Dompé farmaceutici S.p.A.

An 8 Week phase Ib, monocentric, randomized, double-masked, vehicle controlled, parallel group, study with a 24 Week follow-up period to evaluate the safety and potential efficacy of a 180 µg/ml recombinant human nerve growth factor (rhNGF) eye drops solution versus vehicle in patients with glaucoma

Protocol/CIP No: NGF0314

IND Number: 124304

Statistical Analysis Plan

Version 1.0

Final

09 Feb 2018

Author: Paul Koopman/Monika Rost

CROMSOURCE

Signature Page

Signatures for Dompé farmaceutici S.p.A.

Mauro Paolo Ferrari Early Clinical Development Manager	Signature	Date (ddMMMyyyy): 13 FEB 2018
Flavio Mantelli Chief Medical Officer	Signature	Date (ddMMMyyyy): 13 FEB 2018

Signatures for CROMSOURCE

Roberta Baronio Head of Biostatistics and Programming Unit	Signature	Date (ddMMMyyyy):
Monika Rost Senior Statistician	Signature	Date (ddMMMyyyy): 09 FEB 2018

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Signatures for CROMSOURCE

Roberta Baronio Head of Biostatistics and Programming Unit	Signature DAVID JACKSON pp. BIOMETRICS DATA DIRECTOR.	27MAR2018 Date (ddMMMyyyy)
Monika Rost Senior Statistician	Signature	09FEB2018 Date (ddMMMyyyy)

Version History

Version	Date	Reason for Change
Final 1.0	09 Feb 2018	Initial Version

Table of Contents

1 SOPs to be followed

The statistical analysis will be carried out according to the following CROMSOURCE standard operation procedures (SOPs):

SOP number	SOP title
SOP-ST-03	Statistical Analysis Plan
SOP-ST-04	SAS Programming and Validation
SOP-ST-05	Data Review Meeting
SOP-ST-06	Study Unblinding for Analysis
SOP-ST-07	Statistical Report
SOP-ST-08	Trial Statistics File

2 Abbreviations

Acronym	Definition
ADAM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
BCDVA	Best Corrected Distance Visual Acuity
BDRM	Blind Data Review Meeting
CDISC	Clinical Data Interchange Standards Consortium
CSF	Central Subfield Thickness
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
HVF	Humphrey Visual Field
I	Inferior
IIM	Inferior of Inner Ring
IN	Inferior Nasal
INF	Inferior
IOM	Inferior of Outer Ring
IOP	Intraocular Pressure
IT	Inferior Temporal
ITT	Intent-to-Treat Set
MRP	Mitochondrial Redox Potential
N	Nasal
NIM	Nasal of Inner Ring
NOM	Nasal of Outer Ring
OCT	Ocular Coherence Tomography
PT	Preferred Term
QC	Quality Control
rhNGF	Recombinant Human Nerve Growth Factor
RNFL	Retinal Nerve Fiber Layer
S	Superior
SAE	Serious Adverse Event

Acronym	Definition
SAF	Safety Set
SAF-F	Patients in the SAF, who entered the Follow-Up Period
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SIM	Superior of Inner Ring
SN	Superior Nasal
SOC	System Organ Class
SOM	Superior of Outer Ring
SOP	Standard Operation Procedure
ST	Superior Temporal
SUP	Superior
T	Temporal
TEAE	Treatment Emergent Adverse Event
TID	Ter In Die (i.e. Three times a day)
TIM	Temporal of Inner Ring
TLF	Tables, Listings and Figures
TOM	Temporal of Outer Ring
TOT	Total Set
USPON	Unexpected Severe Progression of Optic Neuropathy
VAS	Visual Analogue Scale
WHO-ATC	World Health Organization Anatomical Therapeutic Chemical

3 Protocol / Clinical Investigation Plan

This NGF0314 study is conducted under the sponsorship of Dompé farmaceutici S.p.A. The clinical monitoring, data management, statistical analysis and medical writing are performed by CROMSOURCE under contract and in collaboration with Dompé farmaceutici S.p.A.

This Statistical Analysis Plan (SAP) provides a complete, expanded and detailed description of the planned statistical methods outlined in the study protocol Final Version 2.0 of 04 November 2016. Text that has been copied from the protocol is formatted in italics to indicate that it is identical to the protocol, which will ease the review and will avoid unnecessary alterations to text approved in the protocol.

It lists all Tables, Listings and Figures (TLFs), which will be produced by CROMSOURCE for the main objective and final analyses and are used for inclusion in the Clinical Study Report (CSR) and/or Statistical Report. This excludes presentation of results from mitochondrial redox potential (MRP), which will be reported separately.

3.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of a 180µg/ml TID dose regimen of recombinant human nerve growth factor (rhNGF) eye drop solution administered over 8 weeks versus a vehicle control in patients with progressive primary open-angle glaucoma despite IOP control.

The secondary objectives are to measure the changes in BCDVA, visual field, ERG and structural changes in changes in ganglion cell layer and nerve fiber layer thickness measured by optical coherence tomography. The secondary outcomes will include functional assessments to investigate evidence of a persistent biological effect after discontinuation of the study treatment.

3.2 Study Design

This is a masked, randomized, single-dose, monocentric phase 1b trial of 60 study participants with chronic primary open angle glaucoma. Participants may qualify with either progressive optic neuropathy despite maximal current therapy (i.e. IOP reduction), or with stabilized IOP but diminished vision (central or peripheral). Participants with a qualifying eye will be randomized 2:1 to topical recombinant human nerve growth factor (rhNGF) therapy or vehicle placebo control. Eligible patients will self-administer 1 drop of study medication three times a day in both eyes for 8 weeks of treatment. *Examinations for safety and efficacy will occur one week following initiation of therapy, and at 4, 8, 12 and 32 weeks. All participants in either arm will be followed clinically at 4 weeks after cessation of therapy.*

3.3 Study Schedule

The protocol visit plan and specification of study procedures and examinations per visit is summarized in Table 1 below. *Required procedures for a scheduled visit may be performed over 2 consecutive days.* The Day 0 Therapy Initiation Visit will usually take 2 consecutive days, the 1st day to perform ophthalmologic assessments, to decide on eligibility and to assign randomization at the end of the day, starting the treatments at the beginning of the 2nd day. Administration of the first 2 doses will be performed at site, whereas all consecutive doses will be self-administered by patients.

If a patient returns to the clinic prior to their next scheduled study visit for assessment of an adverse event, an Unscheduled Visit should be conducted. Procedures conducted at the

Unscheduled Visit are at the discretion of the Investigator and may be among the study procedures or additional procedures not performed during the study but deemed necessary by the investigator. The clinical information obtained during any unscheduled visit is to be recorded in the electronic Case Report Forms.

Any patient who exits early from the study must undergo all procedures outlined at Week 8 Visit if the discontinuation occurs at or before Week 8 Visit; the Week 8 Visit assessments should be completed for all patients, as assessments of the Early Exit Visit. Additionally, the Exit (End of Study) *Form must be completed.*

Table 1: Schedule of Events

Scheduled Visit Week	***Baseline Visit (Screening)[1]***	***Day 0 Therapy Initiation***	***Week 1 (± 2 days)***	***Week 4 (±4 days)***	***Week 8 (± 7 days)***	***Week 12 (± 7 days)***	***Week 32 (± 7 days)***
General Assessments							
Informed consent	X						
Randomization		X					
Inclusion / Exclusion criteria	X	X					
Pregnancy test (if applicable)		X			X		
Demographics, Medical History, Medications[2]	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X
Visual System Exams							
Best Corrected Distance Visual Acuity (BCDVA)	X	X			X	X	X
Intraocular Pressure (IOP)[3]	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X
External ocular examination	X	X	X	X	X	X	X
Humphrey 24-2 or 10-2 Visual Field[4]	X[5]	X	X[6]			X[7]	
Dilated Fundus Ophthalmoscopy	X	X			X	X	X
OCT (retinal thickness)		X			X	X	X
Mitochondrial redox potential		X		X	X	X	X
Full field and pattern ERG[8]		X			X	X	X
Study Therapy							
Visual Analogue Scale (VAS) for ocular tolerability		X	X	X	X	X	
Study drug dispensing[9]		X		X			
Assess medication dosing compliance[10]				X	X		

1 *Baseline Screening Visit will occur within 4 weeks prior to initiating therapy.*
2 *Demographic information collected only at screening visit including medications taken within the preceding 30 days.*
3 *IOP testing will be performed using Goldmann Tonometer.*
4 *Visual Field testing will be performed using Sita Standard.*
5 *2 fields on different days for a total of 3 before initiating treatment.*
6 *3 fields within 4 weeks until the end of treatment.*
7 *3 fields within 4 weeks until the end of follow-up.*
8 *Full-field performed once at Therapy Initiation (Day 0) visit, at Week 8, at Week 12 and at Week 32.*
9 *At Day 0 instruct the patient to self-administer drug at home and return to next planned visit.*
10 *At Week 4 and 8 patient will be instructed to return all used and unused investigational product and the freezer bag.*

3.4 Primary and Secondary Outcomes

The primary objective is to evaluate the safety and tolerability of rhNGF vs Vehicle.

The primary safety outcomes of the study are:

- *Unexpectedly severe progression of optic neuropathy as measured by central vision loss, by visual field testing, or by examination of the optic nerve*
- *Intolerance or allergy to the drug*
- *Adverse events affecting ocular function or eye pressure, which differ from those expected in the course of glaucoma, which are thought to be potentially related to the drug*
- *Local or systemic toxicities considered serious adverse events that are potentially related to the drug*

The primary tolerability outcome of the study are:

- Outcome from Ocular tolerability questionnaire using visual analogue scales (VAS)

Exploratory secondary efficacy outcomes based on functional and structural assessments of the study are:

- Change in BCDVA
- Changes in visual field using perimetry
- Changes in ERG including pattern ERG
- Changes in ganglion cell layer and nerve fiber layer thickness measured by optical coherence tomography (OCT)
- Changes in mitochondrial redox potential (not considered in this SAP)

Details for all specified primary and secondary outcomes are provided in section 7.2 of the SAP.

