CLINICAL STUDY PROTOCOL

Study Title

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 Number:	*NGF0314*
Study Phase:	Ib
Sponsor Name:	Dompé farmaceutici S.p.A. Via S. Martino 12-12/A, 20122 Milan, Italy Phone: +39 02 583831; Fax: +39 02 58383324
IND Number:	*124304*
Investigational Product:	*recombinant human Nerve Growth Factor (rhNGF)*

SPONSOR CONTACT INFORMATION

Pharmacovigilance

Dr. Laura Boga
Dompé Drug Safety
Dompé farmaceutici S.p.A. - Milan
Fax: +39 02 36026913
e-mail: farmacovigilanza@dompe.com

Medical Expert

Dr. Flavio Mantelli
Dompé US, New York, NY
+1 646 656 1999
e-mail: flavio.mantelli@dompe.com

Trial Manager

Dr. Paolo Battigello
Dompé farmaceutici S.p.A. - Milan
+39 02 58383422
e-mail: paolo.battigello@dompe.com

CONTACT INFORMATION PROVIDERS

CLINICAL RESEARCH ORGANIZATION (CRO)

CROMSOURCE Srl
Street: Giorgio De Sandre, 3
VERONA
ITALY

Pharmacovigilance email: DOMPE-NGF-GLA-PV@cromsource.com
Medical Monitor email: DOMPE-NGF-GLA-MM@cromsource.com

CONTACT INFORMATION OF PRINCIPAL INVESTIGATOR:

Prof. Jeffrey L. Goldberg, MD, PhD
Professor and Chair, Department of Ophthalmology
Byers Eye Institute at Stanford University
2452 Watson Court
Palo Alto, CA 94303
Jeffrey.Goldberg@Stanford.edu
T: 650-723-6137
F: 650-565-8297 (clinic)

PROTOCOL APPROVAL SIGNATURES

SPONSOR:

Name: _____ Title: _____

Signature: _____ Date: _____

Name: _____ Title: _____

Signature: _____ Date: _____

CLINICAL CENTER: PRINCIPAL INVESTIGATOR

I have read study protocol *NGF0314 "**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**"* and agree to conduct the study as outlined in the protocol, and in accordance with the Declaration of Helsinki, ICH-GCP, United States of America Legislation and any local regulations, being responsible for personally supervise the study conduct and ensure study staff complies with protocol requirement.

Name of Principal Investigator: _____

Signature: _____ Date: _____

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1. PROTOCOL SYNOPSIS

Protocol:	NGF-Glaucoma		
Study Code:	NGF0314		
Protocol Title:	An 8 Week phase Ib, monocentric, randomized, double-masked, vehicle controlled, parallel groups, 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		
Investigational product:	Recombinant human nerve growth factor (rhNGF)	**Study Phase:**	☒ I ☐ II ☐ III ☐ IV ☐ N/A
Description of Investigational Product	Sterile isotonic aqueous solution for ocular administration containing rhNGF 180 µg/ml or Vehicle		
Objective(s):	**Primary objectives:** The primary objective is to evaluate the safety and tolerability of NGF vs vehicle. **Secondary objectives:** The secondary objectives are: • Mean, median, and distribution of change in BCDVA. • Changes in visual field using perimetry. • Changes in ERG including pattern ERG. And structural assessments: • Changes in ganglion cell layer and nerve fiber layer thickness measured by optical coherence tomography. **Exploratory objective:** • Changes in mitochondrial redox potential measured through adaptive optics scanning laser ophthalmoscope (SLO) imaging.		
Study Design:	This is a masked, randomized, single-dose, monocentric 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. 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.		
No. of Subjects	Randomized: 60 (40:20 patients per arm) to active treatment (180 µg/ml) or vehicle three times a day (TID), respectively.		
Region(s):	USA		

Study Population:	Adult patients with chronic primary open angle glaucoma with documented evidence of clinical progression prior to enrollment despite maximal current therapy (i.e. IOP reduction), or with stabilized IOP but diminished vision (central or peripheral).	
Total duration of the study:	Maximum total study duration 32 weeks (8 months). There will be three periods in this study: 1) a 8 week phase Ib double-masked, randomized, controlled treatment period. and 2) a 4 week masked follow-up period. and 3) a 20 week unmasked follow-up period.	
Treatments:	Test product: rhNGF 180 µg/ml eye drops solution	
	Administration:	Topical, ocular
	Duration of controlled treatment period:	8 weeks
	Quantity/Dosage:	Eligible patients will self-administer 1 drop of rhNGF 180 µg/ml three times a day (TID) for 8 weeks in both eyes.
	Control: Vehicle	
	Administration:	Topical, ocular
	Duration of controlled treatment period:	8 weeks
	Quantity/Dosage:	Eligible patients will self-administer 1 drop of vehicle three times a day (TID) for 8 weeks in both eyes.

Subject Selection:	**Inclusion Criteria:**
	1. Patients 18 years of age or older. Participant must understand and sign the informed consent. If the participant's vision is impaired to the point where he/she cannot read the informed consent document, the document will be read to the participant in its entirety.
	2. Participant's clinical diagnosis must be consistent with glaucoma characterized by the following features: a) clinical evidence of progressive RGC dysfunction and degeneration using visual field and/or a structural modality. There must be at least 3 reliable visual fields within 14 months prior to entering into the study. b) residual visual field preservation in at least 1 quadrant.
	3. Participant must be medically able to undergo the testing and study procedures required in the flowsheet of exam procedures.
	4. Females of childbearing potential must agree to use an effective form of birth control.

	Exclusion Criteria:
	1. Participant has another optic nerve or retinal degenerative disease or co-morbidity causing significant vision loss, irrespective of whether it is currently treated or untreated, that could limit the possibility of visual recovery.
	2. Participant is blind in one eye.
	3. Participant has a requirement of acyclovir and/or related products during study duration.
	4. Participant has evidence of corneal opacification or lack of optical clarity.
	5. Participant has undergone lens removal in the last 3 months, with or without intra-ocular lens implantation, or has undergone intra-ocular lens replacement within 3 months, or has undergone any other ocular surgery within 9 months prior to initiation of study drug.
	6. Participant is receiving systemic steroids or other immunosuppressive medications.
	7. Participant is currently participating in or has within the last 3 months participated in any other clinical trial of a non-clinically approved drug by ocular or systemic administration.
	8. Participant has uveitis or other ocular inflammatory disease.
	9. Participant has diabetic macular edema.
	10. Participant has a history of ocular herpes zoster.
	11. Participant is on chemotherapy.
	12. Participant has a history of malignancy, not counting basal cell carcinomas, UNLESS it was treated successfully 2 years prior to inclusion in the trial.
	13. Known hypersensitivity to one of the components of the study or procedural medications.
	14. History of drug, medication or alcohol abuse or addiction.

	15. Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions: a. are currently pregnant or, b. have a positive result on the urine pregnancy test at the Screening/Baseline Visit or, c. intend to become pregnant during the study treatment period or, d. are breast-feeding or, e. not willing to use highly effective birth control measures, such as: Hormonal contraceptives – oral, implanted, transdermal, or injected and/or mechanical barrier methods – spermicide in conjunction with a barrier such as a condom or diaphragm or IUD during the entire course of and 30 days after the study treatment periods. ***Important Notes:*** *All females of childbearing potential must consent to a urine pregnancy test upon entering and exiting the study treatment period. Females of childbearing potential must agree to immediately inform the Investigator if they become pregnant during the study.* *For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the patient becomes heterosexually active during the study treatment period, she must agree to use adequate birth control methods as defined above for the remainder of the study treatment period.* *Pregnancy should be avoided in patients or partners during the first month after completing the treatment with the Investigational Product.*

Assessments:	**Safety**
	• Adverse events • Best corrected distance visual acuity (BCDVA) • Intraocular pressure (IOP) • Slit lamp examination (SLE) • External ocular examination • Humphrey Visual Field 24-2 or 10-2 • Dilated fundus ophthalmoscopy • Ocular Coherence Tomography (OCT) • Mitochondrial redox potential • Electroretinogram (ERG) • Ocular tolerability using visual analogue scale (VAS)
Endpoints	**Safety Endpoints:** Safety will be assessed by the following outcomes (occurrence of these outcomes does not necessarily require cessation of therapy): • 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. Elevation of intraocular pressure, although not seen previously in human use and not expected in this population, will be considered for cessation of therapy in patients with glaucoma. Data on all adverse events will be collected regardless of severity or potential relationship to the drug. Tolerability will be assessed through a Visual Analog Scale (VAS)
Sample size:	As the objectives of this study are to evaluate the safety and explore the biological effects of a single rhNGF dosage, sample size was calculated based on clinical feasibility and no formal sample size calculation has been performed. Proposed sample size is of 60 patients adequate to make appropriate estimation of study variables.
Statistical methods:	Safety and efficacy data will be analyzed by descriptive statistics. All analyses will be detailed in the statistical analysis plan (SAP) and reported at the end of the study. All exploratory efficacy variables will be tabulated with the appropriate descriptive statistics and appropriate inferential tests with 95% confidence limits of the difference between treatments will be produced.

2. STUDY PLAN

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 (SLE)	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 to be 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 IP and the freezer bag.

Table Note: Required procedures for a scheduled visit may be performed over 2 consecutive days.

3. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AEF	Adverse Event Form
AM	Ante Meridien
BCDVA	Best Corrected Distance Visual Acuity
ºC	Degrees Celsius
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
g	Grams
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
h	Hour(s)
HIV	Human Immunodeficiency Virus
IOP	Intraocular Pressure
IRB	Institutional Review Board
IUD	Intra Uterine Device
kg	Kilogram
mg	Milligram
mNGF	Murine Nerve Growth Factor
ml	Milliliter
mmHg	Millimeters of Mercury
ng	Nanogram
P75 ^{NTR}	p75 neurotrophin receptor
PM	Post Meridien
RGC	Retinal Ganglion Cell
rhNGF	Recombinant Human Nerve Growth Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SLO	Scanning laser ophthalmoscope

SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TID	Ter In Die (i.e. Three times a day)
TrKA	Tyrosine Kinase Receptor A
VAS	Visual Analogue Scale
WFI	Water for injection
µg	Microgram

4. INTRODUCTION

Glaucoma is the leading cause of irreversible blindness in the world. [Quigley HA, 1996] This chronic and progressive disease is an optic neuropathy considered a neurodegenerative disease in which glutamate toxicity and increased apoptosis lead to a progressive loss of retinal ganglion cells (RGC) and loss of axons of the optic nerve, with a progressive and consequent deficit of the peripheral and central visual field. [Lambiase A, 2010] Glaucoma is an insidious disease with no warning symptoms: thus, the presence of one or more major risk factors (including elevated intraocular pressure, ageing, black race, a family history of glaucoma, increased corneal thickness) should alert physicians to periodically check for progressive optic nerve damage. In fact, early diagnosis of an elevated intraocular pressure may significantly reduce the risk of progressive nerve degeneration and visual field loss. [Weinreb Rn, 2004] In fact, intraocular pressure is the only risk factor that can be actually modified and is the only current target of glaucoma treatments. Nevertheless, it must be underlined that up to 20% glaucoma patients show progression of visual field defects with RGC and optic nerve degeneration despite successful management of ocular hypertension. [Collaborative Normal-Tension Glaucoma Study Group, 1998] In fact, elevated IOP is thought to be only the primum movens that triggers a cascade of events leading to optic nerve damage [Kwon YH, 2009] and, to date, there is no treatment available to restore neural function.

As a consequence, an approach that would significantly improve the treatment of this challenging disease would involve neuroprotection with exogenous neurotrophic factors. In fact, neuroprotection has gained substantial interest in recent years as a therapeutic approach to prevent neuronal degeneration and loss of function in glaucoma.

Specifically, recent studies reporting the differentiation, survival and function of retinal ganglion cells are regulated by survival growth factors, including neurotrophins, raised the possibility that neuroprotection could be a viable treatment approach in patients with glaucoma and other optic neuropathies [Roberti G, 2014]. Evidence obtained in animals with experimentally induced retinal cell degeneration and in rodents with inherited retinal diseases, indicate that a number of soluble factors, including brain derived neurotrophic factor (BDNF), b-fibroblast growth factor (b-FGF), nerve growth factor (NGF), transforming growth factor-b (TGF-b), tumor necrosis factor a (TNF-a), vascular endothelial factor (VEGF), neuropetide-Y (NPY), and ciliary neurotrophic factor (CNTF) can protect retinal cell degeneration alone or in combination with other growth factors. [Lavail MM, 2005].

NGF is a leading neurotrophin well known to promote survival, function and differentiation of central and peripheral neurons [Levi-Montalcini R, 1987]. NGF and both its receptors, TrkA and p75, are widely expressed in the central visual pathways as well as in the optic nerve and retina [Lambiase A, 2010]. Moreover, NGF has been shown to modulate the development and differentiation of the retina and optic nerve, and to promote the survival and recovery of retinal ganglion cells [Lambiase A, 2009]. In addition, intravitreal NGF injection enhances BDNF, β-FGF, TGF-β, VEGF and NP-Y, suggesting that the neuroprotectant effect of NGF may also be exerted through the stimulation of other biological mediators [Lenzi L, 2005].

More noteworthy, it has been the demonstrated in different animal models that topically applied NGF eye drops can reach the retina and optic nerve in sufficient concentrations to exert a pharmacologic effect, thereby, opening new perspectives for the treatment of retinal and optic nerve diseases [Lambiase A, 2005].

In addition, Lambiase and colleagues investigated the presence of NGF in the aqueous humor and evaluated the protective effect of endogenous and exogenous NGF in retinal damage using an experimental animal model of intraocular hypertension in rabbits [Lambiase A, 1997]. They showed that the highest NGF level was observed after 4 days of intraocular hypertension and histological examination revealed that the number of retinal RGC remained unchanged during the first 4 days but decreased significantly after 10 days. This study also showed that retro-ocular administration of NGF reduced RGC loss, whereas intraocular injection of NGF antibodies, that inhibit endogenus NGF, exacerbated the retinal insult.

These preliminary results suggested that NGF may be helpful in developing a new clinical approach to the treatment of human hypertensive ocular diseases.

Subsequently, after reporting that topical eye drop application of NGF could reach brain cholinergic neurons and suggesting that high molecular weight proteins could be safely delivered into the brain via the ocular surface to promote the recovery of damaged brain cells, Sposato et al. (2009) used a rat model of glaucoma as an approach to investigate the effects of glaucoma on cells of the lateral geniculate nucleus (LGN) and visual cortex (VC) and for understanding the role of topically-applied NGF eye drops on neurodegenerative diseases. [Sposato V, 2009]

They found that glaucoma reduces the concentration of NGF in the cerebrospinal fluid (CSF), LGN and VC, without causing significant changes in NGF serum levels. Topical ocular NGF application for 35 consecutive days enhanced the concentration of NGF in the CSF of

glaucomatous rats and normalized its presence in the VC and LGN. Exogenous NGF application induced up-regulation of TrkA in the LGN (but not in the VC), enhanced the expression of p75 in the LGN and reduced its presence in the VC.

Recently, Lambiase and colleagues [Lambiase A, 2009] also demonstrated that topical application of exogenous NGF to the eye prevents RGC degeneration in an experimental rat model of glaucoma. In this study, the beneficial effect of NGF on RGC survival was induced by the inhibition of RGC apoptosis, as shown by the reduction in TUNEL immunostaining and the greater retinal Bcl-2/Bax ratio.

Based on these findings they used the same dosage regimen to treat 3 glaucoma patients with rapid and progressive visual field loss despite successful control of intraocular pressure.

In line with the above findings, several preliminary reports of patients treated with topically applied NGF provide human evidence that the neurotrophic protein appears to reach the back of the eye in humans and could be a promising treatment for posterior segment ocular diseases. Specifically, in 6 patients, (5 children and 1 adult) with severe visual impairment due to compressive optic neuropathy associated with optic nerve glioma treatment with 10 day courses of topically applied NGF resulted in improved vision and optic nerve function as measured objectively by distance visual acuity, visual field and visual evoked potential (VEP) and improvement persisted up to 1 to 3 months before returning to baseline after the discontinuation of the treatment [Falsini, 2011; Chiaretti et al, 2011]. In 4 patients with advanced glaucoma progressing on maximum medical therapy treatment with topical NGF 4 time daily over 3 months was also reported to result in improved visual function. Upon the discontinuation of treatment, patients showed an improvement in optic nerve function (VEP and PERG). Moreover, at the 6 month follow-up patients maintained improvement in the optic nerve function and additionally showed improvement in visual function (visual acuity and visual field) suggesting a delayed or continued biologic effect of the NGF after the discontinuation of the treatment [Lambiase et al, 2009].

The NGF so far applied in the cited preclinical and clinical studies has been a murine NGF [Lambiase A, 1998] extracted and purified from the male mouse submaxillary glands following the Bocchini&Angeletti method. Murine NGF is 98% unglycosilated, and this unglycosilated fraction has full biological activity [Bocchini V, 1969]. NGF is highly conserved across different species and the two NGF forms, human and murine, show a 90% homology in the amino-acid sequence [Ullrich A, 1983]. Since maintaining an adequate supply of murine NGF would be a hindrance for the clinical development of NGF, a recombinant human form of NGF (rhNGF) has been developed by Dompé. Recombinant

human NGF (rhNGF) manufactured by Dompé is expressed in *E. coli* as a pro-protein. The pro-NGF is first isolated from inclusion bodies of E. coli, solubilized in a strong denaturing agent and subsequently refolded into the natural conformation. Subsequently, the pro-sequence is removed with trypsin generating recombinant mature human NGF, which is then further purified to obtain the API protein solution. The rhNGF formulated as an eye drops solution is being developed for the treatment of anterior and posterior segment ocular diseases such as neutrotrophic keratitis, dry eye disease, optic neuropathy and RP. While a topical formulation of rhNGF directed towards the treatment of ocular disease represents a novel therapeutic approach, the development and utilization of rhNGF in patients is not unprecedented. Clinical data are available in the literature from rhNGF expressed in Chinese hamster ovary (CHO) cells that was investigated in several hundreds of patients for the treatment of HIV- or diabetes-related peripheral neuropathy. In clinical trials rhNGF expressed in CHO cells was subcutaneously administered at doses up to 0.3 µg/kg three times a week for 6 months [Apfel, 1998] or 0.1 µg/kg three times per week for 48 weeks [Apfel, 2000]. The tolerability of systemically administered CHO- derived rhNGF was favorable with local pain at the injection site being the most common side effect. Arthralgia, myalgia, myasthenia, asthenia and peripheral edema were other systemic rhNGF related adverse events recorded in less than 15% of studied patients [Apfel, 1998; McArthur, 2000; Apfel, 2000; Schifitto, 2001].

The *E. coli*-derived rhNGF being developed for the treatment of ocular diseases has the same unglycosilated molecular structure as mNGF and the same amino acid sequence as the systemically administered CHO expressed rhNGF previously evaluated in patients. In *in vitro* preclinical studies both *E. coli* and CHO expressed rhNGF have been demonstrated to have similar activity to mNGF. In preclinical toxicology and safety studies performed in rats and rabbits with the *E.coli* derived rhNGF no ocular or systemic safety concerns have been identified. Of note, in a pharmacokinetic study evaluating the ocular biodistribution of topically applied rhNGF in rats of the three dose concentrations (20, 50 and 200 µg/ml) administered six times during the course of one day only the highest dose was detectable in the retina. In a phase I, randomized, double-masked, placebo-controlled combined single and multiple ascending dose study to evaluate the safety, tolerability and pharmacokinetics of rhNGF (*E. coli*-derived) in healthy male and female volunteers, study subjects were treated in one eye with rhNGF (0.5 to 180 µg/ml) ranging from one drop daily to one drop three times a day over five days with the fellow eye receiving an identical placebo regimen. Following treatment subjects were followed up to one month. During the study there were no systemic or ocular safety concerns and no clinically significant changes in ocular examinations were

noted. No serious adverse events were reported. Adverse events were mild in intensity and transient in nature. Reported ocular adverse events likely attributed to rhNGF include feelings of ocular pain, tenderness, soreness, pressure, burning, warmth and itchiness following instillation of the study medication. No evidence of systemic absorption or immunogenicity has been demonstrated in the serum of subjects tested to date.

