A Multicenter, Prospective, Randomized, Double-Masked, Phase 2 Study Evaluating the Safety, Tolerability, and Efficacy of Topical AG-86893 in Patients with Pterygium

*Trial Name: SURPH – a **S**t**U**dy of the **R**esponse to AG-86893 in patients with **P**terygium **H**yperemia*

Protocol Number	P2-86893-001
National Clinical Trial Identified Number	NCT03533244
Sponsor	Allgenesis Biotherapeutics Australia Pty Ltd ("*Allgenesis*")
Australian Sponsor	Trial Runners Australia Pty Ltd ("*Trial Runners*") Level 8, 555 Bourke St Melbourne VIC Australia 3000
Funded by	Allgenesis Biotherapeutics Australia Pty Ltd

Protocol Version Number: V3.0

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SPONSOR APPROVAL AND SIGNATURE PAGE

The following individuals approve this protocol V3.0 dated 20 Mar 2019.

Madhu Cherukury, PhD Director, Allgenesis Biotherapeutics Australia Pty Ltd	3/20/2019 Date
Dr Robert David, MD Medical Monitor Trial Runners Australia Pty Ltd	3/21/2019 Date

INVESTIGATOR SIGNATURE PAGE

I agree to:

a) Implement and conduct this clinical study diligently and in strict compliance with the protocol, Good Clinical Practice (GCP), and all applicable laws and regulations.
b) Maintain all information supplied by Allgenesis Biotherapeutics Australia Pty Ltd. and Trial Runners Australia Pty Ltd in confidence and when this information is submitted to an Institutional Review Board (IRB), Human Research Ethics Committee (HREC), Independent Ethics Committee (IEC), or other review board, it will be submitted with a designation that the material is confidential.

I have read this protocol, P2-86893-001, Version 3.0 dated 20 Mar 2019, in its entirety and agree to all aspects.

_____ _____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Name of Facility

_____

Location of Facility (City, State)

Please return to Trial Runners

STUDY TITLE

A Multicenter, Prospective, Randomized, Double-Masked, Phase 2 Study Evaluating the Safety, Tolerability, and Efficacy of Topical AG-86893 in Patients with Pterygium

SHORT NAME

*SURPH: a **S**t**U**dy of the **R**esponse to AG-86893 in patients with **P**terygium **H**yperemia*

PROTOCOL NUMBER

P2-86893-001

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STATEMENT OF COMPLIANCE

This study is to be conducted in accordance with Institutional Review Board (IRB) regulations (United States [US] 21 Code of Federal Regulations [CFR] Part 56.103) or applicable Human Research Ethics Committee (HREC), or International Ethics Committee (IEC) regulations. The investigator must obtain approval from a properly constituted HREC/IRB/IEC prior to initiating the study and re-approval or review at least annually. Allgenesis is to be notified immediately if the responsible HREC/IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all HREC/IRB/IEC correspondence with the investigator should be provided to Allgenesis.

The investigator should not implement any deviation from or changes to the protocol without approval by Allgenesis and prior review and documented approval/favourable opinion from the HREC/IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study participants, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Multicenter, Prospective, Randomized, Double-Masked, Phase 2 Study Evaluating the Safety, Tolerability, and Efficacy of Topical AG-86893 in Patients with Pterygium

Short Name: SURPH: a **S**t**U**dy of the **R**esponse to AG-86893 in patients with **P**terygium **H**yperemia

Study Description:

Study Hypotheses:

- AG-86893 has an acceptable safety profile as measured by the incidence and severity of adverse events (AEs) compared with vehicle
- At least 1 concentration of AG-86893 is effective, as measured by the mean change from baseline in conjunctival hyperemia, compared with vehicle

Study Design:

- This is a multicenter, randomized (1:1:1), double-masked, vehicle-controlled, parallel-group, dose-response (0.1% and 0.3% AG-86893) study
- Participants will administer a single eye drop of study drug 3 times daily (TID) for 28 days to the study eye
- The duration of the study is 12 weeks, with 4 weeks of treatment with study drug and 8 weeks of follow-up without medication

Objectives:

Safety Objective:

- Evaluate the safety and tolerability of AG-86893 eye drops in participants with pterygium

Efficacy Objectives:

- Evaluate the dose response of AG-86893 on conjunctival hyperemia
- Evaluate the dose response of AG-86893 on pterygium vascularity, volume and vessel length (exploratory)

Pharmacokinetic Objective:

- Determine plasma concentrations of AG-86893

Endpoints:	Safety Endpoints: • Changes in findings from vital signs, laboratory tests, electrocardiogram (ECG) • Changes in findings from best-corrected visual acuity (BCVA), biomicroscopy, tear film break-up time (TFBUT), lissamine green conjunctival staining, ophthalmoscopy • AEs • Participant assessment of ocular symptoms, including eye dryness, burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, and ocular pain Efficacy Endpoints: • Change from baseline in overall conjunctival hyperemia score at Day 28 (Primary efficacy endpoint) • Change from baseline in overall conjunctival hyperemia score at Day 7 and Day 56 (Secondary efficacy endpoint) • Change from baseline in conjunctival hyperemia score in the quadrant with the pterygium at Days 7, 28 and 56 (Secondary efficacy endpoints) • Change from baseline in pterygium vascularity at Days 7, 28 and 56 (Exploratory efficacy endpoints) • Change from baseline in pterygium volume, as assessed by AS OCT, at Days 7, 28 and 56 (Exploratory efficacy endpoints) • Change from baseline in pterygium vessel length at Days 7, 28 and 56 (Exploratory efficacy endpoints) Pharmacokinetic Endpoint: • Concentration of AG-86893 in plasma over time
Study Population:	Approximately 70 adult male or female participants in good general health, with conjunctival hyperemia secondary to pterygium (score of ≥2 in the quadrant with the pterygium and ≥1 in at least 2 other quadrants) will be enrolled
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Approximately 12 sites
Description of Study Intervention:	AG-86893 is a sterile ophthalmic nanosuspension administered as an eyedrop. Participants will administer a single drop of study drug (AG-86893 vehicle, 0.1% AG-86893, or 0.3% AG-86893) into the study eye TID (approximately every 8 hours) for 4 weeks
Study Duration:	18 months
Participant Duration:	12 weeks from time of enrollment to completion of study

1.2 SCHEMA

Day -14 to -2 — Screening

- Informed consent
- Screen potential participants by inclusion and exclusion criteria
- Submit ocular photos OU to central reading center for qualification

Day 1 — Pre-randomization/ On study drug

- Review all screening laboratory findings
- Concomitant medications, concurrent procedures, vital signs
- Pregnancy test, ECG, BCVA, IOP
- Confirm that participant meets all inclusion and none of exclusion criteria
- Randomization
- Select study eye; if both eyes qualify, then the eye with higher conjunctival hyperemia score will be study eye
- AS-OCT (at selected sites), ocular photography; submit to reading center
- Biomicroscopy, TFBUT, lissamine green conjunctival staining, ophthalmoscopy
- Plasma drug monitoring (at selected sites)
- Study drug dispensing and administration
- Participant questionnaire
- AE evaluation

Day 7 — On study drug

- Visit conducted as a phone call, or optional in-clinic visit at the discretion of the site Investigator
- Concomitant medications, compliance assessment, concurrent procedures, participant questionnaire
- AE evaluation
- If conducted on-site: Laboratory tests (hematology with differentials, serum chemistry, urinalysis), vital signs, ocular assessments (BCVA, ocular photography, AS-OCT [at selected sites], IOP, biomicroscopy)

Day 28 (Week 4) — On study drug

- Study drug administration; compliance assessment
- Concomitant medications, concurrent procedures, participant questionnaire, physical characteristics, vital signs
- Pregnancy test, ECG
- Laboratory tests (hematology with differentials, serum chemistry, urinalysis)
- Ocular assessments (BCVA, ocular photography [1 hour post-dose], AS-OCT [at selected sites], IOP, biomicroscopy, TFBUT, lissamine green conjunctival staining, ophthalmoscopy)
- Plasma drug monitoring (at selected sites)
- AE evaluation

Day 56 (Week 8) — Off study drug

- Concomitant medications, concurrent procedures, participant questionnaire, vital signs
- Ocular assessments (BCVA, ocular photography, AS-OCT [at selected sites], IOP, biomicroscopy, TFBUT, lissamine green conjunctival staining)
- Plasma drug monitoring (at selected sites)
- AE evaluation

Day 84 (Week 12) — Off study drug/Exit

- Concomitant medications, concurrent procedures, participant questionnaire, physical characteristics, vital signs
- Pregnancy test, ECG
- Laboratory tests (hematology with differentials, serum chemistry, urinalysis)
- Ocular assessments (BCVA, IOP, biomicroscopy, TFBUT [optional], lissamine green conjunctival staining [optional], ophthalmoscopy)
- AE evaluation

