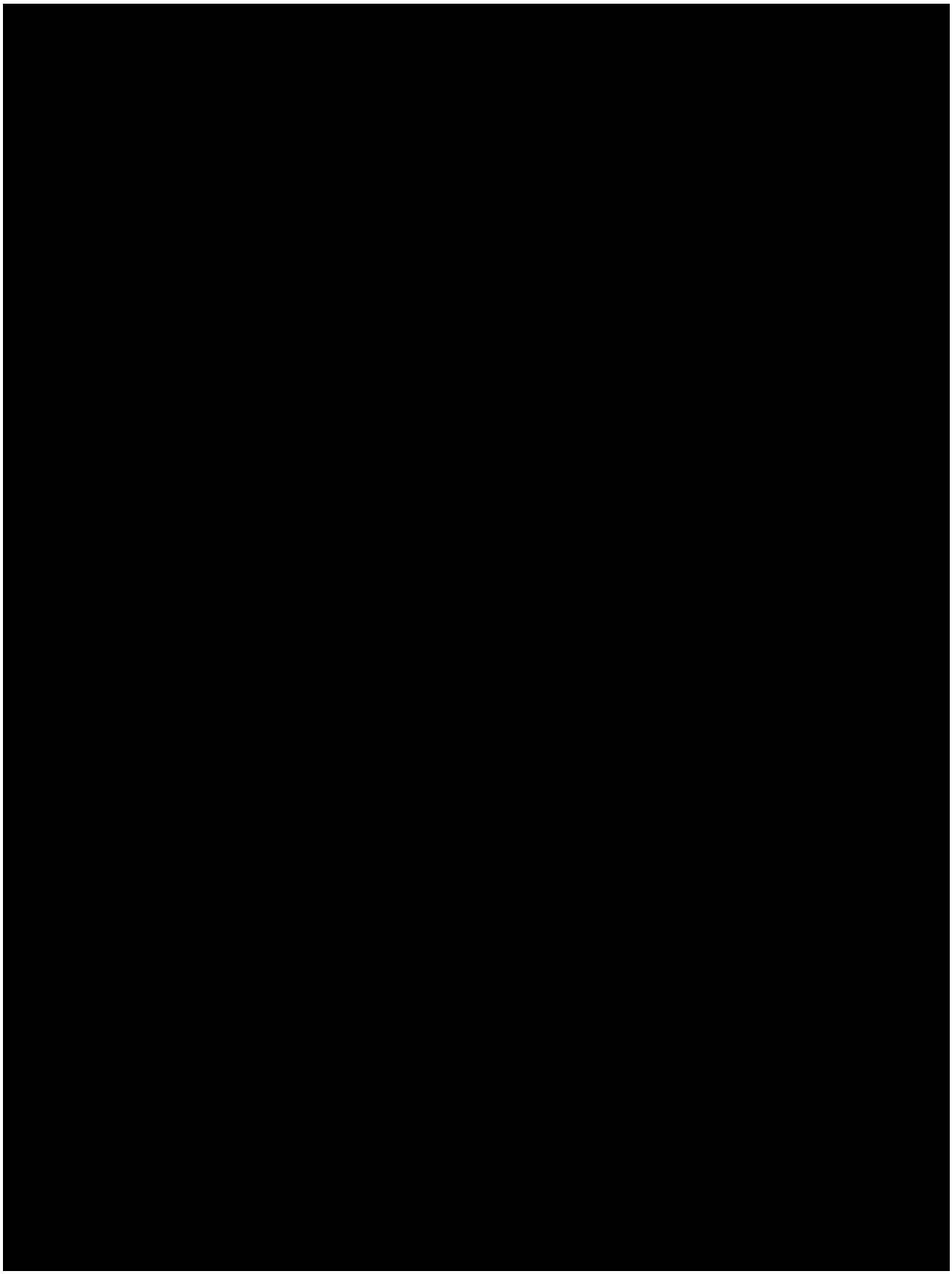

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