



**Effect of Neurotidine[®] (citicoline free acid in oral solution) on
quality of life in patients with glaucoma**

Protocol Number: NEUQOL2018

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1. STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable laws and regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or Competent Authority, except where necessary to eliminate an immediate hazard to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC before the changes are implemented. All changes to the consent form will be IEC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
CACG	Chronic Angle-Closure Glaucoma
CFR	Code of Federal Regulations
CRO	Contract Research Organization
eCRF	electronic Case Report Forms
EFSA	European Food Safety Authority
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
LOCS	Lens Opacities Classification System
MP	Monitoring Plan
MD	Mean Deviation
MedDRA	Medical Dictionary for Regulatory Activities
NTG	Normal Tension Glaucoma
OCT	Optical Coherence Tomography
ONH	Optic Nerve Head
PEX	Pseudoexfoliation
PT	Preferred Term
SAE	Serious Adverse Event
SF-36	Short Form Health Survey – 36 items
SITA	Swedish Interactive Threshold Algorithm
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
VA	Visual Acuity
VF	Visual Field
VFQ	Visual Functioning Questionnaire – 25 items



Clinical Trial Protocol NEUQOL2018

OPKO Health

WHO-DD World Health Organization Drug Dictionary

3. PROTOCOL SUMMARY

Background: Primary open angle glaucoma is a chronic progressive neurodegenerative disease and the only proven effective therapy involves reduction of intraocular pressure (IOP). Although treatment effect is quite large, a significant proportion of patients show disease progression with apparently controlled IOP.¹ Given the similarities with other neurodegenerative diseases – particularly in the mechanisms of cell death – neuroprotective treatments have been tried also in glaucoma. Interesting results from experimental studies and weak evidence from human glaucoma trials have been published in recent years. Citicoline is one of the promising molecules with a putative neuroprotective action and has been tried on patients with a number of neurodegenerative diseases with encouraging results.² Pilot studies on glaucomatous patients showed a possible effect of citicoline in reducing progression of visual field changes,³ though these findings need to be confirmed by larger randomized clinical trials. One of the different explanations for the effect of citicoline on visual field changes is related to its dopaminergic action, which also has positive repercussions on psychophysical performances.

Aims: The main objective of the study is to test whether the intake of Neurotidine[®] (citicoline free acid in oral solution) can be associated with an improvement of quality of life in patients with glaucoma. Other objectives are the assessment of the tolerability and safety of Neurotidine[®].

Design: This is a randomized, double-masked, placebo-controlled, cross-over study. After informed consent and verification of eligibility, patients will be randomized in a 1:1 ratio to a Neurotidine[®]-placebo or placebo-Neurotidine[®] sequence and receive treatment for 3 months

in the first period and for six months in the second period of the cross-over design. The second period will be extended to 6 months in order to control for potential carry over effect in the group receiving Neurotidine[®] in the first period of the cross-over design.

Treatment: Neurotidine[®] or placebo will be administered at a dosage of 10 ml in the morning.

- Neurotidine[®]: 500 ml oral solution containing citicoline free acid 50 mg/ml.
- Placebo: 500 ml oral solution indistinguishable from active product in appearance and taste.

Patients: A total of 200 patients will be evaluated in this study, ideally 40 per center, with a minimum of 20 and a maximum of 50 per centre, though enrollment will be competitive.

- Inclusion criteria:
 - Signed written informed consent.
 - Age \geq 18 years.
 - Patients with bilateral open-angle glaucoma (OAG). PEX and pigmentary glaucoma will be included.
 - Controlled IOP
 - Patients with moderate damage in the better eye, with mean deviation from normal value (MD) ranging from -6 to -12 dB in the 6 months prior to enrollment. At the screening assessment, MD must range from -5 to -13 dB.

Glaucoma definition will be based on visual field (VF) damage (24-2, SITA standard strategy) corresponding to glaucomatous changes at the optic nerve head. Values of IOP will not be an inclusion criterion, though a “controlled IOP” based on the clinician’s judgement will be required.