1.3 SCHEDULE OF ACTIVITIES

Procedures	Screening Day -14 to -2 (SCR)	Enrollment/ Baseline Visit 1, Day 1 (V1D1)	Study Visit 2 Day 7 ±3 days (V2D7) ☎*	Study Visit 3 Day 28 ±3 days (V3D28)	Study Visit 4 Day 56 ±5 days (V4D56)	Final Study Visit 5 Day 84 ±5 days (V5D84)
Informed consent	X					
Demographics	X					
Medical, smoking, alcohol and drug history [a]	X					
Concomitant medication	X	X	X	X	X	X
Compliance assessment [b]			X*	X		
Concurrent procedures	X	X	X	X	X	X
Participant questionnaire [c]		X [c]	X	X [c]	X	X
Physical characteristics [k]	X			X		X
Vital signs [d]	X	X	X*	X	X	X
Hematology	X		X*	X		X
Serum chemistry	X		X*	X		X
Urinalysis	X		X*	X		X
Urine pregnancy test [e]	X	X		X		X
ECG (12-lead)	X	X		X		X
BCVA	OU	OU	OU*	OU	OU	OU
Ocular photography [f]	OU	SE	SE*	SE	SE	
AS-OCT [g]		SE	SE*	SE	SE	
IOP	OU	OU	OU*	OU	OU	OU
Biomicroscopy	OU	OU	OU*	OU	OU	OU
TFBUT		OU		OU	OU	OU [h]
Lissamine green staining		OU		OU	OU	OU [h]
Ophthalmoscopy	OU	OU		OU		OU
Plasma drug monitoring [i]		X		X	X [i]	
Randomization		X				
Study drug [j]		X		X		
AE review and evaluation		X [l]	X	X	X	X

** Study Visit 2 (V2D7) is a phone call follow-up but may be conducted as an optional in-clinic visit at the discretion of the Principal Investigator. Asterisked assessments will only be conducted during in-clinic visit*

a) Medical history will include history of sun exposure
b) On Day 7, study drug bottle will be weighed and returned if the visit is conducted in-clinic. If the visit is via phone, participants will be verbally instructed to maintain compliance and use the provided diary. On Day 28, study drug will be collected after administration of last dose and study drug bottles will be weighed
c) Participant questionnaire will be administered prior to study drug administration at Visits 1 & 28
d) Blood pressure, pulse, temperature, and breathing rate
e) Females of childbearing potential only
f) Ocular photography will be submitted to central reading center for assessment of conjunctival hyperemia, pterygium vascularity and pterygium vessel length
g) At selected sites, AS-OCT imaging will be performed and submitted to central reading center for assessment of pterygium volume
h) Test is optional at Day 84; to be performed if test shows abnormal findings at Day 56
i) At selected sites, blood (~10 mL) for plasma drug monitoring will be collected on Day 1 and Day 28 pre-dose and post-dose at 0.5 and 1 hour after the morning dose; on Day 56, a single sample will be collected
j) On Day 1, study drug will be dispensed and the first dose will be administered in the clinic after all study-related procedures have been performed. On Day 28 (the last day of treatment), the morning dose will be administered in the clinic prior to all study-related procedures, except the participant questionnaire
k) Height and weight at screening; weight only at other timepoints
l) Participants will be questioned on AEs approximately 1 hour after IP administration

Additional examinations and unscheduled visits can be included as safety concerns arise.

AE, adverse event; AS-OCT, anterior-segment optical coherence tomography; BCVA, best-corrected visual acuity; ECG, electrocardiogram; IOP, intraocular pressure; OU, both eyes; SE, study eye; TFBUT, tear film break-up time.

2 INTRODUCTION

2.1 STUDY RATIONALE

Pterygium is a wing-shaped, fibrovascular lesion on the ocular surface that usually originates from the nasal bulbar conjunctiva and extends onto the corneal limbus and beyond. Although pterygium can form nasally or temporally, the predominant form occurs at the nasal limbus. As the disease progresses, the lesion distorts the corneal topography, encroaches on the visual axis, and obscures the optical center of the cornea, causing visual impairment [1, 2].

The pathogenesis of pterygium is mostly unknown; however, multiple mechanisms have been proposed. These mechanisms include ultraviolet radiation, oxidative stress, cytokines, matrix metalloproteinases (MMPs), growth factors, cumulative DNA damage, viral infections, and anti-apoptotic factors. Growth factors can induce proliferation and/or migration of epithelial cells, fibroblasts, or vascular cells, which contribute to the formation of pterygium. These include epidermal growth factor, heparin-binding growth factor, fibroblast growth factor-2 (FGF-2), nerve growth factor, ciliary neurotrophic factor, neurotrophin 4, platelet-derived growth factor (PDGF), transforming growth factor-β, vascular endothelial growth factor (VEGF), and insulin-like growth factor binding proteins [2-4]. FGF-2 is overexpressed in cultured fibroblasts of pterygium and is involved in the corneal healing process and neovascularization [3, 5].

Multiple stimuli, such as ultraviolet radiation, hypoxia, cytokines, and growth factors, may induce VEGF expression [2]. VEGF serves as a major proangiogenic factor, which is expressed in tears, plasma, and ocular tissues of patients with pterygium [2]. VEGF regulates its tyrosine kinase receptors (VEGFR), which increased growth, migration, and survival of the endothelial cells [6]. Elevated levels of MMPs and VEGF have been reported in the epithelial cells of a pterygium leading edge [7]. PDGF may also play a role and mediates the tyrosine kinase receptors (PDGFRβ) in the pterygium, which stimulate VEGF transcription and recruit pericytes to neovessels. Inhibition of the PDGF signaling pathway disrupts pericyte recruitment, which results in apoptosis of VEGF signaling [6].

Patients with pterygium suffer from dry eye-like symptoms, such as redness, irritation, and blurriness. Patients also have reduced TFBUT [2]. Current treatment for pterygium requires a wait-and-see observation until encroachment of the cornea, usually prompting treatment with artificial tears or lubricants until surgery is required. Some patients opt for surgical removal early for cosmetic reasons. Antimetabolites, such as mitomycin C, have been used in conjunction with surgery to minimize recurrence [1, 8], as have anti-VEGF therapies [9, 10]. However, antimetabolites have severe side effects, such as scleral necrosis, corneal perforation, corneal edema, secondary glaucoma, corneal calcification, and cataracts [11-14], and anti-VEGF monotherapies have had little success in controlling recurrence [15, 16].

Pterygium prevalence rates vary widely across the world, depending on the population and region studied. Pterygium occurs more commonly in tropical regions than in temperate climates. Incidence and prevalence rates are highest in the “pterygium belt,” which ranges from 30° north to 30° south of the equator, and lower prevalence rates are found at latitudes >40°. In tropical regions, up to 52% prevalence rates can be observed [17-19]. The prevalence rate of pterygium for Caucasians residing in urban, temperate climates is estimated at 1.2% [20]. Pterygium occurs in about 2.9% of Americans in the US [21]. The pooled prevalence rate of pterygium from 6 studies from China is 9.9% [22].

Currently, there is no approved drug for pterygium on the market. The current treatment for pterygium is surgery, but recurrence and fibrosis are major sequelae of surgery. Therefore, medical treatment for pterygium is still an unmet medical need. Allgenesis' AG-86893 (nintedanib, marketed oral drug reformulated as a topical ophthalmic nanosuspension) may fill this void.

The purpose of this study is to evaluate the safety, tolerability, and efficacy of AG-86893 in patients with pterygium, and obtain preliminary data on its effect on the vasculature in the conjunctiva/pterygium. The pharmacokinetics of AG-86893 have not been evaluated in humans after topical instillation. Therefore, an objective of this study also includes the characterization of the plasma concentrations of AG-86893 following ocular administration.

2.2 BACKGROUND

AG-86893 is a reformulation of an oral drug, nintedanib (marketed as Ofev®, indicated for the treatment of idiopathic pulmonary fibrosis and non-small cell lung cancer), that binds and inhibits the tyrosine kinase found on VEGFR 1-3, PDGFRα and β, and fibroblast growth factor receptor (FGFR) 1-3 [23] . AG-86893 binds competitively to the adenosine triphosphate binding pocket of these receptors and blocks the intracellular signaling that is crucial for the proliferation, migration, and survival of endothelial cells as well as perivascular cells (pericytes and vascular smooth muscle cells), and for the proliferation, migration, and transformation of fibroblasts [25, 26]. As such, AG-86893 is expected to be effective in inhibiting neovascularization and fibrosis.

Non-clinical AG-86893 studies

The efficacy of topical ophthalmic administrations of AG-86893 was demonstrated in animal models of corneal neovascularization. Rabbits, whose corneas were sutured with silk threads to induce new blood vessel growth, were given topical eye drops, TID for 14 days following suturing (preventative model) or for 7 days after new blood vessels had grown (remedial model). In both studies, AG-86893 was able to inhibit and regress blood vessels at the doses tested (0.1%, 0.3%, and 1%).

Following a single drop of 0.1% AG-86893 to rabbit eyes, AG-86893 absorbed well into target tissues, with a maximum plasma concentration (C_{max}) of 821 ng/g in the cornea and 1000 ng/g in the conjunctiva. These concentrations were at least 23 times higher than the half-maximal inhibitory concentration (IC_{50}) values for VEGFR and PDGFR. AG-86893 eliminated from cornea and conjunctiva with a half-life ($T_{1/2}$) of 9 to 13 hours. AG-86893 was well tolerated in rabbits dosed four times daily (QID) to both eyes for 7 days at 0.3%, 0.6%, and 1% dose strengths, and three times daily (TID) to both eyes in rabbits and monkeys for 28 days. The one-month Good Laboratory Practice (GLP) ocular toxicology studies in rabbits and monkeys dosed with 0.3%, 0.6%, and 1% dose strengths, given to both eyes TID for 28 days showed no mortality or drug-related effects, and ocular histopathology examinations showed no adverse effects related to the study drug. The NOAEL dose was identified as 1% TID in both rabbit and monkey.