Similar to studies evaluating murine NGF, recently, E. coli-derived rhNGF administered topically, has been shown to be protective against photoreceptor degeneration in a rat model of optic nerve damage (partial optic nerve transection). Specifically, in a collaboration with Dompé the Cordeiro lab at University College London has demonstrated under masked experiments that topical rhNGF eye drops at 60µg/ml and 180µg/ml significantly reduces RGC apoptosis, increases RGC survival following partial optic nerve transection. Furthermore, they showed that it reduces secondary degeneration of RGC loss at 21 days in his model. In these studies, following the partial optic nerve transection animals were randomly divided into 4 treatment groups, with 6 animals per treatment group (no treatment, vehicle, NGF 180µg/ml eye drops, NGF 60µg/ml eye drops). The adminstrators of the treatment were blinded to identity of treatment throughout the project with labels covered with colour codes. Treatments were started on the day of optic nerve damage, and eye drops were given to both eyes, 2-times/per day, every day for 21 days. Apoptosing RGCs were evaluated in vivo using fluorescently labeled annexin-V, while RGC survival was assessed ex vivo using confocal microscopy in whole retinal whole-mounts stained with a monoclonal anti-mouse Brn3-a primary antibody and Alexa Fluor-643 conjugated secondary antibody.

Based on the available preclinical and clinical data showing the lack of significant systemic or ocular safety concerns associated with rhNGF and the potential for clinical improvement in glaucoma patients the benefit/risk ratio evaluating rhNGF in patients with glaucoma, a progressively debilitating and blinding condition with no proven effective medical or surgical treatment, can be high. Although no safety concerns emerged with the use of rhNGF at 180 µg/ml for 5 days in healthy subjects and, additionally, a multicenter masked randomized clinical trial where rhNGF at 180 µg/ml was administered for 24 weeks in patients affected by retinitis pigmentosa confirming the findings of the phase I study in which no evidence of systemic absorption or immunogenicity was demonstrated, no related serious adverse events were reported, and adverse events were mild in intensity, transitory, and consisted mostly of ocular pain, irritation, itching and photophobia following instillation, for ethical reasons this study was designed as a phase I segment in glaucoma patients since no data is available on the use of rhNGF in patients with a history of increased intraocular pressure and progressive optic nerve disease.

5. ETHICS

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) as described in 21 CFR §312 Consolidated Guideline and other regulations as applicable. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. Before initiating the clinical study, this protocol, the informed consent form any other written information given to patients, and any advertisements planned for patient recruitment must be approved by and by the Institutional Review Board (IRB) of the study sites. The Investigator must provide documentation of the IRB approval to Dompé. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, all applicable recruiting materials and written information for patient. The IRB must be provided with a copy of the Investigator's Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IRB. At the end of the study, the Investigator will notify the IRB about the study completion. The IRB also will be notified if the study is terminated prematurely. Finally, the Investigator will report to the IRB on the progress of the study at intervals stipulated by the IRB.

Voluntary informed consent will be obtained from every patient (and/or impartial witness, as applicable) prior to the initiation of any study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential patient and the patient must indicate voluntary consent by signing and dating the approved informed consent form. The patient must be provided an opportunity to ask questions to the Investigator, and if required by local regulation, to other qualified personnel. The Investigator must provide the patient with a copy of the consent form written in a language the patient can understand. The consent document must meet all applicable local laws and will provide patients with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the investigational product and the established provisions for maintaining confidentiality of personal information. Patients will be told about the voluntary nature of participation in the study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The patient also will be told that their records may be accessed by appropriate

authorities and Dompé-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each patient.

6. PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by Dompé and must be approved by the national competent authorities and/or IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all patients currently enrolled in the study may be required by the IRB to sign the approved, revised informed consent form.

7. PATIENT POPULATION

Adult patients with chronic primary open angle glaucoma with documented evidence of clinical progression prior to enrollment despite maximal current therapy (i.e. IOP reduction), or with stabilized IOP but diminished vision (central or peripheral). 60 patients (2:1 randomization active vs placebo) will be enrolled in the study.

To participate in the study, patients must be 18 or older with primary open angle glaucoma with documented evidence of clinical progression (i.e. progressive optic).

Patients must fulfill all of the study inclusion and none of the exclusion criteria listed in the protocol synopsis in Section 1 and below. If a patient can't read the informed consent due to poor vision, he/she can received the information verbally by another person but this procedure has to be documented, signed and dated by the independent person reading the document.

7.1 INCLUSION CRITERIA

1- Patients 18 years of age or older. Participant must understand and sign the informed consent. If the participant's vision is impaired to the point where he/she cannot read the informed consent document, the document will be read to the participant in its entirety.

2- Participant's clinical diagnosis must be consistent with glaucoma characterized by the following features: a) clinical evidence of progressive RGC dysfunction and degeneration using visual field and/or a structural modality. There must be at least 3 reliable visual fields within 14 months prior to entering into the study; b) residual visual field preservation in at least 1 quadrant.

3- Participant must be medically able to undergo the testing required in the flowsheet of exam procedures.

4- Females of childbearing potential must agree to use an effective form of birth control.

7.2 EXCLUSION CRITERIA

1- Participant has another optic nerve or retinal degenerative disease or co-morbidity causing significant vision loss, irrespective of whether it is currently treated or untreated, that could limit the possibility of visual recovery.

2- Participant is blind in one eye.

3- Participant has a requirement of acyclovir and/or related products during study duration.

4- Participant has evidence of corneal opacification or lack of optical clarity.

5- Participant has undergone lens removal in the last 3 months, with or without intra-ocular lens implantation, or has undergone intra-ocular lens replacement within 3 months, or has undergone any other ocular surgery within 9 months prior to initiation of study drug.

6- Participant is receiving systemic steroids or other immunosuppressive medications.

7- Participant is currently participating in or has within the last 3 months participated in any other clinical trial of a non-clinically approved drug by ocular or systemic administration.

8- Participant has uveitis or other ocular inflammatory disease.

9- Participant has diabetic macular edema.

10- Participant has a history of ocular herpes zoster.

11- Participant is on chemotherapy.

12- Participant has a history of malignancy, not counting basal cell carcinomas, UNLESS it was treated successfully 2 years prior to inclusion in the trial.

13- Known hypersensitivity to one of the components of the study or procedural medications.

14- History of drug, medication or alcohol abuse or addiction.

15- Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions:

a. are currently pregnant or,
b. have a positive result on the urine pregnancy test at the Screening/Baseline Visit or,
c. intend to become pregnant during the study treatment period or,
d. are breast-feeding or,
e. not willing to use highly effective birth control measures, such as: Hormonal contraceptives – oral, implanted, transdermal, or injected and/or mechanical barrier methods – spermicide in conjunction with a barrier such as a condom or diaphragm or IUD during the entire course of and 30 days after the study treatment periods.

Important Notes:
All females of childbearing potential must consent to a urine pregnancy test upon entering and exiting the study treatment period. Females of childbearing potential must agree to immediately inform the Investigator if they become pregnant during the study.
For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the patient becomes heterosexually active during the study treatment period, she must agree to use adequate birth control methods as defined above for the remainder of the study treatment period.

Pregnancy should be avoided in patients or partners during the first month after completing the treatment with the Investigational Product.

8. TREATMENTS ADMINISTERED

Upon entry into the study, patients will be assigned randomization numbers in the appropriate numerical sequence by the Investigator. Each eligible subject will be assigned to a randomization number according to the sequence of study entry, from 01 to 60.

8.1. 8 WEEK RANDOMIZED CONTROLLED TREATMENT PERIOD

The 8 week (2 months) double-masked, randomized, controlled treatment period, (hereafter, also referred to as the controlled treatment period) will be followed by a 24 week (6 months) follow-up period. Enrolled patients will be randomized at baseline in a 2:1 ratio to the active treatment arm (rhNGF 180 µg/ml, one drop TID) or the vehicle control arm (vehicle, one drop TID in the affected eye(s)) as shown below in the Table 8.1-1.

Table 8.1-1. – Treatment Arms

Treatment arm	Treatments
1. Active	180 µg/ml rhNGF, one drop TID (in both eyes if bilateral disease)
2. Control	Vehicle control, one drop TID (in both eyes if bilateral disease)

8.1.1. Study medication

This study is designed as a phase Ib 8 week monocentric, randomized, double-masked, vehicle controlled, parallel groups study (referred to as the controlled treatment period) followed by a 24 week follow-up period (4 weeks masked follow-up and additional 20 weeks unmasked follow-up).

The 60 consecutively enrolled patients will be randomized in a 2:1 ratio to the active treatment arm (rhNGF 180 µg/ml, one drop TID) or to the vehicle arm (vehicle, one drop TID) during the 8 week treatment period.

On the Day 0 Visit the first 2 doses (1 dose = 1 drop) of study medication will be administered in the clinic by study site personnel and the patient will be monitored for adverse events. In the absence of any clinically significant side effects in the opinion of the investigator the patient will be dispensed their study medication and instructed to self-administer the 3rd dose of Day 0 at home 6 hours after the 2nd dose of study medication was given. The patient will also be instructed to return to the study clinic after 1 week for Week 1 Visit.

Patients enrolled in the study will continue their 8 week treatment and will later enter the 24 week follow-up period without interruption.

8.1.2. Other medications

Upon enrolment, the previous topical glaucoma medications of patients will be continued normally, however, it will be required that previous topical ophthalmic medications used for intraocular pressure control will not be changed during the course of the study. Any other topical ocular treatment not related to intraocular pressure control for glaucoma, that is used before enrollment, will need to be discontinued and patients will only be allowed to use the study medication provided by Dompé and preservative-free artificial tears during the course of randomized controlled treatment period.

No rescue medication is planned for this study.