- Exclusion criteria
 - Single-eyed patients (visual acuity <0.1 in one eye).

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- Patients without the psychophysical requirements to adequately participate and complete the trial.
 - Patients with chronic angle-closure glaucoma (CACG) or other types of glaucoma.
 - Patients with other ocular comorbidities interfering with the correct assessment of the glaucomatous damage to the VF.
 - Patients who have undergone surgery within 6 months.
 - Patients taking other potential neuroprotectors, including topical, competing with Neurotidine[®].
 - Patients with Parkinson's disease, dementia or a diagnosis of stroke in the last 6 months.

Study outcomes: The primary outcome will be the mean change of “intra-patient” global score of the VFQ-25 questionnaire after Neurotidine[®] vs placebo at 6 months as compared to baseline. Other outcomes include the change of other scores (e.g. general health, general vision, near and far activities, social, mental, role difficulties, etc.) of two study questionnaires, VFQ-25 and SF-36, as well as the safety and tolerability of citicoline oral solution.

4. SCHEDULE OF ASSESSMENTS

	Screening / Baseline (beginning of 1 st period)	3-month Visit (end of 1 st period, beginning of 2 nd period)	6-month Visit	9-month Visit (end of 2 nd period)
Informed consent	X			
Inclusion/exclusion criteria	X			
Complete ophthalmological examination*	X	X	X	X
Randomization to study sequence	X			
VFQ-25	X	X	X	X
SF-36	X	X	X	X
Dispensing treatment	X	X	X	
Concomitant medications	X	X	X	X
Adverse events		X	X	X

*Including visual acuity (VA), VF (24-2, SITA standard strategy), fundus assessment, biomicroscopy (with specific lens evaluation using Lens Opacities Classification System III (LOCS III) criteria), IOP assessment. Gonioscopy and optic nerve head (ONH) topography parameters measured by optical coherence tomography (OCT) are required at screening to verify inclusion/exclusion criteria.

5. INTRODUCTION

Glaucoma is a chronic and progressive neurodegenerative disease with unknown etiology. A number of factors are involved in the pathogenesis, though increased IOP remains the most important. However, elevated IOP cannot explain disease progression in many cases: data

from large clinical trials are consistently showing a variable (and relevant) proportion of glaucoma patients experiencing worsening of visual field despite apparent IOP control.¹ It is thus very likely that mechanisms other than IOP are involved in the pathogenesis of the disease.

A bulk of experimental data has shown similarities in the mechanisms of cell death across different neurodegenerative diseases. Glaucomatous optic neuropathy shares the way cells die and mechanisms of trans-synaptic neurodegeneration with neurologic diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis etc.^{4,5} There is growing evidence that glaucomatous damage involves all the visual pathways from the retina back to the lateral geniculate nucleus and the visual cortex. Today we can say that glaucoma can be considered a brain disease. As the main and starting event in glaucoma is the death of the retinal ganglion cell, neuroprotective strategies have been postulated. All possible molecules with a putative effect on glaucomatous neurodegeneration have been tested in vitro, in vivo in animal models, but only a few in human glaucoma. Today, there are about a dozen clinical trials in glaucoma showing products with a possible neuroprotective effect. The main problem is that most of these studies are grossly undersized to clearly demonstrate an effect on glaucoma progression.

There have been 2 large trials on neuroprotection in glaucoma, both with surprising outcomes. One tested memantine on about 2,000 patients with high-risk of progressive glaucoma: despite the large sample size the trial failed to reach the primary end-point (required by FDA). There is substantial lack of information about the details of what happened in this study as findings were never published. The other study tested brimonidine on low-tension glaucoma patients and the drug was found unexpectedly to be "extremely" effective in reducing disease

progression.⁶ However, some methodological flaws of the trial casted doubts on the validity of the findings and, as a matter of fact, brimonidine did not become the first-choice therapy for normal tension glaucoma (NTG) patients despite the evidence of a significant effect.