At the proposed highest clinical dose of 0.3%, the daily area-under-the-plasma concentration-time curve ($AUC_{0\text{-}24hr}$) on Day 28 in rabbits and monkeys were 33.0 ng•hr/mL and 3.48 ng•hr/mL, respectively. These values are at least 10 and 98 times lower, respectively, than that observed ($AUC_{0\text{-}24hr}$ of 342 ng•hr/mL) in humans with the reference listed drug (RLD) after oral dosing of 150 mg twice daily for 28 days, which showed no dose-limiting toxicities [27]. The safety margin increases to 20 to 196-fold, when taking into account that the planned human study will dose only 1 eye.

Refer to the Investigator's Brochure [28] for details on these non-clinical studies.

Clinical nintedanib studies

The safety and tolerability of orally administered nintedanib have been well characterized by the Innovator for the reference listed drug (RLD) nintedanib (refer to the Investigator's Brochure for details [28]).

In a Phase 1 study following daily oral doses of nintedanib 50 mg (N = 2) and 100 mg (N = 1) and BID oral doses of nintedanib 150 mg (N = 6) for 29 days to patients with solid tumors, no dose-limiting toxicities were observed [27].

Study P2-86893-001 is the first clinical study with topical AG-86893. With 24 participants dosed in this study (10 completed Day 84 follow-up and an additional 7 completed Day 28 treatment), the data suggest a favourable safety profile: 0 serious AEs (SAEs) and 9 AEs were reported, 7 of which were deemed unrelated to AG-86893. One AE was deemed possibly related to the product ("watery, heavy feeling in the eye" occurring 5 days after treatment commencement and resolving 4 days later). The final AE was determined by the PI to be related to AG-86893 ("yellow stained conjunctiva" occurring 14 days after treatment commencement and resolving 2 months after treatment cessation). Both AEs resolved without any treatment.

Pharmacokinetic nintedanib studies

Absorption: Nintedanib reached C_{max} between 1 and 4 hours following 150 mg oral doses of capsules (Table 2-1, Table 2-2, and Table 2-3). The oral bioavailability of nintedanib in humans is roughly 5%. Exposures increased by approximately 20% in fed conditions [23] .

Table 2-1 Pharmacokinetic Parameters Following Twice Daily Oral Dosing of Nintedanib for 14 Days to Patients With Idiopathic Pulmonary Fibrosis

Dose	N	$C_{max,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•hr/mL)	$T_{max,ss}$ (hr)	$T_{1/2}$ (hr)
BID x 14 days					
100	4	20.0	115	3.4	23.4
150	9	39.7	218	3.9	27.5

$AUC_{\tau,ss}$, area under the plasma concentration-time curve at steady state over a uniform dosing interval tau; BID, twice daily; $C_{max,ss}$, maximum plasma concentration at steady-state; $T_{1/2}$, half-life; $T_{max,ss}$, time to reach maximum plasma concentration at steady-state.
Source: Ogura et. al., 2015 [30]

Table 2-2 Pharmacokinetic Parameters Following Once Daily or Twice Daily Oral Dosing for 29 Days of Nintedanib in Patients With Solid Tumors

Dose	N	$C_{max,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•hr/mL)	$T_{max,ss}$ (hr)	$T_{1/2}$ (hr)
QD x 29 days					
50	1	8.22	32.1	3.07	14.7
100	1	40.8	207	2.00	11.8
200	8	35.4	223	1.98	15.3
250	6	58.6	479	2.53	13.7
300	3	50.5	482	3.00	14.1
BID x 29 days					
150	6	34.8	171	1.03	16.3
150 + 200	6	48.0	260	2.13	15.6
200	6	44.9	303	2.72	19.0

Dose	N	$C_{max,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•hr/mL)	$T_{max,ss}$ (hr)	$T_{1/2}$ (hr)
250	11	44.2	226	2.08	16.7
300	3	68.6	366	2.00	12.9

$AUC_{\tau,ss}$, area under the plasma concentration-time curve at steady state over a uniform dosing interval tau; BID, twice daily; $C_{max,ss}$, maximum plasma concentration at steady-state; QD, once daily; $T_{1/2}$, half-life; $T_{max,ss}$, time to reach maximum plasma concentration at steady-state.
Source: Mross et.al, 2010 [27]

Distribution: In humans, the volume of distribution following an intravenous dose was 1050 L and was highly protein bound (serum albumin). Nintedanib is preferentially distributed into plasma [23]

Metabolism: As with the animal species, the major metabolite of nintedanib is the hydrolytic cleavage product, BIBF 1202 (free acid), and its glucuronide. Minimal cytochrome P450-dependent metabolites were found in human plasma. The major metabolites were not considered active at clinically relevant concentrations [23, 31].

Table 2-3 Pharmacokinetic Parameters of Nintedanib and Its Metabolites Following a Single Oral 100 mg Dose of Nintedanib to Healthy Volunteers

Analyte	N	C_{max} (ng/mL)	AUC (ng•hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
Single Dose					
Nintedanib	12	8.4	56.2	3.0	11.7
BIBF 1202	10	5.7	42.4	5.0	3.2
BIBF 1202 glucuronide	12	11.1	630	10.0	36.8

AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; $T_{1/2}$, half-life; T_{max}, time to reach maximum plasma concentration.
Source: Dallinger et. al, 2016 [32]

Following a 100-mg dose of ^{14}C-nintedanib in humans, BIBF 1202 free acid and its glucuronide accounted for 32% and 47% of total radioactivity [23, 31].

Elimination: Total plasma clearance of nintedanib was 1390 mL/min, with over 90% of the drug excreted in feces/biliary excretion. The plasma $T_{1/2}$ was between 10 and 15 hours [23, 31] .

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks of long-term (52-week) orally dosed nintedanib are described in the Ofev package insert and summarized in the AG-86893 Investigator's Brochure [28]. In brief, there was a dose-dependent increase in liver enzyme levels in patients. Liver enzyme increases were reversible with dose modification or discontinuation and were not associated with clinical signs or symptoms of liver injury. The most common side effects were gastrointestinal irritation (diarrhea, nausea, abdominal pain, vomiting, and decreased appetite), headache, weight decrease, and hypertension [33]. As with most anti-VEGF therapies, arterial thromboembolic events have been reported.

For AG-86893, the risk to the participant is expected to be low. In this study, the highest proposed dose of 0.3% given TID will expose participants to 0.36 mg of nintedanib per day (3 mg/mL x 0.040 mL x 3), which is over 800 times less than what has been approved for the RLD (300 mg; 150 mg

BID). Furthermore, the duration of treatment (28 days) is similar to the above Phase 1 study, in which no dose-limiting toxicities were observed at the 150 mg BID dose [27].

2.3.2 KNOWN POTENTIAL BENEFITS

The commercial product (Ofev®; nintedanib ethanesulfonate) has been approved for the treatment of idiopathic pulmonary fibrosis due to its antifibrotic mechanism, and for non-small cell lung cancer, due to its antiangiogenic mechanism.

For AG-86893, there is potential for the reduction of conjunctival hyperemia with short-term use, as well as reduction of new blood vessel growth and fibrosis that may contribute to the growth of the pterygium with longer-term use.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This study incorporates standard laboratory assessments as well as general and ocular examinations to detect risk to participants. Because the potential systemic and ocular risks to 4 weeks' exposure of AG-86893 are readily detectible and limited, the opportunity to assess the potential benefit for an unmet need is justified.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Safety		
• Evaluate the safety and tolerability of topical eye drops of AG-86893 in participants with pterygium	• Changes in findings detected by vital sign assessment, laboratory tests, ECG • Changes in findings detected by BCVA testing, biomicroscopy, TFBUT, lissamine green conjunctival staining, ophthalmoscopy • Adverse events • Participant assessment of ocular symptoms via questionnaire, including eye dryness, burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, and ocular pain	• These tests are standard investigations of general systemic health • These tests comprise a standard eye examination to investigate ocular health • Severity and causality of AEs are standard endpoints • Because pterygia may be associated with ocular symptoms, it will be important to investigate whether treatment has any effect on these symptoms
Efficacy		
• Evaluate the dose response of AG-86893 on conjunctival hyperemia	• Change from baseline in overall conjunctival hyperemia score at Day 28 (primary efficacy endpoint) • Change from baseline in overall conjunctival hyperemia score at Day 7 and Day 56 (secondary efficacy endpoint) • Change from baseline in conjunctival hyperemia score in the quadrant with the	• Red eye (e.g. Conjunctival hyperemia) is a chief complaint in participants with pterygia. The assessment will be done as a sum of all 4 quadrants to ensure appropriate benefit: risk (i.e., no increase in hyperemia in one quadrant, while decrease in quadrant with pterygium) • This will be assessed to differentiate overall conjunctival