8.2. 24 WEEK FOLLOW-UP PERIOD

At the conclusion of the controlled treatment period at Week 8, patients will be discontinued from study treatment. During the 24 week follow-up period (Weeks 9-32) the patients will be followed without any protocol required study medication, however, preservative-free artificial tears (not provided by Dompé) may be prescribed as needed as at the discretion of the study investigator.

The first 4 weeks of the follow up period will be referred to as masked follow-up (and patients treatment will be kept masked) while the following 20 weeks will be referred to as unmasked follow-up (patients treatment will be unmasked at week 12) and the database will be locked. The database will be locked and the study will be complete after the last randomized patient has completed 4 weeks of the follow up period (Week 12 Visit). However, after the database lock patients still in the follow up period will continue with scheduled visits for the remainder of the 24 week follow up period.

9. INVESTIGATIONAL PRODUCT

9.1. IDENTITY OF STUDY TREATMENT

The Test product is a form of recombinant human Nerve Growth Factor (rhNGF) produced in *E.coli* developed by Dompé R&D Laboratories. rhNGF is a sterile 0.18 mg/mL single use lyophilized preparation, packaged in a glass vial, and administered after reconstitution with 0.3 ml of sterile WFI contained into a glass prefilled syringe. The WFI prefilled syringe is used with an adaptor consisting of a connecting device with dual connections: one end for the glass-syringe and one end for the vial. The drug product will be manufactured under environmental and process aseptic conditions in accordance with GMP guidelines to obtain a final sterile drug product.

Test product:	Recombinant human nerve growth factor 180µg/ml (one 35 µl drop equals to 6.30 µg of rhNGF) reconstituted solution
Vehicle Control:	Ophthalmic Placebo solution of the same composition as the test product with the exception of rhNGF reconstituted solution

Investigational product will be provided as a 4-weeks kit formed by two boxes: the first box containing the vials (lyophilized product) and the second box containing adaptors and prefilled 0.3 ml WFI syringes. Each vial after reconstitution contains a volume of 0.3 ml rhNGF 180 µg/ml or control. A training manual for investigators with detailed instructions on how to reconstitute the eye drops from the lyophilized product is provided in Appendix A.

The clinical labeling of the investigational product will be done in a manner that protects the masking of the study medication. It will include a statement of caution and describe particulars applicable to regulatory requirements (e.g.: kit number, protocol number, storage conditions, name and address of the sponsor, statement that the product is for investigational use only, etc.).

9.1.1. Dose Selection Rationale

The rationale for the rhNGF eye drops solution dosages to be investigated in this study (180 µg/ml) is derived from the results of *in vivo* pharmacology studies, preclinical safety and toxicity studies and a phase I, randomized, double-masked, vehicle-controlled study of rhNGF in healthy volunteers demonstrating no significant ocular or systemic safety concerns with the proposed therapeutic dose.

In a preclinical models, we have investigated the effective dose-regimen of rhNGF by measuring the activation of the high affinity NGF receptor as well as apoptosis biomarkers expressed in the retina of rats with inherited retinal degeneration and with an induced damage of the optic nerve (partial optic nerve transection).

Among the different rhNGF dose regimen tested, only the dose of 180µg/ml given three times a day for three consecutive days induced significant activation of the NGF receptors well as downregulation of pro-apototic biomarkers. Additionally, published reports of patients with advanced optic neuropathies treated with mNGF 200 µg/ml 3 or 4 times a day for variable time periods showing visual function improvements provide objective human evidence that topically applied NGF can achieve pharmacologically active concentrations in the back of the eye. In a preclinical study utilizing radiolabeled rhNGF to investigate the disposition of rhNGF in the eye of the 3 concentrations evaluated (20, 50 and 200 µg/ml) only the 200 µg/ml dose was detectable in the back of the eye. So, while it is clear that topically applied NGF can reach the back of the eye and exert a therapeutic effect, based on the available preclinical and clinical data it is currently unclear which concentration of topical rhNGF will yield the most effective treatment benefit in patients with glaucoma. Therefore, the objective of this study is to assess the safety and potential efficacy of a 180 µg/ml rhNGF treatment to determine its safety for use in subsequent phase 2 and 3 clinical trials in this indication.

9.1.2. Treatment Dispensing and Dosing

Eligible patients will be randomized and randomization numbers will be assigned to the patients by the investigator in ascending sequential order. Each eligible subject will be assigned to a randomization number according to the sequence of study entry, from 01 to 60. Randomization code break envelopes will be provided to the Investigator with the IMP in the event unmasking is required.

The patients will be dispensed a 4 week supply of study medication on the Day 0 visit and at Weeks 4 as shown in Table 9.1.2-1.

Table 9.1.2-1 - Kit Assignments

Weekly visit	**# of kits**
Day 0 - Randomization / Therapy initiation Visit	1 kit
Week 4 Visit	1 kit

Study medications that will be dispensed to the patient during the study visits will be distributed in refrigerated bags. In addition to the study medication to be administered in the clinic on the day of the study visit, patients will also be instructed to bring back to the clinic at each study visit all the used and unused vials by placing them in the refrigerated bag that was given at the Day 0 visit (so that it can be used for dispensing the next kit, if applicable).

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, randomized, double-masked, controlled treatment period.

9.1.3. Usage

All study drugs used in this study are for topical ocular usage only. Dispensing of the study medications to the patients will be performed as described in Section 9.1.2 and table 9.1.2-1.

All patients will be dosed one drop (35 µl) TID in each eye every morning, afternoon and evening as shown in the **Table 9.1.3-1**. The timing of instillation should be adjusted if a patient's awakening and/or bedtime differs.

Patients will begin treatment in the clinic at the Day 0 visit, where he/she will be shown how to resuspend the lyophilized molecule and instill the eyedrops in the eyes. For this purpose, a training manual with detailed instructions on how to reconstitute the eye drops will be provided to the investigators (see Appendix A). Patients will then be instructed to self-administer the study medication one drop three times a day through 8 Weeks of the controlled treatment period. During the 8 week controlled treatment period patients will be instructed to return to the clinic on the monthly visits with the used kits and empty (used) vials as well as

with the daily kit of study medication and vials to be used on the day of the study visit in the refrigerated bag that will be given when the study medication is dispensed.

Table 9.1.3-1. – Dosing Schedule

TREATMENT	TREATMENT DOSING SCHEDULE
rhNGF 180 µg/ml or **Vehicle**	Morning (approximately 8 AM)
	Afternoon (approximately 2 PM)
	Evening (approximately 8 PM)

9.1.4. Precautions of Use

In rats and rabbits no evidence of systemic toxicity was observed following treatment with intravenous rhNGF at doses up to 2.4 mg/kg. In the same species, no local ocular toxicity was observed following treatment with topical rhNGF eye drops at concentrations up to 1.2 mg/ml. In a phase I, randomized, double-masked, vehicle-controlled study of rhNGF in healthy volunteers no ocular or systemic toxicity was demonstrated in patients administered topical rhNGF up to 180 µg/ml 3 times a day for 5 days. Being a recombinant protein, rhNGF it is not expected to be mutagenic, therefore, reproductive toxicity and teratogenicity studies have not been performed. However, as a precaution, the investigational product should not be handled by pregnant females, should be kept away from children and contact with the skin or mucosae other than that for required for topical ocular administration should also be avoided. In case of accidental spills or contact cleanse/wash the exposed area with tap water and soap.

9.1.5. Storage

Investigational product must be stored in a secure area at the investigational site as per the labeling instructions. A temperature probe and data logger will accompany the drug on shipment. It is essential that the Investigational sites verify the temperature range reached during shipment, so that potential stability concerns during shipment can be discovered and appropriate action taken. The box of the investigational product containing the lyophilized preparation must be stored at 2-8°C at the Investigational sites (preferably at the pharmacy of the hospital), whereas the box containing the prefilled syringes and adaptors may be kept at room temperature. Eligible patients will receive the first 4-week kit of study medications in a refrigerated bag containing the investigational product. The vehicle control will be also dispensed in a refrigerated bag. The patient will be instructed to store the study medication (the box of the investigational product containing the lyophilized preparation) at home in the refrigerator at 2-8 °C for the entire 4 weeks until next visit. The box containing the prefilled syringes and adaptors may be kept at room temperature. When the patients will start to use the study medications at home each day they will remove from the refrigerator only the vials to be used over the course of the day. Patients will use one vial to instill one drop in both eyes three times per day.

A daily temperature log will be maintained at the site for documenting appropriate storage conditions and will be made available for the study monitor to inspect. Any deviations from the recommended storage conditions should be immediately reported to Dompé and the use of the drug suspended until authorization for its continued use has been given by Dompé.

Investigational products will be supplied as a lyophilized preparation in glass vials together with a prefilled 0.3 ml sterile WFI syringes and adaptors. The vials will be labeled with the appropriate clinical study labeling. The vehicle of rhNGF will be supplied in glass vials identical to those containing rhNGF with a prefilled 0.3 ml WFI syringes and adaptors. The vials containing the vehicle will be labeled with the appropriate clinical study labeling. Investigational product will be kept in an identical box to ensure double-masking.

9.1.6. Accountability Procedures

Upon receipt, the study staff designated by the Investigator will inventory the clinical investigational products, and complete and sign the Receipt of Clinical Study Investigational products Section of the appropriate form in use. A copy of the form will be maintained in the Investigator's records and the original will be provided to the CRO, delegated by Dompé.

The designated study staff must keep a complete and accurate accountability of all investigational products used on the investigational products Dispensing Log. In no case will the investigational products be used in any unauthorized situation. Investigational products returned to the Dompé for destruction will be recorded in the Return of Clinical Investigational products Form. These records will be made available to the study monitor for the purpose of accounting for all study investigational products. The study monitor will account for all investigational products. It is the Investigator's responsibility to ensure the reconciliation of study medications at the conclusion of the study. Any discrepancies and/or deficiencies in study drug accountability must be recorded along with an explanation.

Investigational product which has been dispensed to a patient and returned unused will not be re-dispensed to a different patient.

Unused investigational products must not be discarded or used for any purpose other than the present study. Any remaining investigational products at the end of the trial will be returned to Dompé or disposed of as determined by Dompé for destruction.

