Tarsius Pharma, Ltd.
Clinical Protocol Tarsius 2020 Trial

Project:	TRS01
Compound Number / Name:	TRS01
Protocol Number:	Tarsius 2020
Protocol Title:	A Phase I/IIa Multicenter, Double-Masked, Randomized, Vehicle-controlled, Dose-ranging Study to Evaluate the Safety of TRS01 Eye Drops in Subjects with Post-surgical Inflammation.
Sponsor:	Tarsius Pharma, Ltd. 19 Yahalom St. Zichron Yaacov 30900 Israel
Medical Monitor:	[redacted]
Issue Date:	Original: 12November2019 Amendment 01: 06March2020

Approved:

[redacted]

11 March 2020
Date

Tarsius Pharma, Ltd.
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Investigator Signature Page

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Contact for Serious Adverse Events:	[redacted]

Investigator Name:

_____

Investigator's Signature:

_____ _____

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SYNOPSIS

Sponsor	Tarsius Pharma Ltd.
Study Title	A Phase I/IIa Multicenter, Double-Masked, Randomized, Vehicle-controlled, Dose-ranging Study to Evaluate the Safety of TRS01 Eye Drops in Subjects with Post-surgical Inflammation.
Study Objective	The primary objective of the study is to investigate the safety of TRS01 [redacted] (w/v) eye drops compared to vehicle in subjects who have undergone cataract surgery.
Study Population	The study population will consist of male and female subjects, aged 18 or older, who have undergone routine uncomplicated cataract surgery and experience ≥ grade 2 threshold level of ocular inflammation 1 day post-operatively.
Number of Subjects	Approximately 60 subjects that meet the selection criteria will be randomized for treatment following cataract surgery (one study eye). The number of subjects that will be screened to obtain 60 randomized subjects is estimated at approximately 100 subjects.
Investigational Product	TRS01-[redacted], TRS01-[redacted], and TRS01-[redacted] eye drops, or vehicle, will be supplied as investigational product.
Route and duration of administration	Study subjects will administer the randomly assigned treatment, as eye drops, four times a day (QID) for 2 weeks.
Study Design	A Phase I/IIa multicenter, double-masked, randomized, vehicle-controlled, dose-ranging study designed to evaluate the safety and preliminary efficacy of TRS01 eye drops ([redacted] compared to vehicle in subjects with post-surgical inflammation. Potential study participants will be asked to sign an informed consent document before the surgery and have to meet all preoperative inclusion/exclusion criteria. Following cataract surgery, subjects who are observed to have anterior chamber cells ≥ grade 2 in the study eye on the Day 1 post-operative visit following a routine, uncomplicated cataract surgery will be eligible to be randomized to treatment (subjects who have < grade 2 anterior chamber cells must be screen failed). Once it is determined that all eligibility criteria have been met, subjects will be enrolled and treated with one of three concentrations of TRS01 or vehicle in a 1:1:1:1 ratio. Approximately 60 eligible subjects will be enrolled in approximately five centers located in the United States (US) and France. Study subjects will administer the randomly assigned treatment four times a day (QID) for 14 (±1) days. All study subjects will return for examination on day 3, day 8 and day 15 post surgery. Day 15 visit will be

	one day after the last day of treatment. Clinical assessments will include subject-rated ocular pain assessment, slit lamp biomicroscopy, dilated ophthalmoscopy, intraocular pressure (IOP) measurement, snellen distance visual acuity (VA) by Pinhole Method. [redacted] The study visits schedule and assessments to be performed are described in Appendix 1.
Primary Safety Endpoints	Assessment of ocular AEs: Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs but will be recorded. AEs will be captured by verbatim term and coded using MedDRA. Relevant clinical findings will also be recorded in the electronic case report form (eCRF) related to the following: 1. Snellen distance VA by pinhole method 2. Slit lamp biomicroscopy 3. IOP measurement 4. Dilated ophthalmoscopy 5. Safety parameters include a change from baseline (1-day post-surgery) to each post-surgery visit in ocular signs such as: o Conjunctival hyperemia o Corneal edema
Exploratory Efficacy Measurements	• Anterior chamber cell count on slit lamp biomicroscopy. At select sites, [redacted] • Anterior chamber flare assessed on slit lamp biomicroscopy • PROs-Subject-rated ocular pain assessment
Eligibility Criteria	**Inclusion Criteria** Pre-operatively, individuals of either gender or any race will be eligible for study participation if they are: 1. 18 years of age or older. 2. Able to provide informed consent, follow instructions and complete all required study visits for the duration of the study. 3. Scheduled for routine cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens (IOL) implantation, and not combined with any other surgery.

	4. Have vision ≥ 20/200 in the non-study eye. 5. Able to self-administer eye drops (tested during screening by self-administration of "artificial tears"), or have a care provider that can administer the drops. 6. Have no known sensitivity /allergy to the TRS01 or formulation excipients as detailed in **TABLE 2** and **TABLE 3**. 7. Using adequate birth control by men and women, if of reproductive potential and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 2 weeks after the last dose of investigational product. a. For females, adequate birth control methods will be defined as hormonal contraceptives, intrauterine device or double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam. b. For males, adequate birth control methods will be defined as double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam. c. For females, menopause is defined as one year without menses; if in question, a follicle-stimulating hormone of >40 IU/L must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable. **Exclusion Criteria** In order for subject to be eligible at Visit 1 they may not: 1. Be scheduled to undergo cataract surgery in the non-study eye for 2 months prior to Visit 1 and during the study. 2. Require use of any topical ophthalmic medications (either eye) other than study required medications for 14 days prior to surgery and for the duration of the trial. Note: Use of PRN artificial tears up to twice a day is allowed and should not be dosed within 10 minutes of investigational product dosing. 3. Require topical ocular therapy (either eye) with antibiotics for 30 days prior to surgery except antibiotic eye drops used as part of the Investigator's routine pre-op, intra-op, and post-op routine care. 4. Require treatment with systemic NSAIDs, within 14 days prior to the surgery and for the duration of the trial. Occasional use (≤ 2 times per week) of NSAIDs or over the counter (OTC) painkillers