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	pterygium at Days 7, 28 and 56 (secondary efficacy endpoint)	hyperemia from that of the quadrant with the pterygium
Pharmacokinetic		
• Determine plasma concentrations of AG-86893	• Plasma concentrations of AG-86893	• Plasma concentrations of AG-86893 will be monitored to evaluate the amount of systemic exposure following ocular dosing
Exploratory		
• Evaluate the dose response of AG-86893 on pterygium vascularity • Evaluate the dose response of AG-86893 on pterygium volume • Evaluate the dose-response of AG-86893 on pterygium vessel length	• Change from baseline in pterygium vascularity at Days 7, 28 and 56 • Change from baseline in pterygium volume, as assessed by AS-OCT, at Days 7, 28 and 56 • Change from baseline in pterygium vessel length at Days 7, 28 and 56	• Pterygium vascularity is a known factor to affect hyperemia • While the ultimate goal of treatment is to reduce the volume of the pterygium lesion, this is likely to only be accomplished with longer dosing than what is provided in this study • Findings from a rabbit corneal neovascularization study demonstrated regression of vessel length in the pterygia over 7 days of treatment

AS-OCT, anterior-segment optical coherence tomography; BCVA, best-corrected visual acuity; ECG, electrocardiogram; TFBUT, tear film break-up time.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The clinical hypotheses for this study are:

- AG-86893 has an acceptable safety profile, as measured by the incidence and severity of AEs compared with vehicle
- At least 1 concentration of AG-86893 is effective, as measured by the mean change from baseline in overall conjunctival hyperemia compared with vehicle

This will be a Phase 2, multicenter, prospective, randomized, parallel-group, double-masked study evaluating the safety, tolerability, and efficacy of AG-86893 topical eye drops in participants with pterygium who are at least 18 years of age with overall conjunctival hyperemia score ≥2 in the study eye. A central reading center will assess conjunctival hyperemia from ocular photography at the screening visit to qualify participant eligibility; in addition, the reading center will assess subsequent visits for conjunctival hyperemia, pterygium vascularity, pterygium volume and vessel length in a masked fashion, to determine efficacy.

The study will have 3 treatment groups—vehicle, 0.1% AG-86893, and 0.3% AG-86893—with participants being randomly assigned in a 1:1:1 ratio to study drug. Study drug will be administered only to the selected study eye, until the Day 28 visit. Compliance with the study drug regimen will be estimated by weighing both eye drop bottles at Day 7 (if visit conducted in-clinic) and again at Day 28.

There will be 6 possible clinic visits, including a 14-day screening period (from Day -14 to -2), followed by a treatment/observation period (Day 1, Day 7 [may be conducted as a phone follow-up], and Day 28), and 2 post-treatment follow-up visits for safety monitoring (Day 56 and Day 84).

Collection of anterior-segment optical coherence tomography (AS-OCT) imaging will be done at sites with the requisite equipment and certified by the reading center. Plasma drug monitoring will be done at selected sites with the required facilities.

Primary database lock will occur after all participants exit the study on Day 84. Assessment of safety, tolerability, efficacy, and plasma concentrations of AG-86893 requires participants to participate for 12 weeks from Baseline to Study Exit (Day 84), plus the 2- to 14-day screening period.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A placebo control is the gold standard clinical trial design appropriate for conditions without any approved treatments so that variability in the disease can be assessed. The use of vehicle of AG-86893 has the potential to provide some relief to the participant because of actions similar to an artificial tear, lubricating the ocular surface and reducing irritation. However, the alternative of an open-label study without a control group introduces too many biases.

It is essential to investigate the dose-response of the proposed treatment in order to select a dose for further study to confirm any potential treatment effects.

4.3 JUSTIFICATION FOR DOSE

The doses selected in this study were based on the doses that were found to be effective in inhibiting new blood vessel growth on the cornea in a rabbit model. In that study, doses of 0.1%, 0.3%, and 1% were equally effective in inhibiting the blood vessel growth caused by suture placement. Rabbits dosed QID bilaterally for 7 days at doses of 0.3%, 0.6%, and 1% showed no signs of discomfort or ocular irritation. These doses were tested for safety and ocular histopathology in a 28-day GLP rabbit and monkey study after topical TID dosing of AG-86893. All the doses tested were safe and 1% identified as the NOAEL (no-observed-adverse-effect-level) dose. It is therefore expected that the doses of 0.1% and 0.3% administered TID will be tolerable and safe, and that at least 1 concentration will be effective in reducing hyperemia in participants with pterygium.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Assessments (Section 1.3). Furthermore, the study will be completed when all participant's images have been assessed by central reading center.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Signed an IRB-/IEC-approved informed consent form (ICF) prior to any study-specific procedures

2. Willingness to comply with the study procedures and study drug administration and to return for all study visits
3. Male or female, 18 years of age or older
4. Body mass index between 18 and 38 kg/m^2, inclusive
5. Females of childbearing potential must have a negative pregnancy test at baseline and must be on established, adequate contraception (e.g., oral contraceptive or bilateral tubal ligation) and males must use condoms if their partner is of childbearing potential and their female partner should also use an additional effective means of contraception (e.g., oral contraceptive or bilateral tubal ligation), or they must agree to abstain from sexual intercourse with a female partner for the duration of the study; contraception should be continued for 3 months after the last dose. Females of non-reproductive potential are permitted to enter the study without the need for a pregnancy test. Non-reproductive potential is defined as one or more of the following: (1) women who are postmenopausal (≥47 years of age who have been amenorrheic for at least 12 consecutive months), (2) women who do not possess a uterus (e.g., previous hysterectomy), (3) women who do not possess both ovaries (e.g., previous bilateral oophorectomy), and (4) women with a bilateral tubal ligation
6. Good health with no clinically significant findings based on the medical history, ECG, vital signs, blood chemistry, hematology, and urinalysis findings, as determined by the investigator. Abnormal laboratory results must be determined as not clinically significant by the investigator
7. Presence of pterygium, extending beyond the limbus, with associated conjunctival hyperemia in the quadrant containing the pterygium of grade ≥2 at screening, as assessed by the central reading center based on ocular photography using a 5-point scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe, AND a conjunctival hyperemia score of ≥1 in at least 2 of the remaining quadrants of the same eye at screening (study eye). If both eyes are affected and meet the inclusion criteria, the eye with the higher overall hyperemia score will be used as the study eye. If both eyes are eligible and have the same hyperemia score, the right eye will be selected as the default study eye

5.2 EXCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must not meet any of the following criteria:

Ocular criteria

a) BCVA in either eye of 35 ETDRS letters or worse (Snellen equivalent of 20/200) at screening or baseline

b) History or presence of any ocular diseases other than pterygium or its sequelae, including neoplasia

c) Diagnosis of ocular hypertension or glaucoma requiring use of intraocular pressure (IOP)-lowering medication

d) Use of contact lenses during the study in the study eye

e) Aphakia or torn posterior capsule in the study eye

f) History or evidence of the following surgeries in the study eye at any time, unless specified:

    a. Pterygium removal

    b. Corneal transplant

c. Glaucoma surgery, shunt, or microstent

d. Refractive surgery

e. Surgery on ocular muscles

f. Any retinal surgery

g. Cataract surgery within 3 months or yttrium aluminium garnet (YAG) capsulotomy within 1 month prior to baseline

g) Current use of any ophthalmic medications in the study eye other than artificial tears or ocular decongestants; ocular decongestants must be washed out for a minimum of 7 days prior to baseline and use is prohibited 2 days before any study visit

h) History of any intravitreal, subconjunctival medication in the study eye within 12 months prior to baseline

Non-ocular criteria

1. Presence of a non-healing/oversize wound, ulcer, or fracture
2. Inadequate liver function, as demonstrated by total bilirubin >1.5 × upper limit of normal (ULN) at screening (unless participant has a documented history of Gilbert's syndrome), aspartate transaminase (AST) and alanine transaminase (ALT) ≥2.5 × ULN or serum albumin <3.5 g/dL
3. Any malignancy other than adequately treated nonmelanomatous skin cancer, or adequately treated prostate cancer in men over the age of 70
4. Any uncontrolled systemic disease, including cardiac disease; hypertension; diabetes mellitus; mental, neurological, respiratory, gastrointestinal, renal, or hepatic dysfunction; infectious disease; or malignancy
5. Use of any immunosuppressive therapy during the study
6. Use of marijuana during the study or within 2 days prior to screening
7. Any disease or condition that the medical monitor or the investigator believes will impact the participant's ability to adhere to the study schedule or may confound the results
8. Participation in any investigational study within 30 days prior to baseline or exposure to an investigational drug must be fully washed out (at least 5 half-lives)
9. Donation of ≥450 mL (e.g., 1 unit) of blood or blood products within 56 days prior to baseline (for participants participating in the plasma concentration blood draw), or plans to donate blood during the study (all participants)
10. Pregnancy, plans for pregnancy, or breastfeeding during the study
11. History of active alcohol or substance abuse as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) criteria

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not assigned to the study intervention or entered into the study. A set of screen failure information is

required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. This information includes participants' demographic information, screen failure details, eligibility criteria, and any SAEs.

In some cases, individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened (e.g., a hypertensive individual with high blood pressure due to missed medication on the day of the screening visit, or an individual willing to discontinue use of ocular decongestants for the duration of the study). Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Sites will recruit participants from their database as well as locally. Any advertisement must be approved by the IRB/IEC. Refer to the Manual of Procedures (MOP) for additional information.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS ADMINISTRATION

6.1.1 STUDY INTERVENTIONS DESCRIPTION

The active study treatment will be the investigational agent AG-86893, which is a topical ophthalmic nanosuspension formulation of nintedanib (Ofev®, Boehringer Ingelheim), delivered at concentrations of either 0.1% or 0.3%, depending on randomized treatment assignment. The control treatment will be AG-86893 vehicle. All 3 study interventions will be delivered to the study eye as a single eye drop TID, using the provided white, opaque, low-density polyethylene (LDPE) eye dropper bottle.