The action of citicoline in patients with neurodegenerative disorders has been known for a long time and today there are hundreds of publications about the efficacy of the molecule in patients with dementia, stroke, Parkinson's disease and glaucoma.² There is a systematic review from the Cochrane database reporting that citicoline can be effective in improving activity scores in patients with some stage of senile dementia.⁷ The mechanisms of action include “cell protection” (as it is part of the cell membrane), reduction of cell apoptosis and a positive effect on the synthesis of neurotransmitters – both dopaminergic and cholinergic.

Citicoline can be administered systemically (intramuscular, oral) and topically. Most of the literature on the effect of citicoline is based on systemic intramuscular administration.⁸ Since some years ago, similar bioavailability can be obtained with oral solution, a more practical and comfortable way of administration for chronic diseases where citicoline needs to be given daily for years.^{9,10} There is evidence that citicoline oral solution has 98% bioavailability.⁹ Recently, citicoline free acid has been authorized in Europe by the EFSA (European Food Safety Authority) as a Novel Food ingredient also for Special Medical Purpose, and according to this new classification, a form in oral solution (Neurotidine[®]) has been registered as Food for Special Medical Purpose with therapeutic Indication: “Glaucomatous patients with stable IOP, but with a progressive loss of Visual Field (VF)”. Citicoline eyedrops are also available in many European Countries.

6. OBJECTIVES

Today there is growing evidence (though still weak) that citicoline can be an effective complementary treatment for glaucoma patients. Awaiting large clinical trials to confirm the effectiveness of citicoline in reducing the progression of glaucoma, the rationale for this study includes the assessment of the role of the molecule on the dopaminergic pathway and particularly its potential implications on psychophysical performance and quality of life. Other objectives are the assessment of the tolerability and safety of Neurotidine[®] (citicoline oral solution).

7. STUDY OUTCOMES

The primary outcome will be the mean change of “intra-patient” global score of the VFQ-25 questionnaire after Neurotidine[®] vs placebo at 6 months compared to baseline. Other outcomes include the change of other scores (e.g. general health, general vision, near and far activities, social, mental, role difficulties, etc.) of two study questionnaires, VFQ-25 and SF-36, as well as the safety and tolerability of citicoline oral solution.

8. PATIENTS

A total of 200 patients will be evaluated in this study, ideally 40 per center, with a minimum of 20 and a maximum of 50 per centre, though enrollment will be competitive. Inclusion and exclusion criteria will be ascertained through a complete ophthalmic examination including VF test, gonioscopy and optic nerve head (ONH) topography parameters measured by optical coherence tomography (OCT).

8.1 Inclusion Criteria

Patients must meet all the following criteria to be eligible for the study:

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- Signed written informed consent.
 - Age \geq 18 years.
 - Patients with bilateral open-angle glaucoma (OAG). PEX and pigmentary glaucoma will be included.
 - Controlled IOP
 - Patients with moderate damage in the better eye, with mean deviation from normal value (MD) ranging from -6 to -12 dB in the 6 months prior to enrollment. At the screening assessment, MD must range from -5 to -13 dB.

Glaucoma definition will be based on visual field (VF) damage (24-2, SITA standard strategy) corresponding to glaucomatous changes at the optic nerve head. Values of IOP will not be an inclusion criterion, though a “controlled IOP” based on the clinician’s judgement will be required.

8.2 Exclusion Criteria

Patients must meet none of the following criteria to be eligible for the study:

- Single-eyed patients (visual acuity <0.1 in one eye).
- Patients without the psychophysical requirements to adequately participate and complete the trial.
- Patients with chronic angle-closure glaucoma (CACG) or other types of glaucoma.
- Patients with other ocular comorbidities interfering with the correct assessment of the glaucomatous damage to the VF.
- Patients who have undergone surgery within 6 months.
- Patients taking other potential neuroprotectors, including topical, competing with Neurotidine[®].
- Patients with Parkinson’s disease, dementia or a diagnosis of stroke in the last 6 months.