	to treat minor non-ocular conditions is acceptable. Low-dose aspirin (81 mg) for cardiovascular prophylaxis is allowed. Acetaminophen is the preferred treatment for post-op pain on the day of surgery. 5. Require treatment with systemic or ocular immunosuppressants or immunomodulators including systemic steroids (oral, inhaled, injectable, nasal, topical dermal) or alpha-1 antagonists for 30 days prior to surgery and for the duration of the trial. 6. Use any ocular, topical or systemic medication that could interfere with wound healing, the test agent, or the interpretation of study results, within 30 days prior to the day of surgery and for the duration of the trial. 7. Use of contact lenses in the study eye are prohibited for the duration of the study. 8. Have history of glaucoma surgery or any incisional ocular surgery in the study eye. History of uncomplicated refractive surgery 3 years prior to the cataract surgery is acceptable. 9. Have any significant ocular disease in the study eye in addition to the cataract that may confound the trial results per the Investigator's judgement. 10. Have proliferative diabetic retinopathy (PDR), not stable for at least one year in the study eye. 11. Currently being treated for wet macular degeneration. 12. Have current or history of herpes keratitis in the study eye. 13. Be diagnosed with Fuchs Corneal Dystrophy (FCD). 14. Have current or history of prior ocular inflammation in the study eye not related to prior allowed surgical procedure. 15. In the opinion of the Investigator, have current clinically significant dry eye requiring therapy of greater than twice a day (BID) eye drops in the study eye. Use of PRN artificial tears up to twice a day is allowed and should not be dosed within 10 minutes of investigational product dosing. 16. Use any Cannabidiol products during the trial. 17. Have history of glaucoma or uncontrolled IOP >22mmHg in the study eye on the day of screening. 18. Have floppy iris syndrome noted for the contralateral eye prior to surgery in the study eye. 19. Have any clinically significant systemic disease or condition (e.g.

	hematological diseases) that, in the Investigator's opinion, may confound the trial results, pose a safety risk to the subject or preclude the subject from adhering to the protocol or completing the trial per protocol and instilling eye drops. 20. Have a known history of alcohol and/or drug abuse. 21. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same. 22. Have been exposed to an investigational drug or investigational medical device within 60 days prior to Visit 1. 23. Be pregnant or lactating. **Randomization Inclusion Criteria (Visit 3/Day 1)** To qualify for randomization at the Day 1 (Visit 3), a subject must: 1. Have undergone routine, uncomplicated cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber IOL implantation, not combined with any other surgery (including but not limited to use of iris retractors, capsular fixation ring or anterior capsule staining with dye). Specifically, have NOT had any cataract surgery complication such as a posterior capsular rupture, vitreous loss or significant iris damage. 2. Have an IOP of ≤ 30 mmHg. Notes: Fluid release from the anterior chamber through the surgical incision is allowed (manual burping). The final IOP post release of fluid must be ≤ 30 mmHg and will be recorded as the visit IOP value. Use of IOP lowering medications are allowed beginning on Day 0, with the exception of prostaglandins. IOP lowering eye drops should be dosed at least 30 minutes before investigational product dosing. 3. Have anterior chamber cells ≥ grade 2. 4. Continue to meet inclusion/exclusion criteria with respect to current ocular and medical conditions and must not be taking prohibited medications (section 6.4).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
ACC	Anterior Chamber Cells
AE	Adverse Event
°C	Degrees Celsius
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
°F	Degrees Fahrenheit
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOL	Intraocular lens
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
ITT	Intent-to-Treat
LDPE	Low-density polyethylene
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)
OTC	Over the counter
OU	Oculus Uterque (both eyes)
PP	Polypropylene
PP	Per Protocol
QID	Four times daily
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
[redacted]	[redacted]
US	United States of America
VA	Visual Acuity
w/v	Weight to Volume

1 INTRODUCTION

Intraocular inflammation is a typical undesirable consequence of intraocular surgery such as cataract surgery. It is manifested principally as conjunctival injection, corneal edema, ciliary flush and aqueous cells and flare. Surgical trauma and phacoemulsification energy activate an inflammatory cascade that ultimately leads to formation of prostaglandins, which results in local vasodilation and increased vascular permeability.

Inflammation may resolve with no treatment in 15-28% of patients. However, inadequately treated inflammation after cataract surgery frequently causes pain, photophobia, increased risk for elevated intraocular pressure (IOP), corneal edema, corneal scarring and cystoid macular edema [Aptel et al., 2017]. Thus, managing and treating postoperative inflammation is an important goal following cataract surgery.

Other ocular inflammatory diseases include, for example, non-infectious uveitis, a potentially blinding condition that is the fifth leading cause of visual loss in the developed world (third leading cause of preventable blindness), has been estimated to account for 10% of all visual impairment in the western world and 10–15% of cases of total blindness [Nussenblatt, 1990; Merida et al., 2015]. Anterior uveitis accounts for approximately 80% of non-infectious uveitis cases in the United States [Thorne et al., 2016].

Uveitis is characterized by an inflammatory process that may be acute, recurrent, chronic or acute-on-chronic. Untreated, recurrent bouts of uveitis eventually lead to tissue destruction from direct inflammation or from complications such as cataract, glaucoma and macular edema.

Topical corticosteroids represent first line treatment for both non-infectious uveitis and postoperative inflammation. In the US, topical corticosteroids are routinely prescribed with four times daily (QID) dosing for at least 2 weeks following cataract surgery [Kim et al., 2019].

The side effects associated with steroid use, significantly limit prolonged treatment. The most common adverse effects of ocular steroids are cataract and elevated IOP which can lead to steroid related glaucoma.