6.1.2 DOSING AND ADMINISTRATION

Once study entry procedures have been completed (see Section 4.1), the independent drug administrator not affiliated with the assessment of the participant will obtain the randomization assignment and drug kit number from the Interactive Web Response System (IWRS). The independent (unmasked) drug administrator will vigorously shake the eye dropper bottle for 10 seconds prior to administration to the study eye.

A single eye drop (~40 µL eye drop) of AG-86893 or AG-86893 vehicle control will be applied TID (morning, afternoon, and evening, approximately 8 hours apart) to the study eye until the Day 28 visit. A single study treatment will be administered to each participant in this study by the independent drug administrator on the morning of the clinic visits on Day 1 and Day 28. The participant will be instructed on Day 1 how to self-dose using the eye dropper bottle for the remaining doses with written instructions provided on a participant dosing diary. Two bottles of AG-86893 or vehicle will be provided to each participant at Day 1; participants will be instructed to bring both of these bottles with them when they return to the clinic for the Day 7 (optional) and Day 28 visits, or to any unscheduled visits during this period. Participants will be required to remain in the clinic for assessment of Adverse Events for at least 1 hour after the first administration on Visit 1 (V1D1).

Study drug should be consistently dosed approximately 8 hours apart on each day (e.g., at 07:00, 15:00, and 23:00). Specific instructions for participants to self-dose are provided in the MOP, including instruction that in the event of a forgotten/delayed dose, the delayed dose is to be skipped if there is less than 2 hours until the next scheduled dose.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator designee or independent drug administrator (not directly involved in the assessment of study participants) must keep an accurate accounting of the number of investigational units received from Allgenesis, and the number of units returned to Allgenesis or designee during and at the completion of the study. A detailed inventory must be completed for the study drug.

The used study bottles from each participant will be weighed at the Day 7 (if conducted in-clinic) and Day 28 visits to estimate compliance; weight will be recorded on the electronic Case Report Form (eCRF). Participants will be reminded to return both of their study bottles at the Day 28 visit.

All clinical study drug and/or supplies will be returned to Allgenesis or its designee for destruction.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

AG-86893 is a topical ophthalmic nanosuspension formulation of nintedanib. AG-86893 is yellowish, while AG-86893 vehicle is clear.

Each active study treatment bottle contains AG-86893 (~5 mg or 15 mg), tyloxapol, hypromellose (HPMC), benzalkonium chloride, sodium chloride, ethylenediaminetetraacetic acid (EDTA) disodium, monobasic potassium phosphate, and sodium hydroxide, at pH 7.0.

Each control treatment bottle contains AG-86893 vehicle, which contains tyloxapol, HPMC, benzalkonium chloride, sodium chloride, EDTA disodium, monobasic potassium phosphate, and sodium hydroxide, at pH 7.0.

AG-86893 and AG-86893 vehicle will be packaged in white, 5-mL LDPE ophthalmic bottles and supplied by Allgenesis or designee. Study medication will be provided in 2 separate bottles. All study medications will be labeled with the protocol number and medication kit numbers. The label will also specify the storage conditions (room temperature) and state that the study medication is limited to investigational use.

6.2.3 PRODUCT STORAGE AND STABILITY

The study drug must be stored at room temperature (15° – 30°C). Temperature will be monitored while stored at sites, and participants in the P2-86893-001 trial will be instructed not to expose the product to refrigerated or frozen temperatures, and that bottles should be protected from direct sunlight.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

Prior to initiation of study treatment, randomization will occur by site personnel via the IVRS or IWRS once it is confirmed that the participant meets the final study entry criteria (see Section 4.1). The IVRS/IWRS will provide the participant identification number used on all study documents and will be used to manage the randomization and treatment assignment based on a central randomization scheme prepared by Trial Runners. Study drug will be labeled with medication kit numbers, and the IVRS/IWRS will provide each site with the specific medication kit number(s) for each randomized participant at the time of randomization. Sites will dispense study drug according to the IVRS/IWRS instructions. Sites will receive the IVRS/IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

To prevent possible unmasking, access to study drug kits will be limited to staff not involved in the care and evaluation of participants or the handling of data throughout the study. To maintain the double mask, an independent drug administrator not affiliated with the care of the participant will apply the single eye drop to the participant at the Day 1 and Day 28 visits. Since AG-86893 and vehicle are different colors, it will be important to advise the participant to not discuss what the medication looks like. In addition, when the used study medication is returned at the Day 28 visit (2 bottles per participant), the unmasked drug administrator should be responsible for collecting and weighing the bottles.

Masking of individual participant treatment assignments will be maintained throughout the study for all participants and required site personnel until the database is locked for the final analysis. If it is necessary for the safety and appropriate treatment of a participant, the treatment assignment can be unmasked by the site via the IVRS/IWRS. When possible, the medical monitor should be notified prior to the unmasking, and the reason for breaking the mask will be documented in the source documentation. The investigator should inform the medical monitor of the unmasking if there is no notification prior to the unmasking. The treatment assignment for the participant can be determined by designated site personnel calling into the IVRS/IWRS via password-protected access. The reason for breaking the code should be recorded in the participant's source documents.

6.4 STUDY INTERVENTION COMPLIANCE

Participants who are inadvertently enrolled, despite significant deviation from protocol-specified inclusion/exclusion criteria, will be discontinued from participation in the study. Participants will be scheduled for follow-up visits and followed for 8 weeks post-treatment for safety per protocol.

At each post-baseline visit, participants will be questioned as to concomitant medications, as well as exclusionary criteria to ensure protocol compliance. Urine drug screens will be performed during the screening visit (Day -14 to Day -2), at the Days 7 (if conducted in-clinic), 28, and 84 visits for all participants. Dosing compliance will be assessed when the participant returns the study drug (both bottles) to the investigator, at which time the study drug bottles will be weighed.

6.5 CONCOMITANT THERAPY

Ocular medications, other than artificial tears and ocular decongestants, are prohibited. Ocular decongestants must be washed out for a minimum of 7 days prior to baseline and use is prohibited 2 days before any study visit. Topical drops for examination procedures, such as anesthetics, dilating agents, fluorescein and lissamine green, are permitted.

Systemic medications that may interfere or confound the evaluation of conjunctival hyperemia are prohibited and should be washed out in the 7 days prior to baseline. Washout should not commence until after written informed consent has been obtained. Refer to the MOP for examples of prohibited medications.

Participants will be instructed on all study procedures and requirements as appropriate. Participants will be instructed on use of permissible topical eye drops and on prohibited medications.

Medication considered necessary for the participant's welfare may be given at the discretion of the investigator. Participants should be instructed to maintain a stable dose of chronic medications during the study whenever possible. All concurrent medications (prescription, over-the-counter and supplements), adjunct therapies, and concurrent procedures will be recorded on the appropriate eCRF page.

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. Whenever possible, the medical monitor should be notified before the prohibited medication/treatment is administered.

6.5.1 RESCUE MEDICINE

As there is no pharmacologic treatment for pterygium, no rescue medication is proposed in this study. Investigators may direct participants to the use of eye drops (e.g., artificial tears, decongestant drops, etc.) as appropriate, to alleviate any symptoms related to the participant's condition.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The investigator may discontinue the study drug at any time if there is a safety concern. If the study drug is discontinued, then the participant will early exit from the study. If the participant has discontinued the study drug because of an SAE related to the study drug, that participant should be monitored for at least 30 days or until the SAE has resolved or stabilized.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The investigator may remove a participant if, in the investigator's judgment, continued participation would pose unacceptable risk to the participant or to the integrity of the study data. Reasons for removal or withdrawal might include:

- Withdrawal of consent
- Administrative decision by the investigator or Sponsor
- Significant protocol deviation
- Participant noncompliance, or other significant protocol deviation
- Safety concern by the investigator or Sponsor
- Lost to follow-up

With the exception of withdrawal of consent, participant withdrawal should be discussed with the Medical Monitor, when possible, prior to withdrawing. Notification of early participant discontinuation from the study and the reason for discontinuation will be made to Allgenesis and will be clearly documented on the appropriate eCRF. If a participant discontinues prior to completing the study, the procedures outlined for the Exit visit should be performed at the last visit the participant attends.

7.3 LOST TO FOLLOW-UP

At any point during the trial, if a participant fails to return for a scheduled visit and is unable to be contacted by the site staff, he or she will be considered lost to follow-up. This does not include a single missed visit of which the site was notified or a missed visit with subsequent contact from the participants indicating an intention to continue on the study. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the visit window and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study. If this make-up visit is outside the allowable window, a protocol deviation will be recorded
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up, and a protocol deviation will be recorded

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Refer to the MOP for details on the efficacy measures.