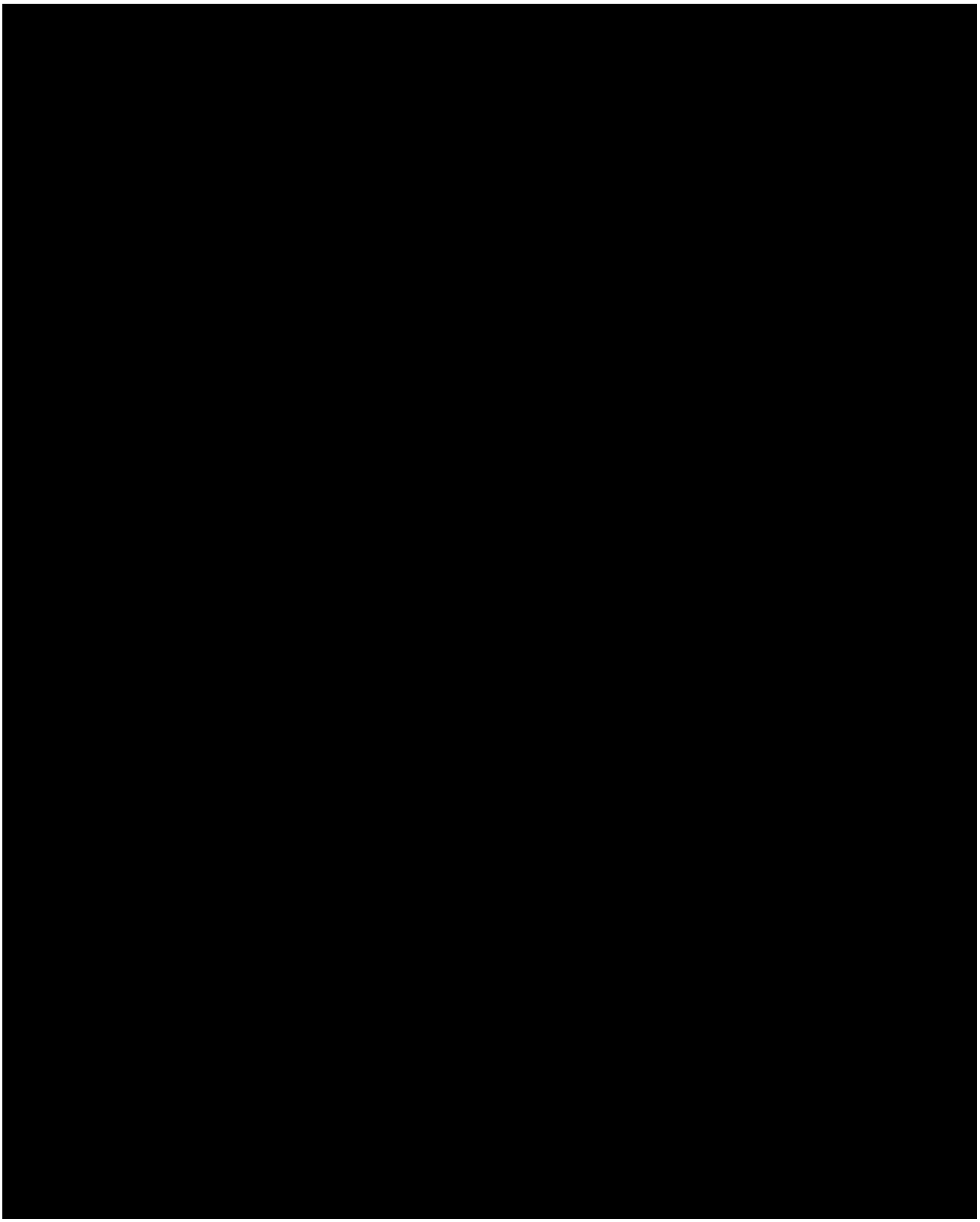

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