Given the limitations of treatment, there is a need for an effective anti-inflammatory drug that does not have an IOP-elevating effect. Tarsius Pharma has developed a novel therapeutic approach for local prevention and treatment of ophthalmic inflammatory diseases. [redacted]

[redacted]

The Tarsius-2020-Trial is a Phase I/IIa multicenter, double-masked, randomized, vehicle-controlled, dose-ranging (3 doses – [redacted] study to evaluate the safety and preliminary efficacy of TRS01 eye drops in subjects with post-surgical inflammation.

1.1 Description of Investigational Product

TRS01 is formulated as a sterile ophthalmic solution of TRS drug substance in a vehicle composed of [redacted]. For this trial, dosing volume and dose delivery of TRS01 investigational product (IP) will be supplied as summarized in **Table 1**. [redacted]. The vehicle control contains the same excipients as TRS01, without the Active Pharmaceutical Ingredient.

Table 1: TRS01 and Vehicle Dosing Volume and Dose Delivery

	Eye Drop Volume of:	Will deliver approximately:
TRS01 Low Dose	[redacted]	[redacted]
TRS01 Medium Dose	[redacted]	[redacted]
TRS01 High Dose	[redacted]	[redacted]
TRS01 Vehicle	~[redacted]	[redacted]

[redacted] Corresponding matching vehicle will also be prepared for use in the planned clinical trial, to ensure masking of the clinical trial. Subjects randomized to the vehicle-control arm will receive the same bottles containing all excipients at the same concentrations used in TRS01 solutions with exception of TRS itself (the active ingredient).

The IP will be packaged and labeled by [redacted] in accordance with current Good Manufacturing Practices as appropriate for clinical supplies and applicable national laws. Study medications will be clearly labeled as to contents and storage conditions. A caution statement will be printed on the label, along with the name and address of Tarsius Pharma.

[redacted]

Subjects are expected to self-administer, or have a care provider administer, one drop four times per day (QID) of TRS01[redacted], TRS01-[redacted], TRS01-[redacted] or vehicle control.

Double-masked doses will be assigned through the randomization program. The treatment schedule is shown in FIGURE 1. TRS01 will be administered no more frequently than four times daily (QID) per protocol.

TABLE 2: COMPOSITION OF TRS01 [redacted] INVESTIGATIONAL PRODUCT

Ingredient	Ingredient name According to USP	Function	Concentration (%w/v)		
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
Wa[redacted]					

TABLE 3: COMPOSITION OF VEHICLE

Ingredient	Ingredient name According to USP	Function	TRS01-Vehicle (%w/v)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

1.2 GCP COMPLIANCE

The study will be conducted in accordance with the study protocol, Good Clinical Practice (GCP), International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use guidelines. Compliance with these requirements is consistent with the ethical principles that have their origins in the Declaration of Helsinki (Declaration of Helsinki, 2013).

1.3 STUDY POPULATION

The study population will consist of male and female subjects, aged 18 or older, who have undergone routine uncomplicated cataract surgery and experience ocular inflammation on the Day 1 post-surgery visit. Approximately 100 subjects who are candidates for cataract surgery will be screened and approximately 60 subjects with anterior chamber cells ≥ grade 2 will be randomized to one of four groups, i.e., three treatment groups or vehicle. Only the study eye (surgery eye) of each subject will be treated with IP.

2 STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety of TRS01 eye drops at concentrations of [redacted] w/v) compared to vehicle in subjects who have undergone uncomplicated cataract surgery.

The exploratory objective of the study is to assess the preliminary efficacy of TRS01 eye drops in reducing inflammation as compared to vehicle.

3 STUDY DESIGN

This is a phase I/IIa multicenter, double-masked, randomized, vehicle-controlled, dose-ranging study.

It is designed to evaluate the safety and preliminary efficacy of TRS01 eye drops ([redacted]) compared to vehicle in subjects with post-surgical inflammation.

3.1 SAFETY ENDPOINTS

The primary safety parameter in this study is the incidence and severity of treatment-emergent and treatment-related adverse events (AEs), both systemic and ocular events in subjects with post-cataract inflammation. Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs but will be recorded.

1. Snellen distance visual acuity (VA) by pinhole method
2. Slit lamp biomicroscopy
3. IOP measurement
4. Dilated ophthalmoscopy
5. Change from baseline (1-day post-surgery) to each post-surgery visit in ocular signs:
    - Conjunctival hyperemia
    - Corneal Edema

All Relevant clinical findings will be recorded in the electronic case report form (eCRF).

3.2 EXPLORATORY EFFICACY ENDPOINTS

1. Anterior Chamber Cell count on slit lamp biomicroscopy. [redacted]
2. Anterior chamber flare
3. Subject-rated ocular pain assessment

3.3 DESCRIPTION OF THE STUDY DESIGN

This is a Phase I/IIa Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Dose-ranging study designed to evaluate the safety and preliminary efficacy of TRS01 eye drops at three dose levels compared to vehicle in subjects with post-surgical inflammation.

Approximately 60 subjects with ocular inflammation following cataract surgery will be randomized at approximately five centers, in the USA and in France.

Subjects who provide informed consent and meet all study randomization criteria will be enrolled in the study and randomized in a 1:1:1:1 ratio to receive TRS01[redacted]%, TRS01-[redacted], TRS01-[redacted]% or vehicle eye drops four times daily.

The eye that underwent cataract surgery is defined as the study eye. TRS01 should not be administered in the fellow eye.

Treatment assignments will be masked to Tarsius, study subjects, Investigators, and site staff. In order to prevent unmasking, all study medications during the Treatment Period will be supplied in identical packages.

The study design includes 14-days of a double-masked treatment period, with the endpoint assessment conducted on Day 15 (FIGURE 1 summarizes the study phases, anticipated visits and number of subjects at each phase and Appendix 1 summarizes the schedule of assessments from Screening through Day 15).

Randomization is employed as an unbiased method of assigning subjects to four groups in equal allocation.

Male and female subjects aged 18 or older and 1-day post cataract surgery with anterior chamber cells ≥ grade 2 in the study eye, are eligible to be randomized to participate in the treatment phase of the study.