9.1.7. Assessment of Compliance

Patient compliance with the study medication will be assessed at each study visit following the dispensing of the study medication for self-administration. Compliance with the study medication dosing schedule will be verified by the monitor during on-site monitoring visits, as per records in the eCRF, versus accountability records.

9.1.8. Patient Confidentiality and Methods Used to Minimize Bias

During the 8 week, randomized, double-masked controlled treatment period the study treatments will be unknown to the patient, the Investigator and the site staff. The identity of the treatments will remain unknown to the patient, Investigator, site staff and Dompé's clinical research personnel until the study is unmasked after the last enrolled patient completes week 12 visit (end of the masked follow-up) and the database is locked, except in case of specific events that will require unmasking of the patient(s).

The vials of rhNGF (180µg/ml) and the vials containing the vehicle of rhNGF will be identical in appearance and the contents of the vials will be indistinguishable. Dompé and CRO Biostatistics staff who are directly involved in the analysis of study results will remain masked to treatment assignments until the end of the masked follow-up.

A list of sequential kit numbers will be generated by a member of the CRO SAS programming group not involved in the conduct of the study. Each kit number will be randomly associated with a treatment group. Patients will be assigned to treatment in numerical order. A tear-off label from the kit box, with the kit number, will be attached to the investigational product dispensing log.

If the Investigator becomes unmasked for any reason, this information will be recorded on source data and in the eCRF of the study, specifying the date and the reason.

In the event of a medical emergency where the knowledge of patient treatment is required to provide the patient with appropriate care, Investigators will have the possibility to unmask the treatment assignment for a specific patient. See Paragraph 12.5 for information on unmasking procedure.

10. STUDY PROCEDURES

10.1. OUTLINE OF STUDY

The study will be conducted as a 8 week monocentric, randomized, vehicle controlled, double-masked, parallel groups study followed by a 24-week follow-up period. The study will be considered completed when the last enrolled patient completes their final study visit at Week 32 of the follow-up period.

The 8 week controlled treatment period will include 7 scheduled clinical evaluation visits: Baseline Screening Visit, Day 0-Therapy Initiation Visit, Week 1, Week 4, Week 8, Week 12 and 32 Visits. 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

10.1.1. 8 Week Randomized, Double-Masked Controlled Treatment Period

Enrolled patients will be randomized at baseline in a 2:1 ratio to the active treatment arm (rhNGF 180 µg/ml three times a day in both eyes) or the vehicle during the 8 week controlled treatment period as shown in the following table:

Treatment Arms	Treatments
1	180 µg/ml rhNGF one drop three times a day in both eyes
2	Vehicle one drop three times a day in both eyes

At the conclusion of the randomized, double-masked, controlled treatment period all patients will discontinue the study medication and enter a 24 week follow-up period (4 weeks masked follow-up and additional 20 weeks unmasked follow-up.

10.1.2. 24 Week Follow-Up Period

During the 24 week follow-up period, patients will be followed without any protocol required study medication; however, preservative-free artificial tears (not provided by Dompé) may be prescribed as needed at the discretion of the study investigator.

Two clinical evaluation visits are foreseen at week 12 and 32.

10.2. VISIT AND EXAMINATIONS

10.2.1. Baseline (*Screening*) Visit

1. **Informed Consent**

   Explain the purpose and nature of the study, and have the patient or legally authorized representative read, sign, and date the IRB approved informed consent document. If applicable, a witness will also sign and date the informed consent document. Provide a photocopy of the signed document to the patient and place the original signed document in the patient chart.

2. **Inclusion/Exclusion Criteria**

   Screen the patient for protocol inclusion/exclusion criteria as per paragraph 7.1 and 7.2.

3. **Demographics, Medical History, Medications**

   Document demographic information and medical history, including information on all concomitant and previous medications used within the past 30 days. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications.

4. **Record Adverse Events**

5. **Ophthalmic Examinations**

   The following examination/procedures will be performed on BOTH EYES unless otherwise indicated:

   a) **Best-Corrected Distance Visual Acuity (BCDVA)**

      Vision must be measured using ETDRS visual acuity chart at 4 meters (13 feet). BCDVA testing should precede the administration of any eye drops to dilate or anesthetize the eye, or any examination requiring contact with the eye.

   b) **Visual Field Testing**

      Visual fields will be evaluated using static (Humphrey visual field 24-2 or 10-2) perimetry. Two perimetries will be performed on different days for a total of 3 before initiating treatment.

      Visual field testing should precede the administration of any eye drops to dilate or anesthetize the eye, or any examination requiring contact with the eye.

      Visual Field testing will be performed using Sita Standard.

   c) **External Ocular Examination**

Assess the motility of the extraocular muscles and the appearance and function of the eyelids before the instillation of any dilating or anesthetic eye drops.

d) **Slit Lamp Examination (SLE) (biomicroscopy)**

SLE will assess eyelids, lashes, conjunctiva, cornea, lens, iris and anterior chamber. SLE must be performed before the instillation of any dilating or anesthetic eye drops or the fluorescein agent.

e) **Intraocular Pressure (IOP)**

IOP testing will be performed using Goldmann Tonometer after the instillation of a topical anesthetic.

f) **Dilated Fundus Ophthalmoscopy**

Fundus ophthalmoscopy to assess the retina, macula, choroid and optic nerve head will be performed after dilation of the pupil.

10.2.2. Day 0 (*Therapy Initiation*) Visit (*scheduled procedures may be performed over 2 consecutive days if needed*)

1. **Inclusion/Exclusion Criteria:** Screen the patient for protocol inclusion/exclusion criteria as per paragraph 7.1 and 7.2.
2. **Pregnancy Test:** Perform a urine pregnancy test on any female of childbearing potential and record the results. If a pregnancy test is not required, indicate as not applicable in the eCRF.
3. **Randomization:** At the end of the Day 0, Baseline/Randomization Visit, if the patient qualifies for randomization in the study, proceed to randomize the patient; randomization numbers will be assigned to the patients by the investigator in ascending sequential order.
4. **Ophthalmic Examinations**

   The following examination/procedures will be performed on BOTH EYES unless otherwise indicated:

   g) **Best-Corrected Distance Visual Acuity (BCDVA)**

   Vision must be measured using ETDRS visual acuity chart at 4 meters (13 feet). BCDVA testing should precede the administration of any eye drops to dilate or anesthetize the eye, or any examination requiring contact with the eye.

   h) **Visual Field Testing**

Visual fields will be evaluated using static (Humphrey visual field 24-2 or 10-2) perimetry. Visual field testing should precede the administration of any eye drops to dilate or anesthetize the eye, or any examination requiring contact with the eye.

Visual Field testing will be performed using Sita Standard.

i) **External Ocular Examination**

Assess the motility of the extraocular muscles and the appearance and function of the eyelids before the instillation of any dilating or anesthetic eye drops.

j) **Slit Lamp Examination (SLE) (biomicroscopy)**

SLE will assess eyelids, lashes, conjunctiva, cornea, lens, iris and anterior chamber. SLE must be performed before the instillation of any dilating or anesthetic eye drops or the fluorescein agent.

k) **Intraocular Pressure (IOP)**

IOP testing will be performed using Goldmann Tonometer after the instillation of a topical anesthetic.

l) **Dilated Fundus Ophthalmoscopy**

Fundus ophthalmoscopy to assess the retina, macula, choroid and optic nerve head will be performed after dilation of the pupil.

m) **Ocular Coherence Tomography**

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.

n) **Mitochondrial redox potential**

Changes in mitochondrial redox potential measured through adaptive optics scanning laser ophthalmoscope (SLO) imaging.

o) **Electroretinography (ERG)**

A full field and pattern ERG will be performed according to international standards at the Day 0 examination. Prior to the ERG procedure patients will be treated with anesthetic and dilating drops.

5. **Study Drug Dispensing:** Randomized patients will be dispensed study medication on the day of Therapy Initiation Visit.
6. **Instructions to Patient:** Schedule the patient to return for Week 1 Visit. Instruct the patient to self-administer the last dose (third) of day 0 at home 6 hours after the

second dose and the study medication one drop three times a day starting at home starting on Day 1, the following day.

7. **Visual Analogue Scale (VAS)** 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.
8. **Medical History, Medications:** Record any change ocular or systemic medical history or in concurrent ocular or non-ocular medications.
9. **Record Adverse Events**

Instruct and remind the patient to come back to the clinic at the week 4 visit with the used kits and empty (used) vials as well as with the daily kit of study medication and vials to be used on the day of the study visit in the refrigerated bag provided. At week 4 the patient receives additional medication to be used for the following 4 weeks.

At all applicable visits instruct the patient to return to the clinic with the 4 weeks kit of study medication in the refrigerated bag.

10.2.3. Week 1 Visit (*with a window of ±2 Days, scheduled procedures may be performed over 2 consecutive days if needed*) Week 4 Visit (*with a window of ±4 Days, scheduled procedures may be performed over 2 consecutive days if needed*)

1. **Medical History, Medications** (Week 1 & 4 Visits)
   Record any change ocular or systemic medical history or in concurrent ocular or non-ocular medications.
2. **Record Adverse Events** (Week 1 & 4 Visits)
3. **Verify patient study medication dosing compliance (Week 4 Visit Only)**
4. **VAS** (Week 1 & 4 Visits)
5. **Ophthalmic Examinations:** The following examination/procedures will be performed on BOTH EYES:
   a) **Humphrey Visual Field 24-2 or 10-2** (3fields within 4 weeks until the end of treatment); Visual Field testing will be performed using Sita Standard
   b) **External Ocular Examination** (Week 1 & 4 Visits)
   c) **Slit Lamp Examination** (Week 1 & 4 Visits)
   d) **IOP** (Week 1 & 4 Visits)IOP testing will be performed using Goldmann Tonometer after the instillation of a topical anesthetic.

Mitochondrial redox potential (Week 4 Visit Only): changes in mitochondrial redox potential measured through adaptive optics scanning laser ophthalmoscope (SLO) imaging.

6. **Study Drug Dispensing and Compliance** (Week 4 Visit Only)
7. **Instructions to Patient** (Week 1 & 4 Visits)
   At Day 0 (Therapy initiation) visit and each visit thereafter schedule patient for next visit.