3.5 Interim Analyses

No interim analysis is planned.

However, the database will be locked after all patients have completed their Week 12 Visit and main objectives analysis will be performed on unmasked data. A Blind Data Review Meeting will take place after the last enrolled patient completes Week 12 Visit and before unmasking of the study

At the end of the study (i.e. after all patients have completed Week 32 Visit), an updated analysis will be performed presenting the complete study data.

Further details on the two distinguished analyses are provided in section 9 of this SAP.

3.6 Changes in the Conduct of Study or Planned Analysis compared to Protocol

The following changes of the study conduct did affect the planned analysis:

- Mitochondrial Redox potential: during the set-up process of the eCRF, test type and Index number were identified as endpoints to evaluate MRP. However, it was not possible at the site to identify an index number for each patient for data entry to the eCRF. In July 2017, it was decided by the sponsor, that no data will be entered on the eCRF and reporting of MRP assessments will be performed separately by the investigator.

- Changes in ERG including pattern ERG: during the set-up process of the eCRF, it was planned to assess the following data from performed ERG into the eCRF: Result (Normal/Abnormal), Amplitude A1-B1 Photopic 3.0 (0.5 Hz), Latency ISO-B1 Photopic 3.0 (0.5 Hz), Amplitude ISO-B1 Scotopic 0.01 (0.5 Hz), Latency ISO-B1 Scotopic 0.01 (0.5 Hz), Amplitude ISO-B1 Photopic 3.0 Flicker 30Hz, Latency ISO-B1 Photopic 3.0 Flicker 30 Hz, Amplitude N1-P1 wave oscillatory potential (1 Hz), Latency N1-P1 wave oscillatory potential (1 Hz).

  In July 2017, based on investigator's proposal, it was decided to use phototopic negative response number (phNR) as a more relevant measure of assessing ERG changes (Kim, Park, Ohn, 2010), which will be chosen for analysis and be recorded on the eCRF alternatively.

- Humphrey Visual Field assessment (HVF): it was recognized at site, that for patients with low vision, HVF assessment could not be performed according to SITA-Standard. For these patients the FASTPAC standard will be applied (see protocol clarification letter as of 04AUG2017). The output for these assessments differ from SITA standard by not providing information on mean deviation, standard deviation and visual field index.
  The eCRF was changed to enable a proper statistical evaluation by adding applied algorithm (SITA/FASTPAC) and a qualitative evaluation of the change in visual fields (pre-treatment assessment/improved/no change/worsened, not assessable) to enable a statistical evaluation of secondary endpoint "Change in HVF". However, completion of this qualitative assessment was refused by the investigator. According to sponsor's decision on 17NOV2017, results of HVF assessments will not be analysed but listed only.

  This does not affect the evaluation of primary outcome "Unexpected severe progression of optic neuropathy measured on HVF or optic nerve examination".

The following refinements of the pre-planned analysis in the study protocol were implemented in this SAP:

- The study protocol defines the Safety Set as all treated patients. However, the Safety Set will serve a primary analysis cohort for the primary study objectives. To ensure formal maintenance of randomization, the Safety Set will be refined to "all randomized patients who received at least one study treatment". It is notable, that randomization and dispensation of first study medication are both performed at site within one process. So, it is not expected that a patient would be treated without being randomized.

- Study protocol section 11.5.4 provides specifications of tables and listings for displaying documented AEs. This presentation of data will be aligned to data presentation of other studies investigating rhNGF to facilitate data interpretation. This change is purely organizational without omitting any data presentation described in the study protocol with one exception: due to the relative few numbers of patients, no separate listing of concomitant disease and medications will be provided for patients with adverse events.

4 General Definitions

4.1 Report Language

The TLFs as output of the analyses will be prepared in English.

4.2 Analysis Software

The statistical analysis will be performed using the SAS® statistical software package (Statistical Analysis System, Version 9.3 or later).

5 Data Preparation

5.1 Data Handling and Medical Coding

For data quality control and medical coding, please refer to the Data Management Plan, including the Data Validation Plan in its most recent version.

5.2 CDISC

All output as defined in the SAP will be generated based on CDISC ADaM datasets following ADaM implementation Guide 1.0, as per contract with Dompé farmaceutici S.p.A. SDTM programming will follow SDTM version 1.3 together with SDTM implementation guide 3.1.3.

Specifications for the ADaM datasets (as well as SDTM datasets) are described in a separate document.

5.3 SAS-Programming Quality Level

The following quality level of programming deliverables will be applied, as per contract with Dompé Farmaceutici S.p.A. All statistical output will receive a tailored Quality Control (QC) approach by:

- Full independently double programmed reproduction of CDISC:
  - SDTM datasets
  - ADaM datasets
- Full independently double programmed reproduction of results of
  - Primary endpoint analysis and its underlying analysis dataset(s) and table(s),
  - Randomization merging
  - Analysis population merging, and
  - Visit windows programming
- Listings will not be double programmed.
- All other tables will be given a reduced QC involving independent reproduction (i.e. double programming or manual cross checking a subset of patients) of approximately 20% of the summary results (selection to be agreed upon with the sponsor).
- All tables and listings will undergo comparison with specification (i.e. SAP and templates), cross checking with other tables and listings, a sensibility review and SAS-log review.

6 Analysis Sets and Subgroups

6.1 Analysis Sets

Evaluability for all patients and visits will be determined during a Blind Data Review Meeting, which will take place before unmasking the study for the main objective analysis (i.e. comprising data up to Week 12 Visit).

The Total Set (TOT) will include all patients that have signed informed consent.

The Intent-to-treat Set (ITT) will include all randomized patients and will be used for all exploratory efficacy analyses. All analyses based on the ITT will be summarized by the treatment randomized.

The Safety Set (SAF) will include all randomized patients who receive at least one dose of study medication. This safety population will be used in the analysis of all safety endpoints.

A subset of all patients in the SAF, who entered the Follow-Up Period (SAF-F), will be used in addition to present event-type analyses of the Follow-Up Period. A patient will therefore be considered as entering the Follow-Up Period, if he/she did not terminated the study at or before the Week 8 visit.

All analyses based on the SAF and SAF-F will be summarized by the treatment received.

For the study, both eyes are under investigation. For each patient, a Primary (Study) Eye and a corresponding Secondary Eye will be defined during a Blind Data Review Meeting (BDRM) to enable a patient based presentation of statistical analyses.

For each patient, an eye will be considered as Primary Eye, if

- the eye was treated and
- the investigator considered this eye as qualifying eye.
  If both eyes are considered as qualifying eye, the right eye will be chosen.

The other eye will then be considered as Secondary Eye, if the eye was treated. If the other eye was not treated with study medication, no Secondary Eye will be assigned for this patient.

6.2 Subgroup Definitions

For the presentation of adverse events by age, age categories ‘≤ 65 years’ and ‘>65 years’ will be applied.

7 Definition of Time Points and Analysis Variables

7.1 Definition of Time Points

The study consists of 7 scheduled clinical evaluation visits: Screening Visit, Baseline Visit (Therapy Initiation), Week 1, Week 4, Week 8, Week 12 and Week 32 Visit. Week 1 Visit has a window of ±2 days, Week 4 Visit has a window of ±4 days, while Week 8, 12, 32 Visits have a window of ±7 days, at the discretion of the investigator, required procedures for a scheduled visit may be performed over 2 consecutive days.

If a patient returns to the clinic prior to their next scheduled study visit for assessment of an adverse event, an Unscheduled Visit should be conducted. Procedures conducted at the Unscheduled Visit are at the discretion of the Investigator.

Any patient who exits early from the study must undergo all procedures outlined at Week 8 Visit if the discontinuation occurs at or before Week 8 Visit.

All assessments except event type data will be analysed according to the nominal Visit identifier on the CRF page, irrespective of meeting the time window as specified in the study plan and of having the procedures performed over 1 or 2 consecutive days.

This rule does not hold for patients, who terminate study during treatment. For these patients, the visit needs to be shifted to Week 1, Week 4 or Week 8 visit depending on the visit window specified below.

Unscheduled visits will not be considered for by-visit analyses but all collected data will be listed. Documented unscheduled visits will be labelled as “Unscheduled Visit x.01”, “Unscheduled Visit x.02”, “Unscheduled Visit y.01” etc. indicating the number of the last preceding visit plus a consecutive sequence number.

The Baseline value is generally defined as the last non-missing measurement collected or derived prior to the first Study Treatment Administration as recorded on eCRF page “Administration of Study Drug’ in variables Date/Time of Application of First Dose.

The Treatment Day of an event/assessment will be calculated relative to the First Study Treatment [defined as Variable “Date of First Dose Treatment’, recorded on “Study Drug Dosing Dates’ eCRF form].

The Treatment Day of events/assessments occurring before the First Study Treatment will be calculated as:

- Treatment Day = (Date of assessment/event - Date of First Study Treatment).

For events/assessments occurring on or after First Study Treatment Administration, Treatment Day will be calculated as:

- Treatment Day = (Date of assessment/event - Date of First Study Treatment) + 1.

Table 2: Study Visits

Scheduled Visit	Scheduled Visit Label	Scheduled Study Day	Visit Window
Screening Visit	Screening	Before Baseline Visit	Up to 4 weeks before date of Baseline Visit
Baseline Visit Day 0	Baseline	0	Date of Baseline Visit – Date of First Study Treatment in [-1, 0]
Week 1	Week 1	7	Visit date – Date of First Study Treatment in [5 – 9]
Week 4	Week 4	28	Visit date – Date of First Study Treatment in [24 – 32]
Week 8	Week 8	56	Visit date – Date of First Study Treatment in [49 – 63]
Follow-up Visit Week 12	Week 12	84	Visit date – Date of First Study Treatment in [77 – 91]
Follow-up Visit Week 32	Week 32	224	Visit date – Date of First Study Treatment in [217 – 231]
Documented unscheduled Visits will be labeled as “Unscheduled Visit x.01”, “Unscheduled Visit x.02”, “Unscheduled Visit y.01”… .			
Date of First Study Treatment is to be taken from eCRF page “Study Drug Dosing Dates’.			