9. TREATMENTS

Patients will be treated with any IOP-lowering agent to control the disease. The type and number of drugs will be decided by the treating clinician. Previous laser and/or surgery will be allowed but not within 6 months prior to study enrollment.

After signing of the informed consent form and ascertainment of eligibility, patients will be randomized in a 1:1 ratio to a Neurotidine[®]-placebo or placebo-Neurotidine[®] sequence and receive treatment for 3 months in the first period and for six months in the second period of the cross-over design. The second period will be extended to 6 months in order to control for potential carry over effect in the group receiving Neurotidine[®] in the first period of the cross-over design.

Neurotidine[®] 500 ml oral solution contains citicoline free acid 50 mg/ml; water; fructose; acidity regulators: sodium citrate, sodium hydroxide; preservative: potassium sorbate; color: riboflavin.

Placebo 500 ml oral solution contains water, fructose, sucralose; acidity regulators: sodium citrate, anhydrous citric acid, sodium hydroxide; preservative: potassium sorbate; color: riboflavin.

In addition to the IOP-lowering medications, Neurotidine[®] or placebo will be administered at a dosage of 10 ml in the morning.

Bottles of Neurotidine[®] and placebo oral solutions will be identical (same ingredients except for citicoline), containing 500 ml of a yellow solution with a measuring cup. Neurotidine[®] and placebo solutions will have similar taste. Each patient will be given the bottles for the first 3-month treatment period by the hospital pharmacist and will be asked to return them at the end

of the period (3 months). Then the patients will be given the other bottles for the next phase of the study (3 months): these will contain placebo if the patient received Neurotidine[®] in the first phase of the study and vice versa. Again, the patients will be asked to return after 3 months with the study bottles and will be given the last set of bottles for the final phase of the study (3 months): in this phase the bottle contents will be the same as in phase 2.

Information about compliance with treatment will be recorded at each visit. All study bottles will be collected and sent to the coordinating center.

10. DESIGN

The trial will be a randomized, double-masked, placebo-controlled, cross-over study. Eligibility criteria will be assessed, and study procedures clearly explained when the potentially eligible patients are initially visited. If the patients accept to participate in the trial, they will have to sign the informed consent form. After this, the patients will be randomized in a 1:1 ratio to one of the two sequences of the cross-over design: Neurotidine[®]-placebo or placebo-Neurotidine[®]. The randomization will be stratified by centre.

- Baseline visit (beginning of 1st period): Enrolled patients will undergo a complete ophthalmologic examination with VA, VF (24-2, SITA standard strategy), fundus assessment, biomicroscopy (with specific lens evaluation using Lens Opacities Classification System III (LOCS III) criteria), IOP assessment. A masked to treatment evaluator will administer the two study questionnaires (VFQ-25 and SF-36). The patients will be given the bottles for the first 3-month period.
- 3-month visit (end of the 1st period and beginning of 2st period): Patients will undergo a complete ophthalmologic examination with VA, VF (24-2, SITA standard strategy),

biomicroscopy, IOP assessment. Patients will be asked about treatment side effects and all complains/considerations will be recorded. The two study questionnaires (VFQ-25 and SF-36) will be administered. The patients will be given the bottles for the second 3-month period.

- 6-month visit: Patients will undergo a complete ophthalmologic examination with VA, VF (24-2, SITA standard strategy), biomicroscopy, IOP assessment. Patients will be asked about treatment side effects and all complains/considerations will be recorded. Patients will be again administered the 2 study questionnaires (SF-36 and VFQ-25). The patients will be given the bottles for the third 3-month phase.
- 9-month visit (end of the 2st period): Patients will undergo a complete ophthalmologic examination with VA, VF (24-2, SITA standard strategy), biomicroscopy, IOP assessment. Patients will be asked about treatment side effects and all complains/considerations will be recorded. Patients will be administered the two study questionnaires (VFQ-25 and SF-36).

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Definition of Adverse Events (AEs)

An adverse event can be defined as any untoward medical occurrence associated with the use of an intervention in humans after providing written informed consent for participation in the study until the end of study visit, whether considered intervention-related or not.