10.2.4. Week 8 Visit (*with a window of ±7 Days, scheduled procedures may be performed over 2 consecutive days if needed*)

1. **Medical History, Medications**
2. **Record Adverse Events**
3. **Verify patient study medication dosing compliance**
4. **VAS**
5. **Ophthalmic Examinations**

   The following examination/procedures will be performed on BOTH EYES:

   a) **Best-Corrected Distance Visual Acuity (BCDVA)**
   b) **Humphrey Visual Field 24-2 or 10-2** (3 perimetries within 4 weeks until the end of treatment); Visual Field testing will be performed using Sita Standard
   c) **External Ocular Examination**
   d) **Slit Lamp Examination (biomicroscopy)**
   e) **Intraocular Pressure (IOP)**; IOP testing will be performed using Goldmann Tonometer after the instillation of a topical anesthetic.
   f) **Dilated Fundus Ophthalmoscopy**
   g) **Ocular Coherence Tomography**
   h) **Mitochondrial redox potential**: changes in mitochondrial redox potential measured through adaptive optics scanning laser ophthalmoscope (SLO) imaging.
   i) **ERG** A full field and pattern ERG will be performed according to international standards at the Day 0 examination. Prior to the ERG procedure patients will be treated with anesthetic and dilating drops.

8. **Pregnancy Test**
9. **Instructions to Patients**

   Schedule patient to return for the week 12 visit (± 7 Days) in follow-up visit.

END OF 8 WEEK RANDOMIZED, DOUBLE-MASKED,CONTROLLED TREATMENT PERIOD

10.2.5. Masked Follow-Up Period - Week 12 Visit (*with a window of ±7 Days, scheduled procedures may be performed over 2 consecutive days if needed*)

1. **Medical History, Medications**
2. **Record Adverse Events**
3. **Ophthalmic Examinations**:
    a) **BCDVA**
    b) **Humphrey Visual Field 24-2 or 10-2 (**3 perimetries within 4 weeks until the end of treatment); Visual Field testing will be performed using Sita Standard
    c) **External ocular examination**
    d) **Slit Lamp Examination**
    e) **Intraocular pressure (IOP)**; IOP testing will be performed using Goldmann Tonometer after the instillation of a topical anesthetic.
    f) **Dilated Fundus Ophthalmoscopy**
    g) **Ocular Coherence Tomography**
    h) **Mitochondrial redox potential**: changes in mitochondrial redox potential measured through adaptive optics scanning laser ophthalmoscope (SLO) imaging.
    i) **ERG**
    j) **VAS**

10.2.6. Unmasked Follow-Up Period - Week 32 Visit (*with a window of ±7 Days, scheduled procedures may be performed over 2 consecutive days if needed*)

1. **Medical History, Medications**
2. **Record Adverse Events**
3. **Ophthalmic Examinations**:
    a) **BCDVA**
    b) **Humphrey Visual Field 24-2 or 10-2 (**3 perimetries within 4 weeks until the end of follow-up); Visual Field testing will be performed using Sita Standard
    c) **External ocular examination**
    d) **Slit Lamp Examination**

e) **Intraocular pressure (IOP)**; IOP testing will be performed using Goldmann Tonometer after the instillation of a topical anesthetic.
f) **Dilated Fundus Ophthalmoscopy**
g) **Ocular Coherence Tomography**
h) **Mitochondrial redox potential**: changes in mitochondrial redox potential measured through adaptive optics scanning laser ophthalmoscope (SLO) imaging.
i) **ERG**

10.3 END OF TRIAL

For the purpose of this trial, the end of study is defined as the date of the last visit of the last patient of the follow up period.

10.4. UNSCHEDULED VISITS

If a subject 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. If the patient is discontinued at the unscheduled visit, the eCRFs for the Week 8 visit should be completed if the withdrawal occurs at Week 8; for all other patients the Early Exit Visit should be completed.

10.5. DISCONTINUED PATIENTS

Discontinued patients are those who withdraw or are withdrawn from the study after the Randomization Visit. Patients may discontinue from the study at any time for any reason. Patients also may be discontinued from the study at any time if, in the opinion of the Investigator, their continued participation poses a risk to their health. Patients may also be discontinued from the study if lost to follow-up. Female patients will be withdrawn in case they become pregnant during the study. Discontinued patients will not be replaced (i.e., their patients numbers will not be re-assigned/re-used).

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 Form must be completed.

Finally, to ensure the safety of all patients who discontinue early, Investigators should assess each patient and, if necessary, advise them of any therapies and/or medical procedures that might be needed to maintain their health.

10.6. CLINICAL STUDY TERMINATION

If the clinical study is prematurely terminated or suspended, Dompé will inform the Investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension. The Investigator should promptly notify the IRB of the trial termination or suspension and of the reasons. Dompé reserves the right to close an investigational site or terminate the study in its entirety at any time, for any reasonable cause. Reasons for the closure of an investigational site or termination of a study may include:

- Successful completion of the study
- The study's enrolment goals are met
- The Investigator fails to comply with the protocol or GCP guidelines in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR §312
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of patients/subjects by the Investigator

The Investigator may also terminate the study at his/her site for reasonable cause. If Dompé terminates the study for safety reasons, it will immediately notify the Investigator(s) by telephone and subsequently will provide written confirmation of and instructions for study termination.

11. ANALYSIS PLAN

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 be examined at 1, 4 and 8weeks of therapy, and at 4 and 24 weeks after cessation of therapy (Week 12 visit and Week 32 visit), and will include functional assessments to investigate evidence of a persistent biological effect after discontinuation of the study treatment.

11.1. SUBJECT EVALUABILITY

Evaluability for all patients and visits will be determined prior to locking the database and breaking the code for masked study medication.

11.2. ANALYSIS DATA SETS

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

The Intent-to-treat (ITT) population will include all randomized patients and will be used for all exploratory efficacy analyses.

11.3. HANDLING OF MISSING DATA

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

11.4. SAMPLE SIZE JUSTIFICATION

As the objectives of this study are to evaluate the safety and explore the biological effects of a single rhNGF dosage sample size was calculated based on clinical feasibility and no formal sample size calculation has been performed.

Proposed sample size is adequate to make appropriate estimation of study variables.

However, considering that the active comparator has already proven safe and effective at the dosage being tested in this study and there is a solid scientific rationale for treating patients suffering of glaucoma with rhNGF, to make the trial more attractive to patients, the randomization has been set to a 2:1 active vs vehicle.

11.5. STATISTICAL ANALYSIS

Data base will be locked after all patients have completed their Week 12 Visit and main objectives analysis will be performed on unmasked data. 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. All analysis will be detailed in a statistical analysis plan (SAP). All exploratory efficacy variables will be tabulated with the appropriate descriptive statistics at the 0, 4, 8, 12 and 32 weeks timepoints and appropriate inferential tests with 95% confidence limits of the difference between treatments will be produced.

11.5.1. General Principles

All patient data collected on the eCRF will be listed by patient, treatment group and center.

Appropriate descriptive statistics will be produced, according to the variable. For continuous data the mean, standard deviation, median and range (minimum and maximum) will be presented. For categorical data, frequencies and percentages will be presented. If appropriate, 95% confidence intervals around the mean or the proportions will be presented.

In tabulations, denominators for calculation of percentages will be taken as the number of non-missing responses in the specified analysis population and treatment group unless otherwise stated.

Unless otherwise specified, the significance level used for statistical testing will be 5% and two-sided tests will be used.

All variables recorded in the follow-up period will be presented using appropriate descriptive statistics, and no formal statistical testing will be performed.

Full details of all planned data summaries and analyses, with any changes in analyses as detailed below will be reported and justified in the Statistical Analysis Plan (SAP).

11.5.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all patients in the safety population, by treatment group.

11.5.3. Extent of Exposure

Extent of exposure, number of days on study medication, is defined as the difference in days between the date of the last instillation of study medication and the date of the first instillation of study medication, plus one. For each treatment group, extent of exposure will be summarized using N, mean, standard deviation, median, minimum and maximum values.

11.5.4. Safety Analysis

Safety variables will be presented for the Safety population.

The primary safety endpoint in this study is Adverse Events (AEs). AEs will be recorded at the scheduled study visits and may also be recorded at any unscheduled visit that occurs during the study.

AEs will be presented, by treatment group, in terms of the incidence, severity and relationship to the study drug, overall and by SOC (System Organ Class) and preferred term. Serious AEs (SAEs) will be presented in the same way. All adverse events will be reported by MedDRA preferred term.

The following adverse event summary tables and listings will be provided:

Tables:

- Frequency and Incidence of Subjects with Adverse Events
- Frequency and Incidence of Subjects Discontinued Due to Adverse Events
- Frequency and Incidence of Subjects with Serious Adverse Events
- Adverse Events by Coded Adverse Event and SOC
- Overall Frequency and Incidence of Adverse Events
- Overall Frequency and Incidence of Adverse Events by Severity
- Overall Frequency and Incidence of Treatment-Related Adverse Events
- Overall Frequency and Incidence of Adverse Events Occurring at Rates Greater Than or Equal to 1.0%
- Overall Frequency and Incidence of Adverse Events by Age

Listings:

- Concomitant Diseases and Medications for Subjects with Adverse Events by Investigator and by Subject
- Coded and Descriptive Terms of Adverse Events by Investigator and by Subject
- Deaths, Other Serious or Clinically Significant Adverse Events
- Adverse Events by Investigator and by Subject

In addition to reporting of adverse events for any untoward (unfavorable and unintended) medical occurrences, adverse events will also be reported for any clinically relevant change from baseline in any assessment evaluated during the study, based upon an assessment by the Investigator.

Ocular tolerability as measured by the VAS will be analyzed by means of analysis of variance, including terms for treatment, time, and treatment by time interaction.

Best corrected distance visual acuity, external ocular examination, slit lamp examination, intraocular pressure, and dilated fundus ophthalmoscopy, will be presented with the appropriate descriptive statistics and shift tables will be used to present shifts from before and after treatment at each recording time points.