7.2 Analysis Variables

This section describes all variables that are used for analysis as well as their source data variables. The other (raw) data variables will be described in section 10. For each variable it is specified how missing values will be handled, if applicable.

7.2.1 Disposition and Protocol Deviations

Disposition parameters are recorded on the eCRF Page ‘End of Study’.

Study discontinuations will be defined only for randomized patients.

A patient discontinued the study prematurely, if the question ‘Did the patient complete the study’ was answered as ‘No’. A patient is considered as study completer, if the question ‘Did the patient complete the study’ was answered as ‘Yes’. Otherwise the patient is considered as ‘Ongoing’.

Primary Reason for Study Discontinuation is documented on the eCRF Page ‘End of Study’ in categories ‘Adverse Event’, ‘Lost to Follow-Up’, ‘Decision unrelated to an Adverse Event’, ‘Non-Compliance’, ‘Study terminated by the sponsor’, ‘Study terminated by the investigator’, ‘Other’.

If the date of study discontinuation/study completion as documented on the eCRF page ‘End of Study’ is less or equal than 63 days after the date of first study drug administration as documented on eCRF Page ‘Study Drug Dosing Dates’, discontinuation will be considered as ‘During Treatment Period’, otherwise it will be considered as ‘During Follow-Up Period’.

A patient is considered as Completer of the Treatment Period, if he has a documented Week 8 Visit and did not discontinue the study during the treatment period.

If the eCRF question 'Was the emergency envelope opened during the study?' was answered 'Yes', the patient will be considered as unmasked.

Protocol deviations will be collected during the study and reviewed during the BDRM according to a separate BDRM plan. During the BDRM, identification of CSR reportable protocol deviations and further categorization of deviations for TLF output will be performed. For the analysis, the CSR reportable protocol deviations as documented in the BDRM minutes will be presented.

7.2.2 Demographics

Demographic characteristics are recorded on the eCRF page "Demography".

Gender (Male, Female), Ethnicity ('Hispanic, Latino, Spanish', 'Not Hispanic, Latino, Spanish'), and Race ('White', 'Black or African American', 'Asian', 'Native Hawaiian or Other Pacific Islander', 'American Indian or Alaska Native', 'Other') will be analyzed as recorded on the eCRF.

Age (years) at Screening is calculated as:

- INT((date of informed consent - date of birth)/365.25).
  In case of incomplete dates, missing days will be set to 1st and missing months will be set to July.

7.2.3 Glaucoma History and Other Medical/Surgical History

Details on Glaucoma history are recorded on eCRF Page 'Glaucoma History'.

Analysis variables for Glaucoma history are:

- Presence of chronic primary open angle glaucoma (Yes/No) as documented on the eCRF Page.
- Symptomatic Eyes (Right Eye only, Left Eye only, Both Eyes) derived from the respective eCRF question
- Primary Eye (Right Eye, Left Eye) as defined in the BDRM minutes.
- Secondary Eye (Right Eye, Left Eye, None) as defined in the BDRM minutes

All other medical history is recorded on the "Medical history" eCRF page, whereas surgical history is recorded on the 'Surgical History' eCRF Page. Medical history contains information about conditions that a patient might have suffered prior to Baseline visit, or conditions that are ongoing at the time of the Baseline visit. The medical history terms as well as surgical history terms as specified by the investigator will be coded to a Preferred Term (PT) and a System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus.

If no coding information will be available for a specific medical/surgical history record, the record will be presented as 'Uncoded Record'. However, for final TLFs it is anticipated that all medical/surgical history records are coded.

7.2.4 Concomitant Medication

Prior and Concomitant medication data will be collected throughout the study on the 'Prior / Concomitant Medications' CRF page.

All medications will have a calculated start and stop day to enable categorization of the medications as 'Prior' or 'Concomitant':

- Start Day is defined as:

- Start Date of Medication – Date of First Study Treatment Administration + 1

  If the Start Date of the Medication is greater than or equal to the Date of First Study Treatment Administration as provided on eCRF page 'Study Drug Dosing Dates'

- Start Date of Medication – Date of Study Treatment Administration

  If the Start Date of the Medication is less than the Date of Study Treatment Administration as provided on eCRF page 'Study Drug Dosing Dates'

- Stop Day is defined as:
  - Stop Date of Medication – Date of First Study Treatment Administration + 1

    If the Stop Date of the medication is greater than or equal to the Date of First Study Treatment Administration as provided on eCRF page 'Study Drug Dosing Dates'

  - Stop Date of Medication – Date of Study Treatment Administration

    If the Stop Date of the Medication is less than the Date of Study Treatment Administration as provided on eCRF page 'Study Drug Dosing Dates'

'Prior medications' are medications that were started before and stopped before or on the day of First Study Treatment Administration as provided on eCRF page 'Study Drug Dosing Dates'.

'Concomitant medications' include all medications that a patient used during the Treatment or Follow-Up Period of the study.

Any medication started prior to First Study Treatment Administration (as provided on eCRF page "Study Drug Dosing Dates'), which was not discontinued on/before Date of First Study Treatment administration, will be considered as 'Concomitant'. Moreover, any medication started at any time after the First Study Treatment Administration (as provided on eCRF page 'Study Drug Dosing Dates') will be considered 'Concomitant'.

Medications started and stopped on the day of First Study Treatment Administration (as provided on eCRF page 'Study Drug Dosing Dates') will be considered to be 'Concomitant'.

The Investigator Terms (Medication Name, and Indication) will be coded to a World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Drug class, a WHO-ATC Drug number and a WHO Drug Name (Preferred Term) using the WHO-DRL Drug Dictionary.

Missing Codes or Medication Dates Imputation:

In the event that coding information will not be available for a specific concomitant medication, the concomitant medications will be presented as 'Uncoded Medication'. However, for final TLFs it is anticipated that all medication records are coded.

Missing and/or incomplete dates for prior and concomitant medications will be imputed for calculating relative start and stop days only. Dates will be listed as missing/incomplete [with "-" replacing missing information] but the Start/Stop Day listed between square brackets to denote it was calculated based on missing data (i.e. [-28], [1], [Ongoing]).

Missing and/or incomplete dates will be imputed in a manner that assumes the worst case scenario.

Technically, incomplete stop dates will be imputed as follows:

- For a missing day (but month and year is available), it will be assumed that medication have been stopped on the last day of the respective month.

- For a missing month (but year is available), it will be assumed that medication have stopped on 31st December of the respective year.
- For a completely missing stop date, the medication will be assumed to be ongoing.

Similarly, incomplete start dates will be imputed as follows:

- For a missing start day (but month and year is available), onset is assumed on the first day of the respective month.
- For a missing start month (but year is available), onset is assumed on 1st January of the respective year.
- For a completely missing start date, no imputation is performed. However, the medication will be considered as concomitant, unless indicated different by stop date.

7.2.5 Measurements of Exposure and Treatment Compliance

The patients will be dispensed a 4 week supply of study medication (1 kit) on the Day 0 visit and at Weeks 4.

Patients will also be instructed to bring back to the clinic at each study visit all the used and unused vials.

Each 4 week kit will be composed of 1 box containing a total of 90 single-use vials of the randomized / assigned medication for daily treatment during 4 weeks and 1 box containing the same number of adaptors and prefilled 0.3 ml WFI syringe.

All patients will be dosed one drop (35 µl) three times a day (TID) in each eye during the 8 weeks treatment period.

Exposure

Information on Exposure will be derived from information on eCRF Pages 'Study Drug Dosing Dates' (Date of First Study Drug Administration, Date of Last Study Drug Administration), 'End of Study' (Date of Study Discontinuation/Completion), 'Study Visits' (Date of Week 8) as well as 'Study Drug Dosing and Accountability' (Date of Vial Dispensed/Returned, Days without Treatment).

Exposure will be presented by displaying Duration of Treatment Period, Duration of Follow-up Period, Extent of Exposure and Days on Study Medication, which will be derived as follows

- Duration of Treatment Period:
  Week 8 Visit Date or Date of Study Discontinuation/Completion – Date of First Study Drug Administration + 1, whatever is earlier.

- Duration of Follow-Up Period:
  Date of Study Discontinuation/Completion – Date of Week 8, for all patients who have completed the treatment period and terminated the study (regularly or prematurely)
  For patients who did not complete the treatment period, Duration of Follow-Up Period is set to 0.
  Main Objectives Analysis only: if a patient has not completed the study yet, the last documented visit during Follow-Up Period (including unscheduled visits) will be considered for calculating Duration of Follow-Up Period.

- Extent of Exposure (days) = (Date of Last Study Treatment – Date of First Study Treatment Administration + 1),

If Date of Last Study Treatment is missing (e.g. due to Lost to Follow-Up), Date of Study Discontinuation/Completion or Date of Last Study Drug Return (as documented on the eCRF Page 'Study Drug Dosing and Accountability'') will be used, whatever is earlier.

- Days on Study Medication = Sum of (Date of Vial Returned – Date of Vial Dispension – Days without Treatment) +1 for all lines in eCRF Page 'Study Drug Dosing and Accountability'.
  If no Vials are dispensed, Days on Study Medication will be set to 0. In case of incomplete/inconsistent documentation on eCRF, Days on Study Medication will be set to Missing.

Compliance

Patient compliance with the study medication will be assessed at each study visit following the dispensing of the study medication for self-administration. For each kit dispensed, the eCRF page 'Study Drug Dosing and Accountability' records per return visit:

- Date dispensed
- Kit number received
- Number of vials dispensed
- Date returned
- Number of vials returned
- Number of vials unused
- Number of days without treatment

Compliance will be evaluated according to the following formula:

$$\text{Compliance (\%)} = 100 * \frac{\text{Number of vials dispensed} - \text{Number of unused vials returned}}{\text{Number of expected days on treatment}}$$

The number of expected days on treatment will be set to 56. For each patient, the number of vials dispensed will be derived as the sum of provided numbers in the column "# Vials Dispensed" on the eCRF Page 'Study Drug Dosing and Accountability; the number of unused vials returned will be derived as the sum of provided numbers in the column "# Vials Unused" on the eCRF Page 'Study Drug Dosing and Accountability'.

Compliance will be presented categorical as <80%, ≥80%.