Double-masked eye drops will be administered four times daily from Day 1 through Day 14 by the study participant (or care provider) to the study eye. The safety endpoint is on Day 15. Exploratory efficacy measurements will be collected.

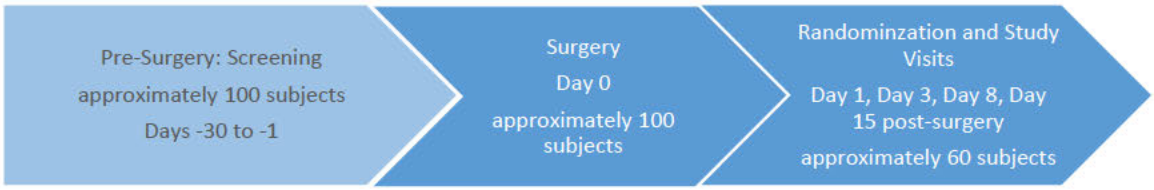
Visits (including the surgery day):

1. Visit 1/Days -30 to -1 – Screening: Initial screening for eligibility – 1-30 days before the surgery.
2. Visit 2/Day 0 – Surgery: Eligible subjects will undergo routine cataract surgery according to investigator's standard procedures. No steroid or NSAID will be given before, during or after the surgery. Acetaminophen on the day of surgery is allowed.
3. Visit 3/Day 1 – Randomization: Subjects who meet the post-surgery qualification criteria of ≥ grade 2 anterior chamber cells in the study eye will be randomized and will initiate dosing with IP. The subject's first dose will occur after randomization under the observation of an Unmasked staff member.

    3.1. 40 minutes ± 10 minutes post first dose, AEs, if any, will be recorded. Changes that are expected due to uncomplicated cataract surgery (such as discomfort, scratchy feeling, significant brightness, changes in the perception of the operated eye, corneal edema) will be collected, but will not be classified as AEs. Subjects will be given one bottle of IP and instructed to dose three more times that day and to begin dosing four times a day on the following day and onward.

4. Visit 4/Day 3: Evaluation
5. Visit 5/ Day 8: Evaluation and replacement of IP.
6. Visit 6/ Day 15: Evaluation, collection of IP and study completion.

FIGURE 1: STUDY VISITS



Please note that both eyes cannot be part of the study – there should be a treated eye (study eye) and an untreated eye (non-study eye). The non-study eye should not undergo any surgical procedure during the trial.

3.3.1 Investigational product kit

[redacted]

3.3.2 Treatments administered

Eligible subjects for Tarsius 2020 Trial will be randomized in a 1:1:1:1 ratio to receive sterile ophthalmic solution of TRS01[redacted], TRS01[redacted]%, TRS01[redacted]% or vehicle during the 14-day Treatment Period. All doses will be administered as eye drops in the inferior conjunctival fornix. Unmasked study personnel will train subjects on drop use during the screening visit.

Subjects will be asked by unmasked study personnel to dose with the drops prior to leaving the clinic on Day 1. Subjects will be advised to gently shake the IP bottle before instillation and to dose approximately every four hours during the day (example: first dose- 8:00am, second dose – 12:00pm, third dose - 4:00pm and fourth dose - 8:00pm). To increase assurance of IP delivery, subjects will be instructed to repeat a dose if they feel they did not effectively dispense adequate IP into their study eye. Every daily application of the drug will be recorded in the subject's dosing diary.

3.3.3 Method to minimize bias

In order to prevent unmasking during the study, the three doses of TRS01 and the vehicle will be supplied in identical packages.

Treatment assignments during the treatment period will be masked to all Tarsius staff, subjects and investigators, except delegated unmasked site personnel. The designated unmasked site personnel should collect all AEs related to IP and will handle all IP related responsibilities but will not perform any study related assessments.

The first dose will be administered under the supervision of an unmasked staff member and will serve as confirmation that the subject was adequately trained on drop administration at the screening visit. In the event that it becomes necessary to unmask a specific subject's treatment assignment, the Principal Investigator will contact Tarsius Medical Officer or the back-up Medical Officer. Unmasking will be allowed for individual subjects after it is determined necessary by the Medical Officer and the Principal Investigator, thus leaving the masking of the remaining subjects intact

4 SELECTION OF STUDY POPULATION

4.1 SUBJECT INCLUSION CRITERIA

Pre-operatively, individuals of either gender or any race will be eligible for study participation if they are:

1. 18 years of age or older.
2. Able to provide informed consent, follow instructions and complete all required study visits for the duration of the study.
3. Scheduled for routine cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens (IOL) implantation, and not combined with any other surgery.
4. Have vision ≥ 20/200 in the non-study eye.
5. Able to self-administer eye drops (tested during screening by self-administration of "artificial tears"), or have a care provider that can administer the drops.
6. Have no known sensitivity /allergy to the TRS01 or formulation excipients as detailed in **TABLE 2** and **TABLE 3**.
7. Using adequate birth control by men and women, if of reproductive potential and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 2 weeks after the last dose of investigational product.
    a. For females, adequate birth control methods will be defined as hormonal contraceptives, intrauterine device or double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam.
    b. For males, adequate birth control methods will be defined as double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam.
    c. For females, menopause is defined as one year without menses; if in question, a follicle-stimulating hormone of >40 IU/L must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable.

4.2 SUBJECT EXCLUSION CRITERIA

In order for subject to be eligible at Visit 1 they may not:

1. Be scheduled to undergo cataract surgery in the non-study eye for 2 months prior to Visit 1 and during the study.
2. Require use of any topical ophthalmic medication (either eye) for 14 days prior to surgery and for the duration of the trial. Note: Use of PRN artificial tears up to twice a day is allowed and should not be dosed within 10 minutes of investigational product dosing.