11.5.5 Efficacy Analysis

Exploratory efficacy evaluations will be obtained through longer-term observations of change in visual acuity and disease modification, that will be collected over a total of 32 weeks as secondary outcomes. These secondary outcomes of efficacy will be examined, applicable, at 1, 4and 8 weeks on therapy, and at 4 and 24 weeks (Week 12 visit and Week 32 visit) after cessation of therapy, and will include functional assessments:

- Mean, median, and distribution of change in BCDVA.
- Changes in visual field using perimetry.
- Changes in ERG including pattern ERG.

And structural assessments:

- Changes in ganglion cell layer and nerve fiber layer thickness measured by optical coherence tomography.

- Changes in mitochondrial redox potential measured by visible light adaptive optics approach, combined with in-line OCT.

12. EVALUATION OF ADVERSE EVENTS AND SAFETY INFORMATION

12.1. DEFINITIONS

12.1.1. Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject who is administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

12.1.2. Adverse Drug Reaction

An Adverse Drug Reaction (ADR) is any noxious and unintended response to an Investigational Medicinal Product (IMP) which is a reasonably likely to have been caused by the drug, at any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. For the purposes of IND safety reporting, "reasonable possibility" means there are facts (evidence) or arguments to suggest a causal relationship between the drug and the adverse event.

12.1.3. Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse experience that, in view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death.
- Is life-threatening.
  NOTE: Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include an event which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: In general, hospitalization means that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.

- Results in persistent or significant disability/incapacity or a substantial disruption of a person's ability to conduct normal life functions.
  NOTE: This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event. *An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.*

Pre-planned hospitalization or hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition are not considered to be SAEs (see Par. 12.4.2). These events must be recorded in the AE page of the CRF where a variable will be ticked to indicate that they are not SAEs.

Death shall always be reported as SAE and a cause of death shall always be specified when known.

12.1.4. Unexpected Adverse Events

An AE or ADR is considered unexpected if it is not listed in the Investigator Brochure (reference safety information) or is not listed at the specificity or severity that has been observed and listed in the Investigator Brochure. Events that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are considered unexpected (21 CFR312.32(a)).

12.1.5 Suspected unexpected serious adverse reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as an adverse reaction that is both unexpected (not consistent with the applicable product information) and meets the

definition of a Serious Adverse Reaction. The determination of expectedness should be made on the basis of the IB (reference safety information).

12.1.6. Adverse Events of Special Interest (Sight-threatening Events)

The following adverse events are considered to be of special interest and by default are to 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.

During the study all sight threatening events will be considered equivalent to a SAE and will be reported following the procedures described below for the reporting of a SAE.

12.2. MONITORING FOR ADVERSE EVENTS

At each visit following study informed consent form signature, after the patient has had the opportunity to spontaneously mention any problems, the Investigator or appropriate designee should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change in concomitant condition(s) that is the result of an untoward (unfavorable and unintended) change in a patient's medical health. Changes in any protocol-specific ocular or systemic parameter evaluated during the study are to be reviewed by the Investigator. In addition, the patient's responses to any questionnaire utilized during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically

relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

The Investigator should report information on SAEs that continue after patient has completed his/her participation in the study (whether study completion or withdrawal), unless patient has withdrawn his/her consent.

In line with ICH E2A provisions, although the Investigator does not usually need to actively monitor subjects for adverse events once the trial has ended, if the Investigator becomes aware of a serious adverse event occurring to a subject after the treatment of that subject has ended, the SAE should be reported by the Investigator to the Sponsor. Such "post-study cases" should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment (by the Investigator and by Dompé) and determination of expectedness (by Dompé) are needed for a decision on whether or not expedited reporting is required.

12.3. RECORDING

Adverse Events: all AEs (non-serious and serious) which occur during the course of the study will be recorded in the eCRF. Any pre-existing medical conditions or signs/symptoms present in a patient prior to the start of the study (i.e., before informed consent is signed), should be entered in the baseline history section of the eCRF of the EDC system. Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on an Adverse Event Form (AEF) in the eCRF of the EDC system. A separate AEF must be filled out for each event. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (i.e., severity), any action with study treatment taken as a result of the event, and an assessment of the adverse event relationship to the study treatment.

12.3.1. Relationship of AEs to the Investigational Product

The Investigator will assess the relationship between the AE and the investigational medication, according to the criteria in Table below:

Relationship of the Adverse Event to the IMP

None (Intercurrent Event)	An event that is not and cannot be related to the investigational product, e.g. patient is a passenger in a road traffic accident or surgical intervention performed during the study, but planned before patient enrolment into the study
Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations
Possible	Relationship may exist, but could have been produced by the patient's condition or treatment or other cause
Probable	Relationship is likely, the AE abates upon discontinuation of investigational product and cannot be due to the patient's condition
Highly Probable	Strong relationship, the event abates upon discontinuation of investigational product and, if applicable, re-appears upon repeat exposure

An ADR is defined as an adverse experience which is reasonably likely to have been caused by the drug. Events considered "Possible", "Probable" and "Highly Probable" related to the IMP treatment and implying a reasonable possibility, if considered serious and unexpected, will be reported to appropriate regulatory authorities.

12.3.2. Severity of AEs

The Investigator will grade the severity of any AE using the definitions in the Table below. For each episode, the highest severity grade attained should be reported.

Severity of the Adverse Event

Mild	Grade 1 - Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])

12.4 Serious Adverse Event Reporting Procedure (from Investigator to CRO/Dompé)

12.4.1. Reporting Procedure from Investigator to Dompé and CRO

The Investigator must record all SAEs, including sight-threatening events, occurring at any time during the study regardless of presumed causal relationship, on the Serious Adverse Event form in the eCRF of the EDC system within 24 hours of learning of the event; information on the SAE must also be recorded on a specific Non-Carbon Repeat SAE form (included in the Investigator's Site File) and forwarded to CRO Drug Safety and Dompé Drug Safety, within 24 hours from first knowledge, to the following addresses:

- by fax through the e-fax number: +1 347 294 3328 (linked to Dompé Drug Safety and to CRO Drug Safety).
- or, via e-mail to all following addresses:

- farmacovigilanza@dompe.com;
- DOMPE-NGF-GLA-PV@cromsource.com;
- DOMPE-NGF-GLA-MM@cromsource.com.

In case of unmasking by the investigator, the investigator will fill in the SAE form and all the other related documents (query template, narrative etc) with only the kit number of the treatment taken by the patient, without disclosing the treatment.

The EDC system will ensure that an automatic email will be generated and sent directly to the Dompé pharmacovigilance, trial management, and CRO accountable to receive the study safety information and to prompt a review of the reported SAE by the Medical Expert.

Follow-up reports (as many as required) should be completed and faxed/e-mailed following the same procedure above, marking the SAE form as "follow up Number XX".

Whenever more than one SAE is observed, the Investigator should identify which is the primary adverse event, i.e. the most relevant one. If other events are listed in the same report, the Investigator, along with their relatedness to the Investigational Product, should identify which adverse events are serious and which are non-serious. In any case, the Investigator is requested to record his/her opinion about the relatedness of the observed event(s) with the investigational medication.

An assessment of expectedness and causality of each serious adverse event will be performed case by case by Dompé/CRO. For SAE reported by an Investigator as not related that is subsequently revised to be related by Dompé, the Investigator will receive a notification.

12.4.2 Conditions that should not be reported as serious adverse events

The conditions listed below, that may require hospitalization of a patient, are not considered to be SAE and shall not be reported as such, but only need to be recorded in the CRF:

- Hospitalizations planned before entry into the clinical study which is part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition.
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Hospitalization for treatments, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.
- Hospitalization for general care not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs given above and not resulting in hospital admission.

In addition, the following situation shall not be considered SAE:

- Trial end points
- Abnormal lab values or test results that do not induce clinical signs and/or symptoms and require intervention/therapy and that therefore are not clinically significant.

12.4. 3. Expedited Reporting Procedure to IRB and to Regulatory Authorities

In addition to reporting the SAE to Dompé (and the CRO), the Investigator must also comply with the requirements related to the reporting of SAEs to the IRB which approved the study. The requirements of IRBs vary from one IRB to another; however, as a minimum requirement, the Investigators must promptly report all suspected unexpected serious adverse reactions (**SUSAR**) to their IRB.

In line with provisions set forth in 21CFR312, Dompé shall notify all participating Investigators in an IND safety report of any suspected adverse reaction that is both serious and unexpected and of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than:

- seven calendar days after becoming aware of the information if the event is fatal or life threatening; to be followed by any relevant information within eight days.

- fifteen calendar days after becoming aware of the information if the event is serious but neither fatal nor life threatening.

The Investigators in turn shall notify their IRB.

If the results of an investigation show that an ADR not initially determined to be reportable is reclassified as reportable, the Sponsor shall report such reaction in a written safety report as soon as possible, but in no event later than 7/15 calendar days after the determination is made.

Considering the number of patients enrolled and that the study is monocentric, to prevent any risk to compromise the integrity of the study, Dompé will notify the Investigator in a blinded fashion of any SUSAR (determined by the Sponsor as related).

Copies of all correspondence relating to reporting of any SUSARs to the IRB should be maintained in the Investigator's Files.

Dompé shall also notify FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible after Dompé determines that the information qualifies for reporting, in particular shall notify of:
- any suspected adverse reaction that is both serious and unexpected. Dompé must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event.
- findings from other studies that suggest a significant risk in humans exposed to the drug. Such a finding would result in a safety-related change in the overall conduct of the clinical investigation.
- findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- increased rate of occurrence of serious suspected adverse reactions.
Treatment will be unmasked by Sponsor Pharmacovigilance prior to submission of a SUSAR to Regulatory Authorities and only cases referred to active treatment will be considered expeditable for regulatory reporting, in line with law requirements.

12.4.4.. Periodical Reporting to Regulatory Authorities

Dompé shall be responsible to prepare and submit annual safety reports (Development Safety Update Report – DSUR) to relevant Regulatory Authorities.

12.5. UNMASKING OF THE STUDY TREATMENT

Individual envelopes identified with the subject assignment number have been prepared. Each one includes the identity of the treatment assigned to each subject. These envelopes, duly closed and sealed, are included into the investigator's File.