8.1.1 PRIMARY EFFICACY MEASURE

- **Overall conjunctival hyperemia**. Digital slit-lamp photos will be captured and submitted to the central reading center for assessment. Conjunctival hyperemia will be measured in 4 quadrants of the ocular surface and graded using a 5-point scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. The overall conjunctival hyperemia is the average of the score of each quadrant

8.1.2 SECONDARY EFFICACY MEASURE

- **Localized pterygium conjunctival hyperemia**. Using the above digital slit-lamp photos and grading, the localized pterygium conjunctival hyperemia is the score of the quadrant with the pterygium as assessed by the central reading center.

8.1.3 EXPLORATORY MEASURES

- **Pterygium vascularity**. Using the above digital slit-lamp photos, the vascularity of the body of the pterygium will be quantified by pixel analysis as assessed by the central reading center.
- **Pterygium volume**. AS-OCT images will be captured at selected sites and submitted to the central reading center for assessment of pterygium volume
- **Pterygium vessel length**. Using the above digital slit-lamp photos, the length of the vessels within the pterygium will be assessed by the central reading center

8.2 SAFETY AND OTHER ASSESSMENTS

Findings that are of clinical significance will be recorded as AEs on the eCRF. Refer to the MOP for details on the assessments.

- **Demographics**. Includes age, gender, race, ethnicity and lifestyle questions (sun exposure; alcohol, drug and contraceptive use)
- **Physical characteristics.** Includes height and weight measured at screening; weight only at other timepoints indicated
- **Pregnancy testing.** Will be performed using a human chorionic gonadotropin pregnancy urine dipstick test
- **Vital signs.** Includes pulse rate, blood pressure, respiratory rate and temperature
- **Hematology.** Includes hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelets, red blood cell (RBC) count, RBC morphology, total white blood cell (WBC) count, and differential (neutrophils, bands, lymphocytes, monocytes, basophils, and eosinophils)
- **Non-fasting serum chemistry.** Includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, creatine kinase, creatinine, direct bilirubin, gamma-

glutamyltransferase, indirect bilirubin, magnesium, non-fasting glucose, HgbA1C, phosphorous, potassium, sodium, total bilirubin, total cholesterol, total protein, urea nitrogen, and uric acid

- **Urinalysis.** Includes clarity, color, bilirubin, creatinine, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, microscopic sediment (WBCs, RBCs, casts, bacteria, crystals, and epithelial cells), and screen for drug use
- **Electrocardiogram.** Electrocardiograms will be obtained using a 12-lead standard equipment. The investigator will be responsible for the initial review of the ECG to assess whether the ECG is within the reference limits. All ECGs will be sent to a central reader for interpretation, including confirmation of eligibility and ongoing safety assessments, and assessed for the following measures: P wave, QRS complex, U wave, QRS duration, QT interval, T wave, ST segment, RR interval, PR interval, and qualitative results
- **Participant questionnaire.** The participant will complete a questionnaire querying about the severity of symptoms either in the last month (V1D1) or since the last visit (subsequent visits), including burning/stinging, grittiness, and conjunctival hyperemia, which are scored on a 4-point scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe. This will be administered prior to application of study drug (visit V1D1 and V3D28, and at any time at other visits) to ensure immediate effects of the eye drops do not confound the results. Any immediate effects of the eye drops will be collected through AE reporting.
- **Best-corrected visual acuity.** Will be quantified using the Early Treatment Diabetic Retinopathy Study visual acuity protocol and the number of letters read correctly will be recorded on the eCRF
- **Intraocular pressure.** Will be measured with a Goldmann applanation tonometer
- **Biomicroscopy.** Will be performed by slit-lamp examination of conjunctiva, cornea, and iris with findings reported on a scale of 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe. The status of the lens will be assessed using the Age-Related Eye Disease Study scale
- **Tear film break-up time.** Will be performed by instilling between 1.0 to 5.0 µL of non-preserved, 2% sodium fluorescein onto the bulbar conjunctiva without inducing reflex. If both eyes are being assessed, the study eye will be assessed first
- **Lissamine green conjunctival staining.** Will be performed using 1 drop (10 µL) of 1% lissamine green solution by pipette, with finding reported on a scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe. If both eyes are being assessed, the study eye will be assessed first
- **Ophthalmoscopy.** A dilated fundus examination will be performed to evaluate any posterior segment abnormalities
- **Plasma drug monitoring.** In a subset of at least 6 participants per study group (at select study sites), blood samples (~10 mL per sample) will be collected for monitoring the plasma concentrations of AG-86893 on Day 1 and Day 28 at pre-dose and at 0.5 and 1 hour after the morning dose from participating participantsAt Day 56, a single blood sample will be collected at the study visit. Plasma drug concentrations will be measured using a validated liquid chromatography, tandem mass spectrometry assay, with a target lower limit of quantitation of 0.020 ng/mL. Allgenesis shall have full ownership rights to any biological samples derived from the study.

Unscheduled visits can be included if safety concerns arise. Additional examinations may be performed as necessary to ensure the safety and wellbeing of participants during the study. Electronic Case Report Forms should be completed for each unscheduled visit.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to that product. Worsening of the pterygium is not an AE, unless the lesion growth is greater than expected.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. See Section 8.3.9 for procedures for reporting an SAE.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.4 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild:** Event requires minimal or no treatment and do not interfere with the participant's daily activities
- **Moderate:** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning
- **Severe:** Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious"

8.3.5 RELATIONSHIP TO STUDY INTERVENTION

A determination will be made of the relationship (if any) between an AE and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug.

- **Not related:** A causal relationship can be excluded and another documented cause of the AE is most plausible
- **Unlikely related:** A causal relationship is improbable and another documented cause of the AE is most plausible
- **Possibly related:** A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the study drug
- **Related:** A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, and there is a reasonable response on withdrawal

8.3.6 EXPECTEDNESS

The investigator will be responsible for determining whether an AE is expected or unexpected based on the information provided in the Investigator's Brochure. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.7 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

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

Changes in the severity of an AE will be documented in the source and eCRF to allow an assessment of the duration of the event at each level of severity to be performed. The AE will be recorded in the CRF under the highest level of severity achieved; i.e. if an event progresses from mild to moderate, the severity of the AE will be changed in the CRF, but the date of onset will remain unchanged. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

The collection of AEs and SAEs will commence from the time the Informed Consent Form is signed and continue until the last day of study participation (D84). Events will be followed for outcome information until resolution or stabilization during the study or continue until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation (D84).

Adverse events will be monitored throughout the study beginning at the time of Informed Consent. After the first administration of AG-86893, participants will be observed for AEs by remaining in the clinic until at least 1 hour after dosing. At this 1 hour post-intial dose timepoint, and at each post-screening visit, the investigator will begin by querying for AEs by asking each participant a general, non-directed question, such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported AEs will be documented on the appropriate eCRF, including seriousness, severity, relationship to study drug, action taken, and outcome (including date of resolution or stabilization, if AE is not ongoing). If AEs occur, the first concern will be the safety of the study participants.

8.3.8 ADVERSE EVENT REPORTING

Any AE should be recorded on the appropriate eCRF. All AEs that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure [28]) are to be reported to the governing HREC/IRB/IEC as required by the HREC/IRB/IEC, local regulations, and the governing health authorities.

8.3.9 SERIOUS ADVERSE EVENT REPORTING

Any SAE occurring during the study period should be immediately (i.e., within 24 hours of learning of the event) reported via the Trial Runners SAE email address listed on the protocol page iii. The SAE is recorded on the appropriate eCRFs. In the event of an early termination within the first 4 weeks after study drug administration, the occurrence of an SAE within 8 weeks from Baseline/Day 1 should be reported immediately to Trial Runners personnel. All participants with an SAE that is related to study drug must be followed for at least 30 days and the outcomes reported until the event is resolved or stabilized. The investigator should supply the sponsor and the HREC/IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

In the event of an SAE, the investigator must:

- Notify the Trial Runners safety office and the medical monitor immediately by email using the SAE reporting forms provided by Trial Runners (see page iv of the protocol for the SAE email address). A fax number will be provided for reporting in the event internet access is unavailable during the required reporting period. Emergency phone numbers and relevant personnel contacts are also on page iii of the protocol
- Obtain and maintain in the participant's files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the participant
- Provide Allgenesis with a complete, written case history (SAE report form) which includes a statement as to whether the event was or was not related to the use of the investigational drug
- Promptly inform the governing HREC/IRB/IEC of the SAE if it is drug-related. For other SAEs, notify the governing HREC/IRB/IEC as required by the HREC/IRB/IEC, local regulations, and the governing health authorities

Adverse drug reactions that are both serious and unexpected (suspected unexpected serious adverse reactions [SUSARs]) will be subject to expedited reporting by the Sponsor to HREC and TGA as required by the relevant regulations. TGA reporting must occur within 15 calendar days of first knowledge, or for fatal or life-threatening events, an initial or full report must be made within 7 calendar days and a follow-up report must be made, if necessary, within the 15-calendar day timeframe.

8.3.10 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.11 EVENTS OF SPECIAL INTEREST

Based on the observed reversible liver enzyme increases in animal models and humans in a clinical setting using the oral formulation nintedanib, abnormal liver function test results meeting the criteria below will be monitored and may trigger a meeting of the Independent Data Monitoring Committee (IDMC):

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (total bilirubin >2x ULN or International Normalized Ratio [INR] >1.5)
- ALT or AST >3x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Any other safety signals observed during routine data review that warrant convening of the IDMC, in the opinion of the Medical Monitor

Any of these parameters also represent a trigger for interruption of dose for the participant until the IDMC has been convened and a recommendation provided.