3. Require topical ocular therapy (either eye) with antibiotics for 30 days prior to surgery except antibiotic eye drops used as part of the Investigator's routine pre-op, intra-op, and post-op routine care.
4. Require treatment with systemic NSAIDs, within 14 days prior to the surgery and for the duration of the trial. Occasional use (≤ 2 times per week) of NSAIDs or over the counter (OTC) painkillers to treat minor non ocular conditions is acceptable. Low-dose aspirin (81 mg) for cardiovascular prophylaxis is allowed. Acetaminophen is the preferred treatment for post-op pain on the day of surgery.
5. Require treatment with systemic or ocular immunosuppressants or immunomodulators including systemic steroids (oral, inhaled, injectable) for 30 days prior to surgery and for the duration of the trial. Require treatment with nasal, topical dermal steroids or immunosuppressants within 14 days prior to surgery and for the duration of the trial. Require treatment with alpha-1 antagonists within 30 days of surgery and for the duration of the trial.
6. Use any ocular, topical or systemic medication that could interfere with wound healing, the test agent, or the interpretation of study results, within 30 days prior to the day of surgery and for the duration of the trial.
7. Use of contact lenses in the study eye are prohibited for the duration of the study.
8. Have history of glaucoma surgery or any incisional ocular surgery in the study eye. History of uncomplicated refractive surgery 3 years prior to the cataract surgery is acceptable.
9. Have any significant ocular disease in the study eye in addition to the cataract that may confound the trial results per the Investigator's judgement.
10. Have proliferative diabetic retinopathy (PDR), not stable for at least one year in the study eye.
11. Be currently being treated for wet macular degeneration.
12. Have current or history of herpes keratitis in the study eye.
13. Be diagnosed with Fuchs Corneal Dystrophy (FCD).
14. Have current or history of prior ocular inflammation in the study eye not related to prior allowed surgical procedure.
15. In the opinion of the Investigator, have current clinically significant dry eye requiring therapy of greater than twice a day (BID) eye drops in the study eye. Use of PRN artificial tears up to twice a day is allowed and should not be dosed within 10 minutes of investigational product dosing.
16. Use any Cannabidiol products during the trial.
17. Have history of glaucoma or uncontrolled IOP >22mmHg in the study eye on day of screening.

18. Have floppy iris syndrome noted for the contralateral eye prior to surgery in the study eye.
19. Have any clinically significant systemic disease or condition (e.g. hematological diseases) that, in the Investigator's opinion, may confound the trial results, pose a safety risk to the subject or preclude the subject from adhering to the protocol or completing the trial per protocol and installing eye drops.
20. Have a known history of alcohol and/or drug abuse.
21. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.
22. Have been exposed to an investigational drug or investigational medical device within 60 days prior to Visit 1.
23. Be pregnant or lactating.

4.3 RANDOMIZATION INCLUSION CRITERIA

To qualify for randomization at the Day 1 (Visit 3), a subject must:

1. Have undergone routine, uncomplicated cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber IOL implantation, not combined with any other surgery (including but not limited to use of iris retractors, capsular fixation ring or anterior capsule staining with dye). Specifically, have NOT had any cataract surgery complication such as a posterior capsular rupture, vitreous loss or significant iris damage.
2. Have an IOP of ≤ 30 mmHg. Notes: Fluid release from the anterior chamber through the surgical incision is allowed (manual burping). The final IOP post release of fluid must be ≤ 30 mmHg and will be recorded as the visit IOP value. Use of IOP lowering medications are allowed beginning on Day 0, with the exception of prostaglandins. IOP lowering eye drops should be dosed at least 30 minutes before investigational product dosing.
3. Have anterior chamber cells ≥ grade 2.
4. Continue to meet inclusion/exclusion criteria with respect to current ocular and medical conditions and must not be taking prohibited medications (section 6.4).

4.3.1 Masking and Randomization Methodology

Eligible subjects will be randomized in a 1:1:1:1 ratio to receive TRS01-[redacted], TRS01[redacted], TRS01[redacted]% or vehicle dose on Day 1.

Randomization will occur after subjects meet all eligibility requirements at Screening and Day 1/Visit 3 (1-day post-surgery). Each subject will be assigned a unique subject number.

Each kit package (containing two IP bottles) will contain a kit number that can be later corelated to the subject number at the site.

Randomization for the US sites will be separate from the French site.

The randomization codes and all data sets will be stored in a secure area accessible only to delegated study personnel and only released on completion of the study and after the study database has been locked.

In this study all parties are to be masked to the allocated treatment; investigators, study staff and subjects. At the site, there will be designated unmasked study staff that will train the subject on all study procedures related to IP administration.

In emergency situations for reasons of subject safety (e.g. serious unexpected /unlisted drug related event; medical emergency; potentially life-threatening drug interaction) the masking code may need to be broken. In those cases, whenever possible, a request for unmasking should be discussed with the sponsor (or designee) prior to unmasking. Detailed instruction on the method for breaking the mask will be provided during site training and noted in the Investigator study file.

Following the first IP administration, if the subject perceives any AE that may be attributed to the IP, these should be reported to the unmasked site personnel.

4.4 INFORMED CONSENT

Prior to undergoing any study-related activity, the Principal Investigator or his/her designee will discuss the purpose and pertinent details of the study with each potentially eligible subject. The explanation will be sufficiently detailed to allow the subject to make an informed decision to participate in the study. If the subject is willing to participate in the study, he/she will be requested to give written informed consent. A copy of the Informed Consent Form (ICF) will be signed by both the subject and the Principal Investigator or his/her designee.

The signed and dated ICF will be retained with the study records, and a copy of the signed and dated ICF will be given to the subject.

5 STUDY ASSESSMENTS

5.1 TIMING OF STUDY ASSESSMENTS

All procedures will be performed according to the following schedule unless otherwise specified. See also the summary of assessments in Appendix 1 that outlines this schedule in tabular form. Note: [redacted]

5.1.1 Visit 1: Screening (Day (-30) to Day (-1)).

This visit is a period where assessments can be collected. Ocular assessments are to be performed on both eyes.