11.2 Definition of Serious Adverse Events (SAEs)

An adverse event (AE) is considered "serious", regardless of relationship with the intervention, if, in the view of either the investigator or Sponsor, it results in any of the

following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3 Classification of an Adverse Event

11.3.1 Severity of Event

The following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

11.3.2 Relationship to study intervention

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. Investigators are to judge the causal relationship of the event with the study intervention as “suspected”, “unsuspected” or “unknown”.

11.3.3 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

11.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with onset dates occurring any time after informed consent is obtained until 30 days after the last treatment, and later if a causal

relationship with the intervention is suspected. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the previous visit. Events will be followed for outcome information until resolution or stabilization.

11.5 Adverse Event Reporting

All identified AEs (serious and non-serious, related and unrelated) must be recorded and described on the eCRF.

11.6 Serious Adverse Event Reporting

Every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until at least 30 days after the subject has stopped study treatment must be reported to the Sponsor within 24 hours of site awareness.

Any SAE experienced after this 30-day period should only be reported to the Sponsor if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Information about all SAEs will be transmitted to the Contract Research Organization (CRO) OPIS, in charge for this trial of vigilance for Food for Special Medical Purposes Neurotidine[®], via email at all_phv@opis.it or by fax using the following number: Fax: +39 0362 633622. Any AE collected by OPIS will be promptly forwarded to Omikron Italia, which is Responsible for the Food for Special Medical Purposes Neurotidine[®].

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study Sponsor and should be provided as soon as possible.

11.7 Reporting Events to Participants

Should an event occur that changes the overall benefit/risk ratio of the study, the Sponsor shall evaluate if a risk minimization measure is needed. Should this measure require a substantial amendment to the protocol, the informed consent and patient information will be revised and submitted to the patient for written consent.

12. DATA MANAGEMENT**12.1 Data Handling and Record Keeping***12.1.1 Data Collection*

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture system until they are trained.

Web-based software will be used, and no installation procedure is needed. Each site will be authorized by the administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring user ID and password and may read, modify, and update only the information entered at his or her site and according to their profile. Each page reports site code and subject code.

On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the CRO working on behalf of the Sponsor. The investigator will certify that the data entered in the eCRF are complete and accurate.

After database lock, the investigator will receive a CD-ROM of subject data for archiving at the investigational site.

12.1.2 Database management and quality control

The CRO working on behalf of the Sponsor will review the data entered in the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. The occurrence of any protocol deviations will also be checked.

If clarifications are needed, the Data Manager will raise queries through the web application. Designated investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses.

Data collection and query flows, as well as the on-line and off-line checks, are detailed in the Data Management Plan and Data Validation documents.

Concomitant medications and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using MedDRA.

The database will be locked after all the above actions have been completed and the database has been declared complete and accurate.

13. SAMPLE SIZE

The sample size has been calculated based on the main outcome of the study, i.e. the mean change vs baseline of the global score of The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25) in patients with moderate-stage glaucoma (*Ophthalmol 2015 Nov Acta 19*).

When the sample size in each sequence group is 100, (a total sample size of 200) a 2 x 2 crossover design will have 80% power to detect a difference in means of 3.0 (the difference between study treatment mean, μ_1 , of 3.0 and placebo mean, μ_2 , of 0) assuming that the crossover ANOVA \sqrt{MSE} is 10.607 (the standard deviation of differences, σ_d , is 15.0) using a two group t-test (crossover ANOVA) with a 0.05 two-sided significance level.

The total sample size is adjusted to 220 patients considering an expected dropout rate of about 10%.

14. STATISTICAL ANALYSIS

Continuous data will be summarized with standard descriptive statistics (i.e. the mean, standard deviation, minimum, median and maximum, 95% confidence limits). Categorical data will be summarized by frequencies and percentages.

No statistical test will be performed for between-group differences in demographic and baseline features (medical history and efficacy data).

Medical history and adverse events will be described according to System Organ Classes (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by treatment group.