In the event of an increase in serum AST or ALT to >3x ULN, the following monitoring will be required:

- Repeat testing within 48 to 72 hours of ALT, AST, ALP, and total bilirubin to confirm the abnormalities and to determine if they are increasing or decreasing
- Participants will be questioned on the presence of symptoms (eg appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia)

- If symptoms persist or repeat testing shows ALT/AST >3x ULN for the participants with normal baseline measures or 2-fold increases above baseline values for participants with elevated values before drug exposure, the following measures will be initiated to determine whether the abnormalities are improving or worsening:
    - Interupt study treatment dosing until advice from the Medical Monitor is provided
    - Repeat liver tests (ALT, AST, ALP, and total bilirubin) 2 or 3 times weekly. Frequency of testing can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and participant is asymptomatic
    - Obtain a more detailed history of symptoms and prior or concurrent diseases
    - Obtain a history of concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
    - Obtain a history of exposure to environmental chemical agents
    - Obtain additional tests to evaluate liver function, as appropriate (e.g., INR)
    - Consider gastroenterology or hepatology consultation

Ocular AEs of special interest include the following and will also be monitored by the Medical Monitor and the IDMC:

- Ocular inflammation, including iritis and uveitis
- ≥2 grade increase in corneal edema, corneal staining or edema
- ≥2 grade increase in any cataract
- IOP change of ±7 mmHg from baseline
- Loss of 15 letters or more BCVA

8.3.12 REPORTING OF PREGNANCY

If a female participant, or the female partner of a male participant, becomes pregnant during the study, the investigator will notify Trial Runners and the medical monitor immediately after the pregnancy is confirmed and the female participant will be exited from the study. The investigator will (1) notify the participant's/partner's physician that the participant was being treated with AG-86893, and (2) follow the progress of the pregnancy to term and the health of the child to 12 months of age, by the participant or partner as appropriate, providing written informed consent for release of this data. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to Allgenesis.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The null hypothesis is that there is no difference between AG-86893 and AG-86893 vehicle in the change from baseline to Day 28 in the overall conjunctival hyperemia score. The alternative hypothesis is that the active group is different from vehicle in the change from baseline to Day 28 in the overall conjunctival hyperemia score.

9.2 SAMPLE SIZE DETERMINATION

As this is an exploratory study, an empirical sample size has been used.

Per sample size calculation using SAS Proc Power procedure, assuming the standard deviation of the mean overall hyperemia score is around 1.0, a study with 20 participants in each group (N=60)

should have at least 90% statistical power to detect a minimal difference of 1 in mean overall hyperemia scores among the three study groups at 95% confidence level.

For each of the 3 AG-86893 dose groups (vehicle, 0.1%, and 0.3%), approximately 20 participants with pterygium exhibiting conjunctival hyperemia are planned to complete the study. Therefore, a total of approximately 70 participants will be enrolled at up to 12 sites in order to achieve an estimated 60 evaluable participants after accounting for potential drop-outs. No more than a total of 70 participants will be enrolled in the study unless requested by Allgenesis.

9.3 POPULATIONS FOR ANALYSES

Three analysis populations will be defined and used in the statistical analyses: (1) a safety population, (2) a modified intent-to-treat (mITT) population, and (3) a per-protocol (PP) population.

Safety analyses will evaluate all randomized participants who received at least 1 dose of study drug and attended a post-baseline visit. Results will be presented based on the treatment received.

The primary statistical analyses will evaluate the mITT population, defined as all randomized participants who received at least 1 dose of study drug and had conjunctival hyperemia evaluated at both the Day 1 and Day 28 visits. Results will be presented based on the treatment assigned during randomization.

As a sensitivity analysis, the primary efficacy endpoint of conjunctival hyperemia will also be evaluated in the PP population of participants, who had no major protocol violations. Nominal data will be analyzed using the Pearson chi-square test or Fisher exact test. Conjunctival hyperemia, pterygium vascularity, BCVA, ophthalmoscopy, AS-OCT, and IOP data will be analyzed using analysis of variance models with dose strength as main effects. The analysis will be based on observed data. Missing values will not be imputed.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The database will be locked after all participants exit the study and all data clarification forms or queries have been resolved. Prior to database lock, a detailed Statistical Analysis Plan (SAP) will be finalized and approved. Final analysis and unmasking of participants' treatment code will occur after database lock.

Wherever appropriate, summary statistics will include the sample size, mean, standard deviation (SD), median, minimum, and maximum for continuous and ordinal variables, and frequency counts and percent for categorical variables. Data will be presented by treatment (0.1% AG-86893, 0.3% AG-86893, AG-86893 vehicle). Additional analyses between vehicle and active drug will be explored, the details of which will be described in the SAP. All testing will be two-sided and will be performed without adjustment for testing multiple measures.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy measure is overall conjunctival hyperemia score of the study eye using the average of the scores of each quadrant, as assessed by the reading center. The primary endpoint is the change from baseline in overall conjunctival hyperemia score at Day 28, so scores from Days 1 and 28 will be analyzed. The primary efficacy analysis will be based on the mITT population. Refer to the MOP for details on the collection of ocular photography.

Statistical analyses will be performed as described in Section 9.4.1 for continuous variables.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Secondary endpoints include:

- Change from baseline in overall conjunctival hyperemia score at Day 7
- Change from baseline in conjunctival hyperemia score in the quadrant with the pterygium at Days 7 and 28
- Concentration of AG-86893 in plasma over time

Statistical analyses will be performed as described in Section 9.3 for continuous and categorical variables.

9.4.4 SAFETY ANALYSES

All safety analyses will be conducted on the safety population using the following safety variables:

- Adverse events
- Concomitant medications
- Concurrent procedures
- Vital signs
- Laboratory tests (urinalysis, hematology, and serum chemistry parameters)
- Electrocardiogram
- Best-corrected visual acuity
- Intraocular pressure using a Goldmann applanation tonometer
- Biomicroscopy
- Tear film break-up time
- Lissamine green conjunctival staining
- Ophthalmoscopy

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs. For each AE reported, the number and percent of participants will be tabulated based on the preferred term. The tables will be generated by relationship to treatment as well as by system organ class and severity. Treatment-emergent AEs will be considered, as will AEs occurring prior to first dose and post-treatment.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline and demographic assessments will be presented descriptively.

9.4.6 PLANNED INTERIM ANALYSES

No interim analyses are planned.

9.4.7 SUBGROUP ANALYSES

No subgroup analyses are planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Line listings will be provided for each participant.

9.4.9 EXPLORATORY ANALYSES

Exploratory endpoints include:

- Pterygium vascularity scores at Days 1, 7, and 28 visits
- Pterygium volume at Days 1, 7, and 28 visits
- Pterygium vessel length at Days 1, 7, 28, and 56 visits

9.4.10 PHARMACOKINETIC ANALYSIS

The plasma AG-86893 concentrations will be summarized for each dose for the Days 1 and 28 visits.

A model-independent approach will be used to calculate plasma PK parameters for AG-86893, including $AUC_{0\text{-}t}$, and C_{max}, whenever possible.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks, that have been reviewed and approved by the relevant HREC/IRB/IEC, will be given to the participant and written documentation of informed consent will be required prior to starting study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The study will be discussed with the participant, and each participant wishing to participate must give written informed consent prior to enrollment into the study and prior to any study-related procedures or change in treatment.

Each participant who provides informed consent will be assigned a participant number by the IVRS/IWRS that will be used on participant documentation throughout the study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The study may be stopped at the participant's study site at any time by the site investigator. Allgenesis may stop the study (and/or the study site) for any reason with appropriate notification.

10.1.3 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the participant's name will not be disclosed in these documents. The participant's name may be disclosed to Allgenesis, the governing health authorities, or the US Food and Drug Administration or the Therapeutic Goods Administration if they inspect the study records as required by law. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Every precaution must be taken to protect the privacy of research participants and the confidentiality of their personal information in accordance with the Australian Privacy Act 1988.

In accordance with Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA) requirements, additional purposes of this study include (1) the publishing of anonymous participant data from the study, and (2) the creation and maintenance of a data repository.

All study-related correspondence, participant records (i.e., source documents listed in Section 11.4.1), ICFs, participant privacy documentation, records of the distribution and use of all investigational products, and participant questionnaires, correspondence with HREC/IRB/IEC, and other essential documents should be maintained on file.

Local regulatory requirements should be followed regarding the retention of clinical study documentation (TGA requires retention for at least 15 years after study completion; the Sponsor will advise once documents can be destroyed).

Allgenesis requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Global Medical Monitor
Robert David, MD Trial Runners 116 W. Villard Dickinson, ND 58601 USA +1 949-200-7988 +1 949-246-8368 (mobile) +1 949-544-0234 (fax) RobertDavid@trialrunners.com

No leadership committees will be used during this study.

10.1.6 SAFETY OVERSIGHT

Should there be any findings of concern that warrant further investigation, the Medical Monitor will convene a meeting of the IDMC to determine whether any changes in the study conduct should be made. Targeted AEs / findings of interest are summarised in section 8.3.11 and described in detail in the IDMC Charter, along with the qualifications for the independent safety experts.