7.2.6 Study Medication

'**Table 3: Study Treatments**' shows the Study Treatments and how they will be labelled in all TLF outputs.

Table 3: Study Treatments

Treatment arm	*Treatments*
rhNGF	*180 µg/ml rhNGF, one drop TID*
Vehicle	*Vehicle control, one drop TID*

7.2.7 Primary Safety Outcomes

The primary safety outcomes of the study are:

Unexpected severe progression of optic neuropathy (USPON)

Unexpected Severe Progression of Optic Neuropathy will be measured a) by a central vision loss; b) by visual field testing; and/or c) by examination of the optic nerve. It is recorded per eye on the Follow-Up Visits of the eCRF pages 'Best Corrected Distance Visual Acuity', 'Humphrey Visual Field Monitoring', 'Electroretinography' and Ocular coherence tomography' via a tick box 'Was an unexpected severe progression measured…' (Yes/No).

USPON will be investigated only for treated eyes, i.e. if an eye is not treated, the respective tick box will not be considered for definition of primary outcome.

For a patient, USPON occurred, if in any of the following assessments the respective question on unexpected severe progression is answered 'Yes':

a) from BCDVA assessments: eCRF question is ticked 'Yes' for at least one treated eye at any Follow-Up Visit after first study treatment administration (including unscheduled visits).

b) from HVF assessments: eCRF questions is ticked 'YES' for at least one treated eye in at least one assessment during Treatment or Follow-Up Period (i.e. performed after first study treatment administration). An assessment is considered as performed during Follow-Up Period, if Test Date and Test time as documented on eCRF Page 'Humphrey Visual Field Monitoring' was after Week 8 Visit (See also Section 7.2.9 for Details).

c) from ERG assessments: eCRF question is ticked 'Yes' for at least one treated eye at any Follow-Up Visit after first study treatment administration (including unscheduled visits).

d) from OCT assessments: eCRF question is ticked 'Yes' for at least one treated eye at any Follow-Up Visit after first study treatment administration (including unscheduled visits).

As supportive variable, the occurrence of USPON during Treatment Period will be derived, which is defined as an USPON, which was recorded between the first study treatment administration and Week 8 Visit/Study termination Visit (for patient withdrawn during the treatment period).

Intolerance or allergy to the drug

The occurrence of intolerance and allergy to the drug will be identified during the BDRM by reviewing reported Preferred Terms of Treatment Emergent Adverse Events (for definition see Section: 7.2.10).

Adverse events affecting ocular function or eye pressure, which differ from those expected in the course of glaucoma, which are thought to be potentially related to the drug (Unexpected Related AEs affecting ocular function/eye pressure)

The occurrence of these events will be identified via the respective question on the AE form. It is expected, that only adverse events, which are occurring during treatment period, will be flagged for this endpoint by the investigator. So, no separate analysis is foreseen by study period.

Local or systemic toxicities considered serious adverse events that are potentially related to the drug

The occurrence of local and systemic toxicities will be identified via the respective question on the AE form. It is expected, that only adverse events, which are occurring during treatment period, will be flagged for this endpoint by the investigator. So, no separate analysis is foreseen by study period.

7.2.8 Primary Tolerability Outcome

VAS Ocular Tolerability Score

Visual Analogue Scale (VAS) will be used to determine ocular tolerability to the study medication. It will be assessed by the patient using a self-administered 100 mm VAS on which 0 means no symptoms and 100 means the worst possible discomfort in either eye. This evaluation is to be performed before any ophthalmic examinations.

The VAS Ocular tolerability scores will be collected on the eCRF page 'Visual Analogue Scale Ocular Tolerability' per eye for the symptoms:

1) foreign body sensation
2) burning/stinging
3) itching
4) ocular pain
5) sticky feeling
6) blurred vision
7) photophobia

The Overall VAS Ocular Tolerability Score is the mean of all VAS Ocular Tolerability symptom scores per visit per eye. In case of missing symptom scores, the mean will be calculated on the remaining VAS scores if at least 5 out of 7 scores are non-missing.

Change from baseline is derived for overall score as well as for all 7 symptom scores will be derived as the difference between the respective values at a scheduled Follow-Up and Baseline Visit.

7.2.9 Exploratory Secondary Efficacy Outcomes

The following examination/procedures will be performed on both eyes and results and derived values as defined below in this section will be derived for each eye individually.

Changes in Best-Corrected Distance Visual Acuity

Vision must be measured using ETDRS visual acuity chart at 4 meters (13 feet) and, if indicated, also at 1 meter (i.e. when less than 20 letters were read at 4m). Results are documented on the eCRF page 'Best Corrected Distance Visual Acuity'.

In case both tables on the eCRF page have been completed (at 4 meter and at 1 meter) then the visual acuity score is the sum of the total number of correct letters from both tables. If only the table at 4 meter is completed and the overall number of letters read is 20 or above then the Visual Acuity Score is the number of total letters read at 4 meter plus 30.

If no letter were read at 4 and 1 meter, the best visual potential ability of the patient is selected from: a) count fingers; b) hand motion; c) light perception; or d) no light perception. The Visual Acuity Score is then set to 0.

The Snellen Equivalent is defined as the acuity equivalent for the smallest line with 1 or no error. The logarithm of the minimal angle of resolution (logMAR) is calculated as "- log (Snellen Equivalent)" with two decimals precisions. The logMAR ranges from 0.30 (20/10) to 1.60 (20/800) and an increase in logMAR reflects a worsening of visual acuity. If for a patient only ability for counting fingers is reported, logMAR will be set to 2.00; if for a patient only recognition of hand motion is reported, logMAR will be set to 3.00 (Holladay 1997).

For Visual Acuity Score and logMAR, change from baseline will be calculated as difference for Week 8, Week 12 and Week 32 Visit.

For safety evaluation, also the incidence of Substantial Worsening of Visual Acuity during Treatment will be derived at each Follow-Up Visit. A Substantial Decrease of Visual Acuity during Treatment is defined as:

- Decrease in BCDVA score of more than 30 compared to Baseline or
- Increase in LogMar of more than 0.6 compared to the Baseline or
- Decrease of Visual Acuity from at least Hand Motion to the Level of Light Perception or worse compared to Baseline

at any assessment (scheduled and unscheduled) after first Study Drug Administration up to and including Week 8 Visit.

A similar derivation will be performed for the incidence of Substantial Worsening of Visual Acuity during Follow-up Period considering all Assessments after Week 8 and Last Study Visit during the Follow-Up Period.

It needs to be noted that a Substantial Worsening of Visual Acuity as defined here will not necessarily implies an adverse event of special interest (AESI) or an USPON, as this definition is addressing a general worsening compared to start of study, whereas AESI and USPON are considering substantial changes from the last observed visit.

Changes in Visual field using Perimetry

Visual fields will be evaluated using static (Humphrey) perimetry and results are on the eCRF pages 'Humphrey Visual Field Monitoring' and 'Humphrey Visual Field'. Two perimetries will be performed on different days for a total of 3 before initiating treatment and these will be reported as Baseline assessments. During treatment 3 assessments will be performed within 4 weeks. During follow up 3 perimetries will be performed within 4 weeks.

Humphrey Visual Field testing will be performed using SITA Standard. If a patient has a low vision and cannot perform the test via SITA Standard, the test is performed with the FASTPAC Standard. On the eCRF it is recorded which test type has been used.

All HVF assessments will be assigned to the respective study period according to the following rules:

- Screening Period: Date/Time of HVF assessment will be before Date/Time of First Study drug administration as documented on eCRF Page 'Administration of Study Drug'
- Treatment Period: Date/Time of HVF assessment on/after Date/Time of First Study Drug Administration (as documented on eCRF Page 'Administration of Study Drug' and on/before Date of Week 8 Visit. If a patient did not perform a Week 8 Visit, all assessments after first Study Drug Intake will be assigned to the Treatment Period.

- Follow-up Period: Date/Time of HVF assessment after Date of Week 8 Visit.

Based on this assignment, the occurrence of USPON assessed via HVF will be determined.

Electroretinography (ERG)

A full field and pattern ERG will be performed according to international standards. On the eCRF page 'Electroretinography' only the PhNR result will be recorded in format 5.2 and used for statistical analysis.

For PhNR, the change from baseline will be calculated as differences for Week 8, Week 12 and Week 32 Visits.

Optical Coherence Tomography (OCT)

Spectral domain OCT acquisitions of macula and optic nerve head will be performed to evaluate changes in ganglion cell layer and nerve fiber layer thickness.

Retinal nerve fiber layer (RNFL) Thickness (µm, format 6.2) is recorded in the eCRF page 'Ocular Coherence Tomography' as follows:

- four RNFL Quadrants, namely superior (S), nasal (N), temporal (T) and inferior (I)
- twelve RNFL Clock Hours (1 to 12)
- average RNFL Thickness as measured by the OCT machine

From PanoMap analysis, Macular Thickness (µm, format 6.2) is recorded in the eCRF page 'Ocular Coherence Tomography' as follows:

- nine Areas, namely superior of outer ring (SOM), nasal of outer ring (NOM), inferior of outer ring (IOM), temporal of outer ring (TOM), superior of inner ring (SIM), nasal of inner ring (NIM), inferior of inner ring (IIM), temporal of inner ring (TIM) and central subfield thickness (CSF)

From Ganglion Cell OU analysis, Macular Cube Thickness (µm, format 6.2) is recorded in the eCRF page 'Ocular Coherence Tomography' as follows:

- six Areas, namely superior (SUP), superior temporal (ST), inferior temporal (IT), inferior (INF), inferior nasal (IN) and superior nasal (SN)

For all these variables, change from baseline will be calculated as differences for Week 8, Week 12 and Week 32 assessments.

7.2.10 Safety Variables – Adverse Events

AE data are collected on the 'Adverse Events' eCRF page. The AE Description (Investigator term) will be analyzed on PT and SOC level using MedDRA.