- Signed and dated informed consent
- Demographic information including iris color
- Medical and Ophthalmic History
- Inclusion/exclusion criteria
- Concomitant Medications
- Urine pregnancy test (if female of child-bearing potential)
- Snellen Distance Visual Acuity (VA) by Pinhole Method
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Self-administration eye drop assessment (self-administration/care provider administration of "artificial tear eye drop")
- Assessment of adverse events

5.1.2 Visit 2: Day 0 – Surgery

This visit will occur no more than 30 days and no less than 1 day after Visit 1 and the following will be performed/assessed:

- Concomitant medication update
- Occurrence of any AEs since the last visit
- Routine pre-surgical care and procedures as determined by the Investigator

5.1.3 Visit 3: Day 1 (1-day post-surgery)

This visit should be scheduled to occur in the morning, if possible, to allow for QID dosing on Day 1 for randomized subjects. Perform the following assessments. Ocular assessments are to be performed on both eyes, unless otherwise noted:

- Subject-Rated Ocular Pain Assessment – prior to any other assessments
- Assessment of adverse events following subject rated ocular pain assessment. Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs but will be recorded.
- Concomitant medication update
- Snellen Distance VA by Pinhole Method
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Randomization: subjects that meet eligibility criteria (section 1) should be randomized to one of the treatment groups through the Interactive Web Response System (IWRS).
- [redacted]
- Dispensation of IP and Dosing Diary: the subject will receive one bottle from the study kit and will be instructed to self-administer the first drop prior to leaving the clinic, under the supervision of the unmasked personnel. The subject will be instructed to record this first dose and all subsequent doses in the dosing diary.
- 40 minutes ± 10 minutes post IP administration the subject will be assessed for AEs in both eyes. If any AEs are reported at visit 3 that may be attributed to the IP, these should be handled by the unmasked personnel.
- The subject will be instructed to take the bottle home and administer the IP three more times that day. Following the day of this visit the subject will be instructed to begin using the drops four times a day and to continue for the duration of the study.

5.1.4 Visit 4: Day 3 (± 1 day) post surgery

Perform the following assessments. Ocular assessments are to be performed on both eyes, unless otherwise noted:

- Subject-Rated Ocular Pain Assessment – prior to any other assessments
- Assessment of adverse events. Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs but will be recorded.
- Concomitant medication update
- Snellen Distance VA by Pinhole Method
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- [redacted]
- Review subject's dosing diary for compliance by unmasked personnel

5.1.5 Visit 5: Day 8 (± 1 day) post surgery

Perform the following assessments. Ocular assessments are to be performed on both eyes, unless otherwise noted:

- Subject-Rated Ocular Pain Assessment – prior to any other assessments
- Assessment of adverse events. Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs but will be recorded.
- Concomitant medication update
- Slit-lamp biomicroscopy
- Snellen Distance VA by Pinhole Method
- Intraocular pressure by Goldmann Applanation Tonometry
- [redacted]
- Collect used IP and review subject's dosing diary for compliance by unmasked personnel
- Dispense second bottle of IP from subject's assigned kit by unmasked personnel. Subject should be reminded to withhold dosing on the day of Visit 6.

5.1.6 Visit 6/Early Termination: Day 15 (± 1 day) post surgery

Perform the following assessments. Ocular assessments are to be performed on both eyes, unless otherwise noted:

- Subject-Rated Ocular Pain Assessment – prior to any other assessments
- Assessment of adverse events. Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs but will be recorded.
- Concomitant medication update
- Urine pregnancy test (if female of child-bearing potential)

- Snellen Distance VA by Pinhole Method
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated ophthalmoscopy
- [redacted]
- Collect used IP and the subject's dosing diary by unmasked personnel
- Confirm study completion

5.1.7 Unscheduled Visits

If at any time during the study, outside of the above scheduled visits, the subject requests or the physician determines the subject should be assessed for retreatment or of an AE, an unscheduled visit may occur. Adverse events and concomitant medications will be recorded and the following assessments should be performed on the study eye (and non-study eye if applicable/necessary.):

- Snellen Distance VA by Pinhole Method
- Slit lamp biomicroscopy
- IOP by Goldmann Applanation Tonometry
- Dilated ophthalmoscopy, if indicated

5.2 WITHDRAWAL CRITERIA / EARLY TERMINATION

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. Where possible, subjects will be followed for safety and encouraged to return for follow-up visits for any unresolved safety events.

In addition, the Investigator or Tarsius' Medical Officer can discontinue a subject from further study medication administration for other reasons related to the best interest of the subject.

If a subject is discontinued from study medication administration at any point of the Treatment Period, he or she will be encouraged to remain in the study for follow up through Day 15.

The reason a subject discontinued from the study is to be clearly described on the Study Exit electronic case report form (eCRF).

Subjects who withdraw from the study will not be replaced. Subjects who withdraw from the study prior to Visit 6 (Day 15) will be asked to complete all procedures outlined in Visit 6.

6 TREATMENT OF SUBJECTS

6.1 PRIOR AND CONCOMITANT THERAPY

At the Screening visit, medications that were taken within the previous 30 days will be collected. At each study visit thereafter, subjects will be questioned concerning any new medications or changes in their current concomitant medications since their previous study visit.

For all medications, the generic name, indication, route of administration, frequency, dose, start date and end date (if applicable) will be collected.

6.2 PERMITTED MEDICATIONS

Therapy considered necessary for the subject's welfare that does not interfere with the evaluation of the study medication will be permitted to be given at the discretion of the Principal Investigator.

The decision to administer a prohibited medication or treatment would be taken with the safety of the subject as the primary consideration. Whenever possible, the Tarsius Medical Monitor will be notified before any prohibited medications or treatments are administered. The Tarsius Medical Monitor should also be contacted if the permissibility of a specific medication or treatment is in question.

Any subject placed on rescue therapy will discontinue use of the study medication and continue study participation through Visit 6.