10.1.7 CLINICAL MONITORING

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

- A representative of Allgenesis will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations, such as the objective, purpose, design, complexity, masking, size, and endpoints of the study
- Authorized representatives of Allgenesis or regulatory authority representatives will conduct on-site visits to review, audit, and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., GLP, Good Manufacturing Practice).

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring that data are properly recorded on each participant's eCRFs and related documents in a timely manner. An investigator who has signed the protocol signature page should electronically sign the eCRFs to ensure that the observations and findings are recorded on the eCRFs correctly and completely. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

- Clinical data will be entered into eCRFs. Data entered into the eCRF will correspond with and be supported by source documentation maintained at the site(s). A final report of all participant data will be provided to each site at the end of the study to serve as eCRF documentation
- Blood chemistry panel, hematology, and urinalysis will be analyzed at a central clinical laboratory
- Electrocardiogram data will be collected and provided to a centralized reading center for analysis and interpretation, including eligibility for study entry. A final report of all participant ECG data will be provided to each site at the end of the study to serve as ECG documentation
- IVRS/IWRS will be used for randomizing the participant population

- Images for conjunctival hyperemia/pterygium vascularity scoring, and AS-OCT lesion volume data will be collected and provided to a centralized reading center for analysis and interpretation, including eligibility for study entry. A report of all participant hyperemia/ vascularity data and lesion volume will be provided to each site
- Plasma drug concentration samples will be analyzed using validated assays to measure drug concentrations

Source documents may include a participant's medical records, diaries, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests, such as x-rays, laboratory tests, and ECGs. The investigator's copy of the eCRFs serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

- Participant's name
- Participant's contact information
- Date that the participant entered the study, participant number, and participant medication kit number
- Study title and/or the protocol number of the study and the name of Allgenesis
- Statement that informed consent was obtained (including the date) prior to any study procedures being performed and that the participant was provided a copy of the signed informed consent. A statement that country and local participant privacy-required documentation for this study has been obtained (including the date)
- Dates of all participant visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any AEs (including any procedure-related AEs)
- The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation
- The results of laboratory tests performed by the central laboratory (hematology, serum chemistry, urine analysis, urine culture and sensitivity)
- The results of laboratory tests performed by the site (e.g., urine pregnancy test)
- The results, if applicable, of any procedures performed to confirm eligibility criteria
- Concurrent procedures performed during the study
- Documentation of the participant's medical history
- Vital signs and physical characteristics (height and weight)
- Electrocardiogram traces
- Results of biomicroscopy/ophthalmoscopy exams
- Documentation of whether any procedure, including study treatment administration, was performed according to the protocol, noting any deviations (if applicable)
- Study drug accountability and reconstitution records (stored separately with the accountability logs in order to maintain masking status for site staff with direct contact with participant and/or data)

10.1.9.2 STUDY RECORDS RETENTION

According to the TGA in Australia, study documents should be retained for a minimum of 15 years after the last approval of a marketing application. These documents should be retained for a longer period, however, in the event of product liability claims. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any non-compliance with the clinical trial protocol, ICH GCP, or MOP requirements. The non-compliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be required by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It is the responsibility of the site investigator to use continuous vigilance to identify, document, and report protocol deviations. All deviations must be addressed in study source documents and reported to Allgenesis or its designee. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Allgenesis, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allgenesis personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allgenesis.

This study will be registered on the ClinicalTrials.gov registry.

10.1.12 CONFLICT OF INTEREST POLICY

Due to potential conflict of interest, participants or members of the participant's household who are employees of the investigative site are not eligible for enrollment in the study.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCVA	best-corrected visual acuity

BID	twice daily
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
DSM V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDTA	ethylenediaminetetraacetic acid
FGF-2	fibroblast growth factor-2
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information
HPMC	hypromellose; hydroxypropyl methylcellulose
HREC	Human Research Ethics Committee
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	International Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDPE	low-density polyethylene
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMPs	matrix metalloproteinases
MOP	Manual of Procedures
NOAEL	no-observed-adverse-effect-level
PDGFR	platelet-derived growth factor
PDGFRβ	platelet-derived growth factor receptor β
PK	pharmacokinetic(s)
PP	per-protocol
RBC	red blood cell
RLD	reference listed drug
QC	quality control
QID	4 times daily
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TID	3 times daily
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
YAG	yttrium aluminium garnet

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Section affected	Description of Change	Brief Rationale
1.0	25 Apr 2018		**Original Document**	
2.0	21 Jun 2018	**Cover page**	**National Clinical Trial Identified Number provided**	**Trial registration completed**
		1.3 Schedule of activities	**Correction: participant questionnaire administered pre-IP administration**	**Correction of error; pre-IP administration of questionnaire will ensure an average of all symptoms from last month/since last visit is not confounded by immediate effects of IP**
		5.1 Inclusion criteria	**BMI upper limit increased from 30 to 35 kg/m^2**	**Increase recruitment capacity: the non-clinical data, nor the clinical data on the active ingredient, suggests a safety risk in moderately obese**
		6.1.2 Dosing and administraion	**Participants will be questioned on Adverse Events 1 hour after first IP administration on V1D1**	**Additional safety measure**
		Table 8.1 Laboratory and Vital Sign Criteria for Serious Adverse Events	**INR flag for SAE removed**	**Not necessary to ensure participant safety; remaining safety measures more appropriate**
		8.3.12 Preganacy reporting	**Detail added on collecting data until child is 12 months of age**	**As per Bellberry HREC guidelines**
		9.2 Sample size determination	**Provided additional information on sample size and power**	**N/A**
		10.1.6 Safety Overview	**The involvement of independent experts in safety monitoring has been added**	**Additional safety measure**
3.0	20 Mar 2019	**1.1 Synopsis**	**Added the exploratory endpoints and outcomes to the synopsis**	**Clarification: missing from Versions 1.0 and 2.0 of the protocol**
		1.1 Synopsis	**Changed *12 sites throughout Australia* to *Approximately 12 sites***	**It is unlikely 12 sites will be inititated**
		1.2 Schema **4.1 Overall Design**	**Day 7 visit: Visit conducted as a phone call, or optional in-clinic visit at the**	**Due to participant burden and favourable safety profile observed, sites are able to conduct the Day 7 follow-up visit as a phone follow-up to conduct AE questioning, participant symptom questionnaire, concomitant medications and procedures,**

		6.2.1 IP Acquisition and Accountability **6.4 Study Intervention Compliance**	**discretion of the site Investigator**	**and discussion and re-training on dosing compliance. The in-clinic component will remain in the protocol as an optional visit at the discretion of the PI, in the event of any safety concerns or signals.**
		4.1 Overall Design	**Removed the requirement for 30% of participants to contribute to the PK data**	**As this is an exploratory endpoint, this endpoint is not powered so there is no minimum amount of data required.**
		5.1 Inclusion criteria (#4)	**BMI upper limit increased from 35 to 38 kg/m^2**	**Increase recruitment capacity: neither the non-clinical data, nor the clinical data on the active ingredient, suggest a safety risk in those not morbidly obese**
		5.1 Inclusion criteria (#7)	**Guidance provided to sites on how to select study eye if both eyes are affected to the exact same severity**	**Missing from Versions 1.0 and 2.0 of the protocol**
		5.2 Exclusion criteria (non-ocular #2)	**Amended the Liver dysfunction criterion**	**This criterion is too restrictive. The FDA guidance on Drug-Induced Liver Injuries will be adhered to in order to reduce impact on recruitment without compromising participant safety *https://www.fda.gov/downloads/guidances/UCM174090.pdf***
		5.2 Exclusion criteria (non-ocular #11)	**Added exclusion criterion: *History of active alcohol or substance abuse as defined by DSM V criteria***	**Added to exclude potential participants likely to have abnormal liver function due to lifestyle factors**
		6.1.2 Dosing and Administration	**Updated dosing and administration instructions to include vigorous shaking**	**New information has confirmed the nanosuspension can settle after a period, so vigorous shaking for 10 seconds is recommended to ensure adequate dosing**
		6.2.2 Formulation, Appearance, Packaging, and Labelling	**Corrected the fill volumes from 4 mg and 12 mg for the 0.1% and 0.3% active IP respectively to 5 mg and 15 mg**	**An error in Versions 1.0 and 2.0 of the protocol now corrected**
		8.2 Safety and Other Assessments **Schedule of Assessments**	**Clarified that "physical assessments" involves weight and height at screening and weight only at subsequent visits**	**Height not expected to change over trial duration – included in error**
		8.2 Safety and Other Assessments	**Reduced the PK sampling protocol to pre-dose then 0.5**	**Reduced sampling presents a lower participant burden and possibly an**

		Schedule of Assessments	**and 1 hour after dosing**	**increased uptake of those consenting to PK blood draws**
		8.3.2 Definition of SAEs	**Removal of Laboratory and Vital Sign Criteria for Serious Adverse Events**	**These criteria do not represent SAEs unless also resulting in one or more of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect**
		8.3.11 Events of Special Interest	**Provided detail on the safety signals that would trigger a meeting of the Independent Data Monitoring Committee, as well as guidance to sites on the clinical management of such events**	**This detail was not present in Versions 1.0 and 2.0 of the protocol**
		10.1.6 Safety Oversight	**Clarified that the safety experts engaged for this trial are in the format of an Independent Data Monitoring Committee**	**This detail was not present in Versions 1.0 and 2.0 of the protocol**

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