Based on the information provided on the 'Adverse Events' eCRF page, the following definitions will be utilized:

- An ocular event will be identified, if the question 'Is this an ocular event?' is answered 'Yes'.
- An AE with missing severity will be counted as severe.
- A Serious Adverse Event (SAE) is any adverse event where the question 'Is the event serious?' has been answered as 'Yes'. If this question is not answered the event will be considered as 'Serious' for analysis purposes.
- *The following adverse events are considered to be of special interest (AESI) and by default shall be reported as SAEs (medically important criteria):*

- *Adverse Events that cause an unexpectedly severe progression of optic neuropathy as measured by central vision loss (i.e. decrease in visual acuity of >30 ETDRS letters or > +0.6 LogMAR lasting >1 hour compared with the last assessment of visual acuity at the last visit), by visual field testing, or by examination of the optic nerve.*
- *Adverse Events that cause a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour.*
- *Adverse Events that require surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.*
- *Adverse Events associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis).*
- *Adverse Events that, in the opinion of the investigator, may require medical intervention to prevent permanent loss of sight.*

For analysis purposes, AESI will be identified by ticked box 'Medically significant or important medical condition' in the eCRF section 'SAE criteria'. This means in particular, that all AESIs will be considered as SAEs.

- An AE leading to premature withdrawal of the study treatment is defined as an AE where in the eCRF section 'Action taken with study treatment' the boxes 'Withdrawn' and 'Permanently' are ticked.
- An AE leading to study treatment interruption is defined as an AE where in the eCRF section 'Action taken with study treatment' the boxes 'Withdrawn' and 'Temporarily' are ticked.
- An AE leading to study discontinuation is defined as an AE where in the eCRF section 'Action regarding Patient' the box 'Patient Withdrawn' is ticked (this should match with the primary reason for early withdrawal of 'Adverse Event' on the End of Study eCRF page).
- An AE is classified as 'Related' to Study Treatment if the relationship to study medication recorded as 'Possible' or 'Probable' or 'Highly Probable'. An AE will be classified as unrelated to study medication if the relationship to study medication was recorded as 'None' or 'Unlikely'. AEs with missing relationship to study treatment will be counted as 'Related' to Study Treatment.
- A Fatal AE is defined as an AE where the outcome is recorded as 'Fatal'.

These definitions will apply accordingly also for the subsequent sub-classes of AEs.

Non Treatment-emergent adverse events (Non-TEAEs)

A Non-TEAE is defined as any AE, which started before the first administration of study treatment. An AE is considered as Non-TEAE, if the eCRF question 'Did the event occur:' was answered with 'Before Treatment Period'.

Treatment-emergent adverse events (TEAEs)

A treatment-emergent adverse event is defined as an AE that started on or after the date of the First Study Treatment Administration. An AE is considered as TEAE, if the eCRF question 'Did the event occurred:' was answered either with 'During Treatment Period' or 'During Follow-Up Period'.

TEAEs in Treatment Period

This is defined as a TEAE (as defined above) that started on or after the date of the First Study Treatment Administration but on or before the Week 8 Study Visit. A TEAE in

Treatment Period will be identified, if the eCRF question 'Did the event occurred:' was answered with 'During Treatment Period'.

TEAEs in Follow-Up Period

This is defined as an TEAE with a start date after the Week 8 Visit. An TEAE will be considered as TEAE in Follow-Up Period, if eCRF question 'Did the event occur:' was answered with 'During Follow-Up Period'.

For listing purposes, treatment day of onset of AE will be derived according to the definition given in section 7.1.

Missing Codes or Incomplete AE start dates:

In the event that coding information will not be available for a specific AE, the event will be presented as 'Uncoded Event'. However, for final TLFs it is anticipated that all events are coded.

If the eCRF question 'Did the event occur:' was not answered, AEs will be classified to sub-class Non-TEAE, TEAE in Treatment Period or In Follow-Up Period based on the AE onset date utilizing the definitions given above. If this is not possible, the event will be classified as TEAE in Treatment Period.

Missing and/or incomplete AE onset dates will be imputed for calculating relative start and stop days only. Dates will be listed as missing/incomplete [with "-" replacing missing information] but the onset Day listed between square brackets to denote it was calculated based on missing data (i.e. [1]).

Missing and/or incomplete dates will be imputed in a manner that assumes the worst case scenario:

- For a missing start day (but month and year is available), onset is assumed on the first day of the respective month.
- For a missing start month (but year is available), onset is assumed on 1st January of the respective year.
- For a completely missing start date, no imputation will be performed.

If for Non-TEAEs this procedure results in an onset date before date of informed consent, informed consent date will be used.

If for TEAEs in the Treatment Period this procedure results in an onset date before date of first study treatment, date of first study treatment will be used.

If for TEAEs in the Follow-Up Period this procedure results in an onset date before date of Week 8 visit, date of Week 8 visit will be used.

7.2.11 Other Safety Parameters

Best Corrected Distance Visual Acuity

For additional safety variables associated to BCDVA assessment please refer to section 7.2.9.

External Ocular Examination

External Ocular Examination assesses the motility of the extraocular muscles and the appearance and function of the eyelids before the instillation of any dilating or anesthetic eye drops.

Motility of extraocular muscle and appearance/function of eye lids is assessed separately for each eye at each Study Visit and is recorded on the eCRF pages 'External Ocular Examination' and 'Appearance and Function of Eyelids'.

For the analysis, the motility of the extraocular muscle will be evaluated by the field of movements Right and up ('Normal', 'Abnormal'), Right ('Normal', 'Abnormal'), Right and Down ('Normal', 'Abnormal'), Left and Up ('Normal', 'Abnormal'), Left ('Normal', 'Abnormal'), Left and Down ('Normal', 'Abnormal') as documented at the eCRF. No imputation will be envisaged for these parameters.

Appearance and function of eyelids will be summarized by the following parameters:

- Incidence of proven eyelid deformity/abnormality, which will be considered as present, if the question 'Evidence of eyelid deformity or abnormality' on the eCRF page 'Appearance and Function of Eyelids' is answered 'Yes'.

- Incidence of abnormal motor function of eyelids (i.e. upper lid elevation and forceful lid closure), which will be considered as present, if the question 'Motor function of eyelids' on the eCRF page 'Appearance and Function of Eyelids' is answered 'ABNORMAL'.

- Incidence of corneal exposure in case of closed eyelids, which will be considered as present, if the question 'Is there corneal exposure when the eyelids are closed?' on the eCRF page 'Appearance and Function of Eyelids' is answered 'Yes'.

- Incidence of proven punctal occlusion, which will be considered as present, if the question 'Is there evidence of punctal occlusion?' on the eCRF page 'Appearance and Function of Eyelids' is answered 'Yes'.

- Incidence of punctal plugs, which will be considered as present, if the box 'Punctal plugs' is ticked on the eCRF page 'Appearance and Function of Eyelids'.

- Incidence of thermal or surgical occlusion, which will be considered as present, if the box 'Thermal or surgical occlusion' is ticked on the eCRF page 'Appearance and Function of Eyelids'.

- Incidence of Other punctal occlusion, which will be considered as present, if the respective 'Other' box is ticked on the eCRF page 'Appearance and Function of Eyelids'.

Slit Lamp Examination

Slit lamp examination is performed separately for each eye at each Study Visit and is recorded on the eCRF page 'Slit Lamp Examination (Biomicroscopy)'.

The following assessments will be performed:

Eye Structure	Rating

Eye Structure	Rating
Eye Lids	1 = None (normal) 2 = Mild (redness localized to a small region of the lid(s) margin OR skin) 3 = Moderate (redness of most of all of lid margin OR skin) 4 = Severe (redness of most or all of lid margin AND skin) 5 = Very Severe (marked diffuse redness of both the lid margin AND skin)
Lashes	1 = Normal 2 = Abnormal (specify)
Conjunctiva	1 = None 2 = Mild 3 = Moderate 4 = Severe
Cornea	1 = Normal 2 = Abnormal
Lens	1 = No Opacification (normal lens) 2 = Mild Lens Opacification 3 = Moderate Lens Opacification 4 = Severe Lens Opacification 5 = Cataract Extraction with Intraocular Lens Implant In addition there is also a field to specify Other findings
Iris	1 = Normal 2 = Abnormal
Anterior Chamber Inflammation	1 = None (no Tyndall Effect) 2 = Mild (Tyndall Effect barely discernable) 3 = Moderate (Tyndall beam in the anterior chamber is moderately intense) 4 = Severe (Tyndall beam in the anterior chamber is severely intense)
Other	Specification and assessment of other investigated eye structure

For each eye structure, the investigator will have the opportunity to tick also 'Not done/Not evaluable', which will be treated as 'Missing' for analysis purposes.

All grading assessments of different eye structures will be evaluated as collected on the eCRF. No imputation will be envisaged for these parameters.

No aggregated presentation is planned for other assessments done during Slit lamp evaluation.

Intraocular Pressure (IOP)

Intraocular Pressure testing will be performed using Goldmann Tonometer and the resulting value (mmHg, format 4.1) is recorded on the eCRF page 'Intraocular Pressure'. The change from baseline will be calculated as differences from Baseline.

Dilated Fundus Ophthalmoscopy

Fundus ophthalmoscopy to assess the eye structure will be performed and results recorded on the eCRF page 'Fundus Ophthalmoscopy' by utilizing the following assessments.

Eye Structure	Rating
Vitreous	1 = Normal 2 = Abnormal (specify) 3 = Not done/Non-Evaluable
Retina / Macula	1 = Normal 2 = Abnormal (specify) 3 = Not done/Non-Evaluable
Choroid	1 = Normal 2 = Abnormal (specify) 3 = Not done/Non-Evaluable
Optic Nerve	1 = Normal 2 = Abnormal (specify) 3 = Not done/Non-Evaluable
Cup/Disc Ratio	1 = Normal 2 = Abnormal (specify) 3 = Not done/Non-Evaluable For abnormal values the Cup/Disc Ratio will be included in the 'Specify' field.

All grading assessments of different eye structures will be evaluated as collected on the eCRF. No imputation will be envisaged for these parameters. Information on Cup/Disc Ratio will be listed only, as no investigator assessment on abnormality was performed.

No aggregated presentation is planned for recorded details.