Subjects on rescue will be considered treatment failures, but the need for rescue therapy will not be considered an AE. Rescued subjects experiencing an AE at the time of rescue will be followed through stabilization or resolution of the AE or the end of the study (whichever comes last). Rescued subjects should not be withdrawn from the study, but rather followed to resolution of signs and symptoms or until the Investigator has deemed the subject is stable.

6.3 RESCUE MEDICATION USE

Rescue medications will be administered in cases detailed in section 7.2.2. Rescue therapy will be defined as any treatment that would have a therapeutic effect on inflammation in the anterior segment, other than the IP (e.g., systemic treatment with an immunosuppressant agent, or topical corticosteroids in the study eye), regardless of the purpose of administration and whether it was recorded as a rescue therapy on the eCRF.

Systemic immunosuppressive therapy (e.g., methotrexate, cyclosporine, cyclophosphamide, chlorambucil, mycophenolate mofetil, tacrolimus, azathioprine, or adalimumab) or other therapy considered as a rescue therapy, would be administered based on the Investigator's best judgment and only after discussion with Tarsius' Medical Director. Prior to treatment with rescue medication, the subject should answer the "Subject-Rated Ocular Pain Assessment". Only then, rescue medication can be administered and treatment will be recorded as a rescue therapy in the Medications eCRF.

6.4 MEDICATIONS NOT PERMITTED

Use of the following medication is not permitted during the study and **14** days prior to Visit 2 (Day of Surgery):

1. Any topical ophthalmic medications (either eye) other than study required medications. Note: Use of PRN artificial tears up to twice a day (BID) is allowed, and should not be dosed within 10 minutes of investigational product dosing.
2. Prostaglandins. Use of IOP lowering medications, other than prostaglandins, are allowed beginning on Day 0 and during the study, as needed. IOP lowering eye drops should be dosed at least 30 minutes before investigational product dosing.
3. Systemic NSAIDs. Occasional use (≤ 2 times per week) of Systemic NSAIDs or OTC painkillers to treat minor non-ocular conditions is acceptable. Low- dose aspirin for cardiovascular prophylaxis is allowed. Acetaminophen may be administered pre and post-operatively as needed for pain on the day of surgery.
4. Treatment with nasal, topical dermal steroids or immunosuppressants.

Use of the following medication is not permitted during the study and 30 days prior to Visit 2 (Day of Surgery):

1. Use of topical ocular therapy (both eyes) with antibiotics. Note: Antibiotic eye drops that are routinely administrated prior/during and post cataract surgery are allowed.
2. Use of systemic or ocular immunosuppressants or immunomodulators including steroids (oral, inhaled, injectable, nasal, topical dermal).
3. Use of systemic alpha-1 antagonists.
4. Any ocular, topical or systemic medication that could interfere with wound healing, the test agent, or the interpretation of study results.
5. Other investigational drugs or devices

6.5 TREATMENT COMPLIANCE

In order to obtain reliable safety and efficacy data, it is critical that each subject comply with the dosing schedule specified in the protocol.

Subjects will be instructed to record administration information from Day 1 and for the duration of the study in a dosing diary .

7 SAFETY AND EFFICACY VARIABLES

7.1 SAFETY VARIABLE

Incidence and severity of treatment-related AEs and SAEs, both systemic and ocular events.

7.2 SAFETY VARIABLES

Safety measures include AEs/SAEs and clinical assessments from the slit-lamp biomicroscopy findings, IOP, and dilated ophthalmoscopy findings.

AEs and ocular safety measures to be collected in this study are listed in Table 4.

TABLE 4: OCULAR SAFETY MEASURES

Safety Measure	**Note**
Slit-lamp biomicroscopy: *Lid hyperemia, lid edema, conjunctival hyperemia, chemosis, corneal edema, conjunctival discharge/exudate*	The status of each of these biomicroscopy parameters will be rated as 0 = None, 1 = Mild, 2 = Moderate, or 3 = Severe. For each abnormal record, the clinical significance (Clinically Significant or Not Clinically Significant) will also be determined. Slit-lamp biomicroscopy will be performed at all study visits, except Visit 2 (Surgery).
Intraocular pressure	The IOP measurements will be performed by Goldmann applanation tonometry. IOP pressure recorded in mmHg (e.g., 18mmHg). IOP measurements will be performed at all study visits, except Visit 2 (Surgery).
Dilated Ophthalmoscopy: *IOL (post-surgery), vitreous haze, retina vessels, macula, optic nerve, cup/disc ratio.*	The status of IOL position, macula and optic nerve will be determined as Normal or Abnormal. The cup/disc ratio will be recorded with two decimal points (e.g., 0.80). Dilated ophthalmoscopy will be performed at Visit 1 (Screening) and at Visit 6 (Day 15).

Intraocular Pressure (IOP) – IOP will be measured using Goldmann Applanation Tonometry with a single measurement.

These ocular safety measures will be summarized using descriptive statistics. For continuous ocular safety measures, changes from Baseline (Day 1 / Visit 3) variables will also be summarized descriptively.

7.2.1 Adverse Events

Adverse events will be collected for subjects following signing of the ICF through the end of the study. The information will include at least a description of the event, onset date, and resolution date, as well as seriousness, severity and relation to study medication (as determined by the Investigator), location (right eye [OD], left eye [OS], both eyes [OU] or other), action taken, and outcome. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, current version. Ocular and non-ocular AEs will be summarized separately.

Suspected adverse reactions (SARs), also known as adverse drug reactions or suspected adverse drug reactions, are AEs considered by the Investigator to be related to the study medication and included in the Investigator's Brochure.

An AE will be considered as an *ocular AE* if the Investigator selects 'OD', 'OS', or 'OU' for the AE eCRF field "Eye(s) affected".

Any AE that causes loss of vision of 15 or more letters (i.e., 3 lines) should be recorded as a serious adverse event (SAE). Examples include endophthalmitis, retinal vascular occlusion, retinal detachment involving the macula/fovea, etc. AEs that cause loss of 15 or more letters (i.e., 3 lines) that are expected to resolve should not be recorded as an SAE. Examples include corneal edema, corneal abrasion, cystoid macular edema or other conditions that are known to affect vision but expected to resolve and not results in a permanent impact on vision.