During the study the integrity of the envelopes will be regularly checked by CRO Monitor during the visits at site. At the end of the study all the individual envelopes must be returned to Dompé.

The sealed envelope can only be opened in case of emergency, when knowledge of the treatment identity is essential for treating the subject.

A copy of the Individual envelopes identified with the subject assignment number will be also sent to the Dompé Pharmacovigilance Responsible. Dompé Pharmacovigilance will unmask a patient treatment only for safety reason and will document envelope opening.

If the treatment code needs to be broken in the interest of patient safety for a medical emergency, the Investigator is allowed to break the treatment code for the specific patient, even before informing the Sponsor. The Investigator must always notify the Sponsor, so that the reason for any premature unmasking can be documented, by means of a communication to CRO/Dompé Drug Safety to the addresses specified at Par. 12.4.1 and to Dompé Medical Expert.

The Investigator will inform the Dompé representative (Dompé Medical Expert) if an emergency unmasking was performed without revealing the treatment identity, but only referring to the kit number involved in the unmasking in order to avoid a dissemination of unmasked information.

Additionally, Dompé Drug Safety may need to unmask the patient's treatment if a reported SAE meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfill expedited regulatory reporting requirements. Unmasked information shall not be disclosed to Investigators.

The identity of the treatments will remain unknown to the patient, Investigator, site staff, CRO and Dompé's Development personnel until the study is unmasked after the last enrolled patient completes week 12 visit and the database is locked (end of the masked follow-up); afterwards, 20 additional weeks of follow-up (unmasked follow-up period).

12.6. FOLLOW-UP OF PATIENTS WITH ADVERSE EVENTS

The Investigator is responsible for adequate and safe medical care of patients during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. All AEs should be followed-up to determine outcome of the reaction. The

Investigator should follow up the event until resolution or stabilization of the condition. It is the Investigator's responsibility to assure that the subjects experiencing AEs receive definite treatment for any AE, if required.

If patient was hospitalized due to a SAE, a copy of the discharge summary is to be forwarded to CRO/Dompé as soon as it becomes available. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests also may be requested. Further, depending upon the nature of the SAE, Dompé may request copies of applicable segments of the patient's medical records. In case of death, a copy of the autopsy report, if performed, should also be provided.

The Investigator shall inform CRO/Dompé Drug Safety with an appropriate written communication, whenever he becomes aware of new available information regarding the SAE, once the condition is resolved or stabilized and when no more information about the event is expected. Follow-up SAE information should be entered into the EDC and communicated through the specific Non-Carbon Repeat SAE form to CRO/Dompé Drug Safety within 24 hours from awareness to the addresses specified at Par. 12.4.1.
For pharmacovigilance purposes, all SAEs should be followed-up in order to clarify as completely as possible their nature and/or causality and until all queries have been resolved. All SAEs will be followed up until the events resolve or the events or sequelae stabilize, or it is unlikely that any additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e. subject or Investigator is unable to provide additional information, or the subject is lost to follow up), unless patient has withdrawn his/her consent.

12.6. PREGNANCY IN THE CLINICAL TRIAL

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Adequate birth control methods are summarized in the protocol's exclusion criteria in paragraph 7.2.

Prior to enrolment in the clinical trial, female patients of childbearing potential and their partners must be advised of the importance of avoiding pregnancy during the entire course of the study treatment and for the 30 days after the study treatment period ends and of the potential risks associated with an unintentional pregnancy. During the trial, female patients are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. In the same way, male patients who become aware that the partner might be pregnant, are to be instructed to contact the Investigator immediately.

The Investigator must report every pregnancy on a pregnancy report form as soon as possible within 24 hours of learning of the pregnancy to the CRO/Dompé Drug Safety contacts reported at Paragraph 12.4.1, even if no AE has occurred, and follow it to term. If, however, the pregnancy is associated with an SAE (eg, if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form must be filed as described in Section 12.4.1 with the appropriate serious criterion (eg, hospitalization) indicated on the SAE report form. Miscarriage, stillbirth and any malformation/disease must be reported as a SAE. Any pregnancy during the 8-week treatment period leads to the immediate exclusion from the trial.
A form prepared by Dompé will be utilized to capture all pregnancy-related information until the birth of the child.

12.7. ADVERSE EVENTS CAUSING TREATMENT DISCONTINUATION

If a patient is withdrawn from the study as a consequence of an AE, this must be recorded and reasoned in the eCRF, and the patient must be followed up until the resolution of the AE or as instructed by the medical monitor.

12.8. OVERDOSE

Cases of overdose (accidental or intentional) which result in serious adverse reactions are to be handled following emergency procedures, and reported within 24 hours from the Investigator's knowledge of its occurrence. This includes reports related to drug intake through different routes (e.g. ingestion), or drug intake with suicidal intentions and consequent drug overdose.
Since in the preclinical toxicology studies in animals and in the multiple ascending dose study performed in healthy volunteers none of the doses has caused an overdose, as documented by adverse reaction, for the purpose of this study it has been defined that the administration of more than 3 times the total daily dose on any given treatment day will be reported as an overdose.
Overdose shall be reported, even if not associated with adverse reactions, within 24 hours, in a SAE form, to CRO/Dompé Drug Safety contacts reported at Paragraph 12.4.1 and to Dompé Medical Expert, who should be contacted to discuss corrective treatment, if necessary.

13. DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 COMPLETION OF SOURCE DOCUMENTS AND CASE REPORT FORMS

The nature and location of all source documents will be identified to ensure that original data required to complete the eCRFs exist and are accessible for verification by the site monitor. If source documents are kept on electronic records, a verification of the electronic database software used at each site must be performed in advance of starting the study. At a minimum, source documents should include the following information for each patient:

- Patient identification (name, sex, race/ethnicity)
- Subject identification number (randomization number)
- Documentation of patient eligibility
- Documentation relevant to informed consent signature
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- Trial medication accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of trial completion and reason for early discontinuation, if applicable.

It is required that the author of an entry in the source documents is identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

With the EDC system, the sites will be given access to complete online the eCRFs; only designated individuals may complete the eCRFs. The eCRFs will be submitted at regular intervals based upon the clinical trial visit schedule. It is expected that all data reported will have corresponding entries in the source documents and that the Principal Investigator will review the reported data and certify that the eCRFs are accurate and complete. No patient identifiers should be recorded on the eCRFs beyond patient number, and demographic information.

13.2. DATA REVIEW AND CLARIFICATIONS

The eCRF data will be reviewed against the patient source data by the study monitors to ensure completeness and accuracy. After monitoring has occurred at the clinical sites and the eCRFs

have been submitted, additional data clarifications may be needed. Data clarifications are documented and are part of each patient eCRFs.

13.3 AUDIT PLANS

Audit activities will be performed by Dompé Quality Assurance or by CRO or other third party delegated by Dompé under the supervision of Dompé Quality Assurance.

On one or more occasions the study site may be audited by Dompé (or designee). The Investigator will be informed in advance of audit visits.

Additionally the study site may be inspected by a regulatory agency on one or more occasions.

13.4. REGULATORY DOCUMENTATION AND RECORDS RETENTION

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by Dompé and the Investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is not subject to regulatory inspection and should be kept separately. Additionally, the Investigator must keep study records and source documents until Dompé provides written approval for their destruction. The essential documents include at least: the signed protocol, signed Patient Informed Consent Forms from all patients who consented, hospital records and other source documents, and all other documentation included in the Investigator Site File and Pharmacy/Dispensing File. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, Dompé must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations (2 years after discontinuing clinical development or after the latest marketing approval).

Dompé will inform the Investigator in writing when these documents no longer need to be retained.

13.5. COMPENSATION FOR MEDICINE-INDUCED INJURY AND INDEMNIFICATION

Before the trial formally starts, Dompé will take out a study-specific insurance contract covering the amount requested by the respective national laws for patients/Investigators/Institutions participating in the clinical trial.

In case of questions about medical care, cost for medical care or insurance, patients can talk to their Investigator. Contact details will be given in the Patient Informed Consent Document.

Insurance and any updates will be provided to the Investigator before trial commencement for filing into the Investigator Site File.

13.6. STUDY REPORT AND PUBLICATION POLICY

The data resulting from this study will be the proprietary information of Dompé and will be made public after all data have been analyzed and the study results are available. Any manuscript, abstract or other publication or presentation of results or information arising in connection with the study must not be presented or published in any form, by the investigator or any other person, without the prior approval of Dompé and must therefore be submitted to Dompé for review and comment at least 45 days prior to submission for publication or presentation. At the end of the study, a clinical study report will be written by Dompé or its designee. The draft reports will be discussed with the coordinating investigators.

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13.7. CONFIDENTIALITY

All information obtained during the conduct of the study will be regarded as confidential. An agreement for disclosure will be obtained in writing by the patient and will be included in the Patient Informed Consent Document. Patient's data collected during the study will be handled in accordance with applicable data protection laws and regulations.

On the eCRFs, patients will be identified ONLY by the assigned patient number. If patient names are included on copies of documents submitted to Dompé (or to the CRO appointed by Dompé), the names will be obliterated or masked and the assigned patient number added to the document.

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15. APPENDIX A

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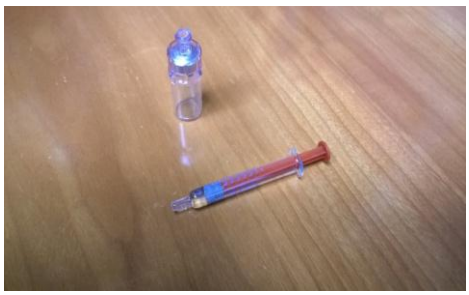

Instructions for the reconstitution of freeze-dried drug product

1) take out vial, syringe and adaptor from relative secondary packaging
2) put the adaptor on the top of the vial (after removing the plastic seal) by piercing the septum
3) put the syringe on adaptor inlet
4) deliver the syringe content in the vial and gently shake until the powder dissolves
5) put the vial/syringe assembly upside down and withdraw part of the content
6) remove the syringe and use it as a dropper