8 Analysis Methods

8.1 General Methods

For the study, both eyes are under investigation. For analysis purposes all eye-related assessments will be displayed separately by Primary/Secondary Eye. Untreated eyes will not be considered for analysis and be listed only indicated with 'Untreated'.

For continuous variables, the mean, standard deviation, minimum, median and maximum will be presented by treatment group, together with the total number of observations and the number of missing and non-missing values. Unless otherwise specified minimum and maximum values will be reported to the same number of decimal places as the recorded measurements, mean and median are reported to one more decimal place and standard deviation one additional decimal place more than the mean.

For categorical variables, absolute and relative frequencies will be reported by treatment group. Relative frequencies will be based on all observations and reported as a percentages to one decimal place. Unless otherwise specified, percentages will be based on the number of patients with data in the considered analysis set and will not be calculated for missing categories.

Incidences over a specific time interval like adverse events, medical history and concomitant medication will be reported on a patient basis. The percentages will be calculated using the number of patients in the treatment group for the considered analysis set as denominator. For the presentation of incidences during the Follow-Up Period, the SAF-F set will be used, which results in a reduction of the denominator to the number of patients in the SAF, who have entered the Follow-Up Period.

All hypotheses will be tested at a 5% level of significance using a two-sided test.

P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999.

Statistical significance will be declared if the rounded p-value will be less than 0.050 unless stated otherwise. Two-sided 95% confidence intervals of the differences between the treatment groups will be calculated as indicated in sections 8.2 and 8.3.

Post-Text TLFs will be provided in collated electronic MS Word .rtf files (i.e. table columns and rows appear as free text instead of MS Word Table format).

8.2 Specific Methods for Primary Safety and Tolerability Analyses

All primary safety and tolerability analyses will be performed on the SAF.

Generally, the analysis of the Primary Eye will be considered as the primary result, whereas the analyses in Secondary Eye will be considered as supportive.

No statistical inference is foreseen for the analyses of primary safety outcomes.

For the VAS Tolerability Scores, the change from baseline in the respective score will be compared between treatment groups in an explorative manner per Eye and Visit.

The null hypothesis will be tested that there is no difference between rhNGF and Vehicle in the mean overall change from baseline between both treatments with respect to evaluated score:

$$H_0: \mu_{rhNGF} = \mu_{Vehicle}$$
$$H_1: \mu_{rhNGF} \neq \mu_{Vehicle}$$

Where μ is the mean change from baseline at considered visit within the given treatment group. This hypothesis will be tested with an Analysis of the Covariance (ANCOVA) with treatment and respective baseline value in the model.

The Least-squares means estimate of the treatment effect and the treatment group difference (both with 95% confidence intervals) will be reported. The analysis will be performed in the SAF.

These analyses will be performed for the Overall Tolerability Score as well as for all subscores per eye for the Week 1, Week 4 and Week 8 visits.

8.3 Specific Methods for Exploratory Efficacy Analyses

Generally, the analysis of the Primary Eye will be considered as the primary result, whereas the analyses in Secondary Eye will be considered as supportive. Exploratory efficacy analysis will be performed on the ITT.

A similar analysis as foreseen for VAS tolerability scores (see section 8.2) will be performed for exploratory efficacy outcomes at Week 8. This comprises the following inferential analyses:

- Change from Baseline in Visual Acuity Score at Week 8
- Change from Baseline in LogMAR at Week 8
- Change from Baseline in PhNR at Week 8
- Change from Baseline in Average RNFL Thickness, all single quadrants and clock hours at Week 8
- Changes form Baseline in Macular Thickness at Week 8 for all respective areas
- Changes from Baseline in Macular Cube Thickness at Week 8 for all respective areas

8.4 Statistical/Analytical Issues

8.4.1 Adjustments for Covariates

No adjustment for covariates is planned.

8.4.2 Handling of Dropouts or Missing Data

All data obtained will be used in the analysis and no imputation will be carried out for missing data.

8.4.3 Data Review

In order to perform the statistical analysis of the main objective analysis, a decision needs to be made *on evaluability of patients and visits prior to locking the database and breaking the code for the blinded study medication*. In particular, data situations constituting protocol deviations may need to be defined. This will be done at the Blind Data Review Meeting.

Performance of Blind Data Review Meeting for the main objectives analysis will require a clean database, i.e. all data are available and coded and no data queries are open (on safety and efficacy data up to Week 12 and all AE data documented until the date of data base soft lock).

No data entry should be performed between the data base Soft Lock for Main Objectives analysis and database lock for Main Objective Analysis. Exception would be Queries, which raised during the BDRM requiring a solution before data base Lock.

A reduced Data Review will be performed before the data base lock for the final analysis focusing on review of data issues. More details on scope and performance of data review meetings will be described in a separate BDRM plan.

After the BDRM is performed, all decisions will be summarized in BDRM Minutes, which will be approved before the database will be locked for the analysis.

8.4.4 Multicentre Studies

Not applicable since this is a monocentric study.

8.4.5 Multiplicity of Endpoints

Due to this is being a Phase I safety and tolerability study, no adjustment of any p-values will be made to account for inflation of the Type 1 error rate arising from multiple endpoint testing.

9 Main Objective and Final Analyses

9.1 Main Objective Analysis

The database will be locked after all patients have completed their Week 12 Visit and main objectives analysis will be performed on unmasked data.

For visit-based tables, only study visits up to Week 12 will be presented for the analysis. However, for event-type data (i.e. adverse events and concomitant medication) and the assessment of primary safety outcomes (i.e. AE, BCDVA, ERG, OCT and HVF assessments), also data AFTER Week 12 Visit will be considered.

For the listings, all data as recorded in the data base will be reported. Respective footnotes will be added to the output to indicate that calculated figures of data after Week 12 needs to be considered as preliminary. As a consequence, interpretation of provided TLFs in the CSR should focus on the results of data assessed before Week 12.

9.2 Final Analysis

At the end of the study (i.e. after all patients have completed Week 32 Visit), an updated analysis will be performed presenting the complete study data. Section 12 indicates which TLFs will be reproduced because they will contain additional data from the period after the first 12 weeks until Week 32. These newly produced TLFs will be reported in a Statistical Report that is to be considered as an addendum to the CSR.

10 Overview of Tables, Listings and Figures

In this section, TLFs will be presented content wise. The full set of TLFs will be tabulated in section 12, where it will also be indicated whether the item is unique (or first mentioned) or a repeat. Mock shells for unique TLFs will be presented in a separate document.

10.1 Disposition of Patients

Patient disposition data will be collected on the 'End of Study' eCRF page when a patient completed or discontinued from the study. Whether the patient completed the study is recorded along with the single primary reason for withdrawal. It is also recorded whether the emergency envelope was opened during the study and if so, the date and reason of unmasking has been provided.

A disposition summary of patients includes the number (n) and percentage (%) of patients in all analysis sets defined in Section 6.1. All percentages will be based on the number of patients randomized, i.e. ITT. Percentages will not be shown for the Total Set.

The primary reason for study discontinuation will also be summarized for the ITT separately by study periods providing counts (n) and percentages (%). This summary will also include counts and percentages for unmasking.

A listing presents for the ITT the randomized allocation to study treatment as well as dispensing of kit numbers. Furthermore, a listing is provided displaying assignment of patients to SAF and ITT.

For the Total Set, a listing will be provided by summarizing study termination/completion information, date of informed consent (from eCRF page 'Informed Consent'), unmasking information and duration of study periods.

10.2 Protocol Deviations

The number of patients who had at least one CSR reportable protocol deviation and all categories of Protocol Deviations will be summarized by counts (n) and percentages (%) for the ITT. Percentages will be calculated based on the number of patients in the ITT.

A listing presents all Protocol Deviation data for the ITT.

10.3 Inclusion and Exclusion Criteria

The eligibility of all patients for entry into the study will be assessed at the Screening visit and confirmed at the Day 0 Therapy Initiation visit by the inclusion and exclusion criteria ('Inclusion/Exclusion Criteria' eCRF page).

Two listings will be provided for all patients in the ITT displaying status of Inclusion and Exclusion criteria, respectively.

10.4 Demographic and Other Baseline Characteristics

10.4.1 Demographic Characteristics

The following demographic variables will be collected on eCRF page 'Demography' or derived as detailed in section 7.2.2: Date of Birth, Gender ('Male', 'Female'), Race ['White', 'Black or African American', 'Asian', 'Native Hawaiian or Other Pacific Islander', 'American Indian or Alaska Native' or 'Other (with specification text box)'], Ethnicity ('Hispanic, Latino or Spanish', 'Not Hispanic, Latino or Spanish'), Age at Screening (years).

Demographic data including collected and derived, continuous and categorical variables will be summarized per treatment group and overall by summary statistics or absolute counts (n) and percentages (%) for the SAF.

A listing presents all demographic data for the ITT.

10.4.2 Glaucoma and Other Medical/Surgical History

10.4.2.1 Glaucoma History

Presence of Chronic Primary Open Angle Glaucoma, Symptomatic Eyes, Primary Eye and Secondary Eye will be summarized for the SAF and listed for the ITT. A listing will present all recorded glaucoma history data including details of other diagnosis than chronic primary open angle glaucoma, if any.

10.4.2.2 Medical/Surgical History

The medical and surgical history terms will be coded to a PT and SOC.

Medical History will be summarized per treatment group and overall by absolute counts (n) and percentages (%) for the number of patients with at least one medical history event for the SAF. Percentages will be calculated based on the number of patients in the population.

A listing presents all reported medical history data based on the ITT.

Surgical History will be summarized per treatment group and overall by absolute counts (n) and percentages (%) for the number of patients with at least one surgical history event for the SAF. Percentages will be calculated based on the number of patients in the population.

A listing presents all reported surgical history data based on the ITT.

10.4.3 Prior/Concomitant Medications

Further to section 7.2.4, the 'Prior and Concomitant Medications' eCRF records information on total daily dose, dose unit and other dose unit and whether the medication is to treat eyes, and if so, which eyes are involved.

Prior and Concomitant medications will be summarized by treatment group and overall for the SAF separately on a per-patient basis (i.e. if a patient reported the same medications repeatedly the medications will be counted only once at the specific level of display). Absolute counts (n) and percentages (%) will be presented for the number of patients taking at least one medication and per WHO Drug class 2 (ATC therapeutic main class) and per WHO Drug Name (Preferred Term) within ATC Drug class 2. Percentages will be calculated based on the number of patients in the SAF.