Previous/concomitant medications will be presented by treatment group using the World Health Organization Drug Dictionary (WHO-DD).

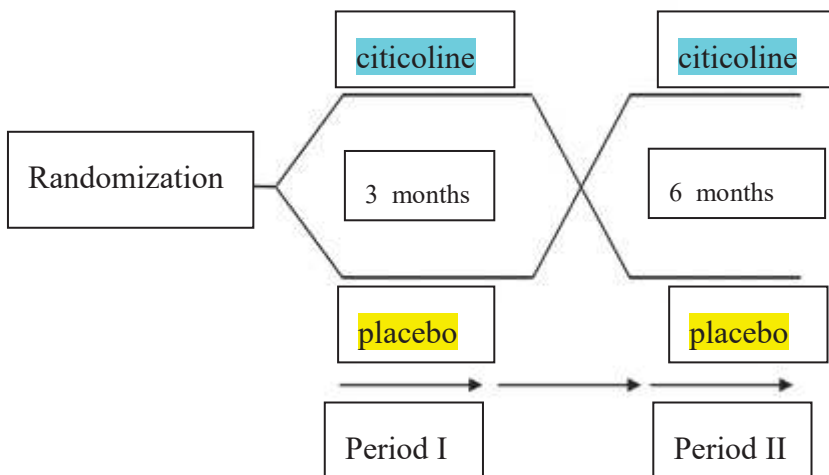
The primary efficacy variable will be analysed using crossover ANOVA, considering sequence, subjects, period and treatment as sources of variation.

All study centers will fill in a web-based e-CRF. The Data Center will check the e-CRF and solve all the queries. The Coordinating Center will do the statistical analysis of collected data.

The association between quality of life and measures of visual symptoms, of the ability to perform vision-related activities and clinical findings will be analysed by means of linear regression models.

All analysis will be performed using SAS version 9.4.

15. EXPERIMENTAL DESIGN



16. REGULATORY, EHTICAL AND STUDY OVERSIGHT CONSIDERATIONS

16.1 Informed consent procedures and documentation

Consent forms describing in detail the study intervention, study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Consent forms will

be approved by the IRB/IEC and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

16.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants, the IRB/IEC, Regulatory Authorities and Sponsor, and will provide the reason(s) for the termination or

suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IEC and regulatory authorities.

16.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Contract Research Organization (CRO) (OPIS s.r.l.) working on behalf of the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Only the study center will be able to link the study ID number to the patient's identity. The study data entry and study management systems used by clinical sites and by OPIS research staff will be secured and password protected.

16.4 Future Use of Stored Specimens and Data

Not applicable, no biological samples will be stored for future use during this study.

16.5 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is compliant with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The field monitor will visit the site at the beginning of the study and will then check the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrolment remotely via the eCRF system.

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

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific Monitoring Plan (MP). No information in source documents about the identity of the patients/subjects will be disclosed.

16.6 Quality Assurance and Quality Control

Following written Standard Operating Procedures, monitors will verify that the clinical trial is conducted and that data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related facilities, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by regulatory authorities.

Independent audits may be conducted by the Sponsor to ensure compliance with the protocol and GCP, and that monitoring practices are performed consistently across all participating sites and that monitors are following the MP.

16.7 Study Records Retention

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than twenty-five (25) years from the completion of the study unless the Sponsor provides written permission to dispose of them, requires their retention for an additional period because of applicable laws, regulations and/or guidelines. The subjects' medical files will be archived in accordance with national laws.

16.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP). The noncompliance may be on the part of either the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report protocol deviations. All deviations must be addressed in study source documents.

16.9 Insurance

The Sponsor certifies that it has taken out a liability insurance policy covering this clinical trial. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC and/or regulatory authorities.

16.10 Publication and Data Sharing Policy

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor, who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators or publication in International Journals.

The main publication reporting the results of the study will include as main authors the names of Principal Investigators of the five centers enrolling the patients.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioural treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or subjects, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as



ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

16.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17. REFERENCES

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