A Listing will present all documented medication data for the ITT and will include a flag for Prior medication.

10.5 Exposure and Compliance to Study Medication

The exposure variables Duration of Treatment Period, Duration of Follow-up Period, Extent of Exposure and Days on Study Medication will be summarized for the SAF per treatment group.

Compliance will be summarized for the ITT as counts and percentages in categories as defined in section 7.2.5. The percentages will be based on the number of patients in the ITT.

All eCRF data related to the assessment of exposure and compliance will be listed for all patients in the ITT. In addition, all data recorded on eCRF page 'Administration of Study Drug' including details on first 2 doses of study drug administration at site and occurrence of immediate AEs will be listed for all patients in the ITT.

10.6 Primary Study Outcomes

10.6.1 Primary Safety Outcomes

The incidence of USPON, USPON during treatment period, Intolerance/Allergy to the drug, Unexpected Related AEs affecting ocular function/eye pressure, Local toxicities and systemic toxicities will be summarized for SAF by counts and percentages of affected patients per treatment group. In addition, number of reported events will be provided.

A listing will be provided for the SAF summarizing all incidences on the patient level. The original source of presented events will be flagged in respective listings for AEs, BCDVA, HVF, ERG and OCT, respectively.

10.6.2 Primary Tolerability Outcomes

The Overall VAS Ocular Tolerability Scores as well as the seven symptoms scores will be summarized per Primary/Secondary Eye and treatment group for the SAF at each scheduled study visit. In addition, Change from Baseline summaries will be provided together with respective inferential statistics for the SAF as described in section 8.2.

All data of tolerability will be listed for all patients of the SAF.

10.7 Secondary Explorative Efficacy Outcomes

All exploratory efficacy analysis will be performed on the ITT by Primary and Secondary Eye according to the treatment randomized.

10.7.1 Change in Best-Corrected Distance Visual Acuity

The Visual Acuity Score and logMAR are summarized per Primary/Secondary Eye respectively for each treatment group at all scheduled study visits and changes from baseline for Visual Acuity Score and LogMAR at week 8, week 12 and week 32.

No imputation for missing values will be performed for these analysis. For safety tables associated for BCDVA please refer to section 10.8.

A listing will be provided describing all recorded data as well as changes from baseline for the ITT.

10.7.2 Changes in Visual Field Testing

All HVF data will be listed for the ITT by date and eye including derived information on corresponding treatment period and occurrence of USPON. No changes from baseline will be calculated for these data.

10.7.3 Changes in ERG

PhNR results as well as changes from baseline will be summarized for Primary/Secondary Eye respectively for each treatment group at all scheduled visits.

A listing will present all recorded ERG results for the ITT flagging also records reflecting the occurrence of USPON due to ERG assessments.

10.7.4 Ocular Coherence Tomography (OCT)

All 17 (4+12+1) RNFL variables will be summarized by Primary/Secondary Eye for each treatment group at all scheduled visits as well as changes from baseline at Week 8, Week 12 and Week 32.

A listing will present the above variables over time for each eye as well as the changes from baseline for these variables for all patients in the ITT.

All nine variables associated with PanoMap analysis will be summarized by Primary/Secondary Eye for each treatment group at all scheduled visits and changes from baseline at Week 8, Week 12 and Week 32.

A listing will present all PanoMap assessments as well as the changes from baseline for all patients in the ITT.

All 6 variables associated with Ganglion Cell Analysis will be summarized by Primary/Secondary Eye for each treatment group at all scheduled visits and changes from baseline at week 8, week 12 and week 32.

A listing will present all Ganglion Cell Analysis results as well as the changes from baseline for all patients in the ITT.

All assessments associated with an USPON will be flagged in the 3 listings describing OCT results.

10.8 Adverse Events and Further Safety Assessments

10.8.1 Adverse Events

10.8.1.1 Brief Summary of Adverse Events

An overview summary will be provided for the SAF by presenting of events as well as number and percentages of affected patients for AEs, TEAEs, TEAEs in the Treatment Period, TEAEs in the Follow-Up Period, TEAEs leading to Premature Withdrawal of Study Treatment, TEAEs leading to Study Discontinuation, Treatment Related TEAEs, Serious AEs, Serious TEAEs, Treatment Related Serious TEAEs Fatal AEs, AESIs, TEAEs by severity, TEAEs in the Treatment Period by severity, TEAEs in the Follow-Up Period by severity, TEAEs by age category, TEAEs in the Treatment Period by age category, TEAEs in the Follow-Up Period by age category.

10.8.1.2 Display of Adverse Events

Adverse event descriptive tables will be summarized separately for each study treatment and overall.

They will be summarized on a per-patient basis (i.e. if a patient reported the same event repeatedly the event will be counted only once at the specific level of display). Absolute counts (n) and percentages (%) will be presented for the number of patients with at least one adverse event, and per SOC and per PT within SOC, for the SAF. Percentages will be based on the number of patients in the population. In addition, number of events will be provided.

Descriptive tables will be ordered by descending frequency of the overall number of patients within each SOC regardless of treatment group, and then ordered within each SOC by the overall number of patients within each PT regardless of treatment group. In the event of equal frequencies tables will be ordered by active treatment frequency and then alphabetically.

The following tables will be provided:

- AEs for the SAF
- TEAEs for the SAF
- Treatment related TEAEs for the SAF
- TEAEs leading to premature withdrawal of Study Treatment for the SAF
- TEAEs leading to study discontinuation for the SAF
- Serious TEAEs for the SAF
- TEAEs by severity for the SAF
- TEAEs by age category (‘≤ 65 years’ vs ‘>65 years’) for the SAF
- TEAEs in the Treatment Period for the SAF
- TEAEs in the Treatment Period by severity for the SAF
- TEAEs in the Treatment Period by age category (‘≤ 65 years’ vs ‘>65 years’) for the SAF
- TEAEs in the Follow-Up Period for the SAF-F
- TEAEs in the Follow-Up Period by severity for the SAF-F
- TEAEs in the Follow-Up Period by age category (‘≤ 65 years’ vs ‘>65 years’) for the SAF-F

10.8.1.3 Listing of Adverse Events

The following listings will be presented for patients in the SAF:

- AEs
- TEAEs leading to premature withdrawal of study treatment
- TEAEs leading to study treatment interruption
- Treatment Related TEAEs
- Serious AEs
- Fatal AEs.

10.8.2 Laboratory Assessments

A listing will be provided for female patients in the SAF displaying the results of pregnancy test assessments during study as documented on the eCRF Page 'Urine Pregnancy Test'.

10.8.3 BCDVA assessments for Safety Evaluation

The incidences of Substantial Decrease of Visual Acuity during Treatment and Substantial Decrease of Visual Acuity during Follow-Up will be summarized by Primary/Secondary Eye for the SAF. Each occurrence of a Substantial Decrease will be flagged in the corresponding listing describing BCDVA assessments for the ITT.

10.8.4 External Ocular Examination

All evaluations of the motility of extraocular muscle Right and Up, Right, Right and Down, Left and Up, Left, Left and Down will be summarized descriptively by treatment group and study visit for the Primary Eye as well as the Secondary Eye. This analysis will be performed on the SAF. In addition, a shift table will be provided displaying the status of all scheduled Post-Baseline Visits in relation to the Baseline status. The percentages are based on the number of SAF patients in the respective baseline stratum of considered treatment group. These data will also be listed.

Incidences of proven eyelid deformity/abnormality, abnormal motor function of eyelids, corneal exposure in case of closed eyelid, proven punctal occlusion, punctal plugs, thermal or surgical occlusion or other punctal occlusion will be presented by treatment group and study visit for the Primary Eye as well as for the Secondary Eye. In addition, a shift table (Presence, Absence of considered abnormality) will be provided displaying the status of all scheduled Post-Baseline visits in relation to the Baseline status.

Incidences will be calculated as number and percentages of affected patients in respective treatment groups of the SAF. The percentages in the shift tables are based on the number of SAF patients in the respective baseline stratum of considered treatment group. The analysis will be performed on the SAF. Moreover, these date will be listed.

10.8.5 Slit Lamp Examination

All grading assessments of different eye structure (excluding assessment for other structures) will be summarized descriptively by treatment group and study visit for the Primary Eye as well as the Secondary Eye. In addition, a shift table will be provided displaying the status of all scheduled post-baseline visits in relation to the baseline status. The percentages are based on the number of SAF patients in the respective baseline stratum of considered treatment group. These analyses will be performed on the SAF.

All data recorded on the eCRF page 'Slit Lamp Examination (Biomicroscopy)' will be listed for the SAF.

10.8.6 Intraocular Pressure

Intraocular Pressure is summarized for the SAF by Primary/Secondary Eye for each treatment group at all visits as well as changes from baseline at all post-baseline visits.

A listing will present all documented assessments of intraocular pressure as well as the respective changes from baseline.

10.8.7 Dilated Fundus Ophthalmoscopy

All grading assessments performed during Dilated Fundus Ophthalmoscopy will be summarized descriptively by treatment group and study visit for the Primary Eye as well as the Secondary Eye. In addition, a shift table will be provided displaying the status of all scheduled post-baseline visits in relation to the baseline status. The percentages are based on the number of SAF patients in the respective baseline stratum of considered treatment group. These analyses will be performed on the SAF.

All data including details on detected abnormalities recorded on the eCRF page ‘Dilated Fundus Ophthalmology’’ will be listed for the SAF.

11 References

1	Cox, D. R. and Snell, E. J., *The Analysis of Binary Data*, Second Edition, London: Chapman & Hall, 1989
2	Holladay, JT (1997) Proper Method for Calculating Average Visual Acuity. Journal of Refractive Surgery, 13, pp. 388-391
3	Kim, HD et al. (2010) Clinical Applications of Photopic Negative Response (PhNR) for the Treatment of Glaucoma and Diabetic Retinopathy, Korean J Ophthalmol 24(2), pp. 89-95

12 Tables, Listings and Figures

In agreement with Medical Writing, numbering of the actual output will be accommodated to numbering into appendices 14 and 16.

In the column U/R it is indicated whether the item is U=Unique TLF (or first instance of a table to be repeated) or R=Repeat item.

In the column SR it is indicated whether the item will be repeated for the Final Analysis (Y=yes, N=no).

TLF number	Title	Analysis Set	U/R	SR
Tables				
Table 14.1-1.1	Summary of Patient Disposition	TOT	U	N
Table 14.1-1.2	Summary of Study Discontinuation	ITT	U	Y
Table 14.1-2.1	Summary of Protocol Deviations	ITT	U	Y
Table 14.1-3.1	Summary of Demographic Data	SAF	U	N
Table 14.1-4.1	Summary of Glaucoma History	SAF	U	N
Table 14.1-5.1	Summary of Medical History	SAF	U	N
Table 14.1-5.2	Summary of Surgical History	SAF	U	N
Table 14.1-6.1	Summary of Prior Medications	SAF	U	N
Table 14.1-6.2	Summary of Concomitant Medications	SAF	R	Y
Table 14.1-7.1	Summary of Exposure	SAF	U	Y
Table 14.1-7.2	Summary of Compliance	ITT	U	N
Table 14.2-1.1	Summary of Primary Safety Outcomes	SAF	U	Y
Table 14.2-2.1	Summary of VAS Ocular Tolerability Scores	SAF	U	N
Table 14.2-2.2	Summary of Changes from Baseline in VAS Ocular Tolerability Scores	SAF	U	N
Table 14.2-2.3	Analysis of Changes from Baseline in VAS Ocular Tolerability Scores	SAF	U	N
Table 14.2-3.1	Summary of BCDVA Scores	ITT	U	Y
Table 14.2-3.2	Summary of Changes from Baseline in BCDVA Scores	ITT	U	Y
Table 14.2-3.3	Analysis of Changes from Baseline in BCDVA Scores	ITT	U	N
Table 14.2-4.1	Summary of LogMAR	ITT	U	Y
Table 14.2-4.2	Summary of Changes from Baseline in LogMAR	ITT	U	Y
Table 14.2-4.3	Analysis of Changes from Baseline in LogMAR	ITT	U	N
Table 14.2-5.1	Summary of PhNR	ITT	U	Y
Table 14.2-5.2	Summary of Changes from Baseline in PhNR	ITT	U	Y
Table 14.2-5.3	Analysis of Changes from Baseline in PhNR	ITT	U	N

TLF number	Title	Analysis Set	U/R	SR
Table 14.2-6.1	Summary of RNFL Variables	ITT	U	Y
Table 14.2-6.2	Summary of Changes from Baseline in RNFL Variables	ITT	U	Y
Table 14.2-6.3	Analysis of Changes from Baseline in RNFL Variables	ITT	U	N
Table 14.2-7.1	Summary of PanoMap Variables	ITT	U	Y
Table 14.2-7.2	Summary of Changes from Baseline in PanoMap Variables	ITT	U	Y
Table 14.2-7.3	Analysis of Changes from Baseline in PanoMap Variables	ITT	U	N
Table 14.2-8.1	Summary of Ganglion Cell Variables	ITT	U	Y
Table 14.2-8.2	Summary of Changes from Baseline in Ganglion Cell Variables	ITT	U	Y
Table 14.2-8.3	Analysis of Changes from Baseline in Ganglion Cell Variables	ITT	U	N
Table 14.3.1-01.1	Overall Summary of Adverse Events	SAF	U	Y
Table 14.3.1-02.1	Summary of Adverse Events by System Organ Class and Preferred Term	SAF	U	Y
Table 14.3.1-03.1	Summary of TEAEs by System Organ Class and Preferred Term	SAF	R	Y
Table 14.3.1-04.1	Summary of Treatment Related TEAEs by System Organ Class and Preferred Term	SAF	R	Y
Table 14.3.1-05.1	Summary of TEAEs leading to Premature Withdrawal of Study Treatment by System Organ Class and Preferred Term	SAF	R	Y
Table 14.3.1-06.1	Summary of TEAEs leading to Study Discontinuation by System Organ Class and Preferred Term	SAF	R	Y
Table 14.3.1-07.1	Summary of Serious TEAEs by System Organ Class and Preferred Term	SAF	R	Y
Table 14.3.1-08.1	Summary of TEAEs by Severity, System Organ Class and Preferred Term	SAF	U	Y
Table 14.3.1-09.1	Summary of TEAEs by Age Category, System Organ Class and Preferred Term	SAF	U	Y
Table 14.3.1-10.1	Summary of TEAEs in the Treatment Period by System Organ Class and Preferred Term	SAF	R	N
Table 14.3.1-11.1	Summary of TEAEs in the Treatment Period by Severity, System Organ Class and Preferred Term	SAF	R	N
Table 14.3.1-12.1	Summary of TEAEs in the Treatment Period by Age Category, System Organ Class and Preferred Term	SAF	R	N

TLF number	Title	Analysis Set	U/R	SR
Table 14.3.1-13.1	Summary of TEAEs in the Follow-Up Period by System Organ Class and Preferred Term	SAF-F	R	Y
Table 14.3.1-14.1	Summary of TEAEs in the Follow-Up Period by Severity, System Organ Class and Preferred Term	SAF-F	R	Y
Table 14.3.1-15.1	Summary of TEAEs in the Follow-up Period by Age Category, System Organ Class and Preferred Term	SAF-F	R	Y
Table 14.3.2-1.1	Summary of Substantial Worsening of Visual Acuity	SAF	U	Y
Table 14.3.3-1.1	Summary of Motility of Extraocular Muscle	SAF	U	Y
Table 14.3.3-1.2	Shift Table for Motility of Extraocular Muscle	SAF	U	Y
Table 14.3.3-2.1	Summary of Appearance and Function of Eyelid	SAF	U	Y
Table 14.3.3-2.2	Shift Table for Appearance and Function of Eyelid	SAF	U	Y
Table 14.3.4-1.1	Summary of Slit Lamp Examination	SAF	U	Y
Table 14.3.4-1.2	Shift Table for Slit Lamp Examination	SAF	U	Y
Table 14.3.5-1.1	Summary of Intraocular Pressure	SAF	U	Y
Table 14.3.5-1.2	Summary of Changes from Baseline in Intraocular Pressure	SAF	U	Y
Table 14.3.6-1.1	Summary of Dilated Fundus Ophthalmology	SAF	U	Y
Table 14.3.6-1.2	Shift Table for Dilated Fundus Ophthalmology	SAF	U	Y
Listings				
Listing 16.1.7-1.1	Randomized Allocation to Treatment and Assigned Kit Numbers	ITT	U	N
Listing 16.2.1-1.1	Listing of Study Completion, Unmasking and Duration of Study Periods	TOT	U	Y
Listing 16.2.2-1.1	Listing of Protocol Deviations	ITT	U	Y
Listing 16.2.2-1.2	Listing of Inclusion Criteria	ITT	U	N
Listing 16.2.2-1.3	Listing of Exclusion Criteria	ITT	U	N
Listing 16.2.3-1.1	Listing of Allocation to Analysis Sets	TOT	U	N
Listing 16.2.4-1.1	Listing of Demographic Data	ITT	U	N
Listing 16.2.4-2.1	Listing of Glaucoma History	ITT	U	N
Listing 16.2.4-3.1	Listing of Medical History	ITT	U	N
Listing 16.2.4-3.2	Listing of Surgical History	ITT	U	N
Listing 16.2.4-4.1	Listing of Prior and Concomitant Medication	ITT	U	Y
Listing 16.2.5-1.1	Listing of Exposure, Compliance and Days on Study Treatment	ITT	U	N
Listing 16.2.5-1.2	Listing of First Study Drug Administration	ITT	U	N

TLF number	Title	Analysis Set	U/R	SR
Listing 16.2.6-1.1	Listing of Primary Safety Outcomes	SAF	U	N
Listing 16.2.6-2.1	Listing of VAS Ocular Tolerability Scores	SAF	U	N
Listing 16.2.7-1.1	Listing of BCDVA Assessments	ITT	U	Y
Listing 16.2.7-1.2	Listing of BCDVA Scores, Snellen Equivalent and LogMAR	ITT	U	Y
Listing 16.2.8-1.1	Listing of HVF Assessments	ITT	U	Y
Listing 16.2.9-1.1	Listing of ERG Assessments	ITT	U	Y
Listing 16.2.10-1.1	Listing of OCT Assessments – Part I	ITT	U	Y
Listing 16.2.10-2.1	Listing of OCT Assessments – Part II	ITT	U	Y
Listing 16.2.10-3.1	Listing of OCT Assessments – Part III	ITT	U	Y
Listing 16.2.11-1.1	Listing of Adverse Events	SAF	U	Y
Listing 16.2.11-1.2	Listing of Action Taken due to Adverse Events	SAF	U	Y
Listing 16.2.11-2.1	Listing of TEAES leading to Premature Withdrawal of Study Treatment	SAF	R	N
Listing 16.2.11-3.1	Listing of TEAEs leading to Study Treatment Interruption	SAF	R	N
Listing 16.2.11-4.1	Listing of Treatment Related TEAEs	SAF	R	Y
Listing 16.2.11-5.1	Listing of Serious AEs	SAF	R	Y
Listing 16.2.11-6.1	Listing of Fatal AEs	SAF	R	Y
Listing 16.2.12-1.1	Listing of Pregnancy Tests (Females only)	SAF	U	N
Listing 16.2.13-1.1	Listing of Motility of Extraocular Muscle	SAF	U	Y
Listing 16.2.13-2.1	Listing of Appearance and Function of Eyelids	SAF	U	Y
Listing 16.2.14-1.1	Listing of Slit Lamp Examination – Part I	SAF	U	Y
Listing 16.2.14-1.2	Listing of Slit Lamp Examination – Part II	SAF	U	Y
Listing 16.2.15-1.1	Listing of Intraocular Pressure	SAF	U	Y
Listing 16.2.16-1.1	Listing of Dilated Fundus Ophthalmology	SAF	U	Y

13 Appendices

None