7.2.2 Criteria for Rescue Therapy

Rescue therapy will be offered if one or more of the following criteria are met and a rescue therapy treatment plan is discussed with the Tarsius Medical Director.

- [redacted]

If rescue therapy is administered, the generic name, indication, route of administration, frequency, dose, start date, and stop date (if applicable) will be recorded on the eCRF. In addition, if other local therapy (i.e., periocular or intravitreal corticosteroids) is administered in the non-study eye, then the generic name, indication, route of administration, frequency, dose, start date and end date (if applicable) would also be recorded on the eCRF.

[redacted]

7.2.3 Other Safety Variables

Other safety measures are discussed in section 7.2 above.

7.3 ADVERSE EVENT DEFINITIONS

Adverse Event (AE): Any untoward medical occurrence associated with the use of an investigational product in humans, whether or not considered drug related.

Adverse Reaction (AR): any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Suspected Adverse Reaction (SAR):
Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Unexpected: An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Life-threatening: An AE or SAR is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

A **SERIOUS ADVERSE EVENT (SAE)** is any AE or suspected adverse reaction occurring at any dose that:

- Results in death.
- Is life-threatening.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization.
- Prolongs inpatient hospitalization.
- Is a congenital anomaly/birth defect.
- Is a significant medical event (i.e., one that may jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above).

A **NON-SERIOUS ADVERSE EVENT** is any AE that does not meet the definitions for SAEs as described above.

Each **AE** will be classified as **SERIOUS or NON-SERIOUS** using the definitions provided above.

The **SEVERITY** of each AE will be classified as **MILD, MODERATE, or SEVERE.**
The Investigator will review each event and assess its **RELATIONSHIP** to use of investigational product (unrelated, probably, definitely). The AE will be assessed using the following definitions**:**

Unrelated:

- Event occurring before dosing.
- Event easily explained by uncomplicated cataract surgery
- Event or intercurrent illness due wholly to factors other than investigational product use.

Probable:

- Reasonable temporal relationship with investigational product use.
- Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot easily be explained by subject's clinical state or other factors.

Definite:

- Distinct temporal relationship with investigational product use.
- Known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot be explained by subject's clinical state or other factors.

7.4 PROCEDURES FOR AE REPORTING BY THE INVESTIGATOR

AEs will be monitored throughout the study and will be recorded on the CRF with the date and time of onset, date and time of resolution, severity, seriousness, causality (relationship to use of investigational product), treatment required, and the outcome.

To elicit AEs, simple questions with minimal suggestions or implications should be used as the initial questions at all evaluation points during the trial. For example:

- How have you felt since your last assessment?
- Have you had any health problems since your last assessment?

The severity of each AE should be categorized as mild, moderate, or severe.

The causality of use of investigational product in relation to the AE will be assessed by the Principal Investigator after careful medical consideration and categorized as unrelated, probable, or definite.

If an AE occurs, the Investigator will institute support and/or treat as deemed appropriate. If a non-SAE is unresolved at the time of the last day of the study, an effort will be made to follow

up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event.

7.5 SERIOUS ADVERSE EVENT REPORTING BY THE INVESTIGATOR

Serious Adverse Event Reporting

It is the responsibility of the Investigators or their designees to report any event of this nature to the sponsor or a designee within 24 hours of the event being brought to the Investigators' or their staffs' attention. It is also the responsibility of the Investigator to report all SAEs reported at their site to their Institutional Review Board (IRB), as required. The Investigator should make every attempt to follow all SAEs to resolution.

The following information should be provided when an SAE is reported to the sponsor or designee:

1. Protocol Number
1. Site Number
2. Subject Number
3. Subject Demographic information, including:
    - Date of Birth
    - Sex
    - Race
4. Investigational product start date
5. Date of last dose of investigational product
6. Date investigational product reinitiated (if investigational product interrupted)
7. SAE information, including:
    - SAE term (diagnosis only; if known or serious signs/symptoms)
    - Description of SAE/narrative
    - Date/time of onset
    - Severity
    - Outcome
    - Date/time of resolution or death (if duration < 24 hours)
    - Relationship to investigational product
    - Action taken with investigational product
8. Criteria for classifying the event as serious, including whether the SAE:
    - Resulted in death.
    - Was life-threatening
    - Required inpatient hospitalization.
    - Prolonged inpatient hospitalization.
    - Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
    - Was a congenital anomaly/birth defect

- Important medical events that may not result in death, were not life-threatening, or did not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9. Concomitant medications
10. Relevant history
11. Possible causes of SAE other than investigational product
12. Copy of AE page from the CRF

NOTE: If an SAE occurs in any study involving TRS01 that is unexpected and is determined to be related or possibly related to investigational product, all sites will be notified by the sponsor and each site should report it to its IRB.

8 EXPLORATORY EFFICACY

Measures of efficacy will be based on Investigator assessments of ACC and flare.

8.1 EFFICACY VARIABLES

Efficacy of TRS01 will be assessed by evaluation of anterior chamber inflammation by Investigator assessment with slit-lamp biomicroscopy.

Slit-lamp biomicroscopy of the both eyes will be used to examine eye structures at each study visit. At Day1/Visit 3 (1-day post-surgery), slit-lamp biomicroscopy will be performed prior to IP administration. Areas assessed will include lids, conjunctiva, cornea, anterior chamber cells and flare, iris, pupil, lashes, ocular motility, lens and cataract status.

8.1.1 Anterior Chamber Cells

Note: The same investigator must assess and score anterior chamber cells and flare at Visit 3, Visit 4, Visit 5 and Visit 6 for an individual subject.

8.1.1.1 Slit-lamp biomicroscopy

At each visit, slit-lamp biomicroscopy under halogen illumination system will be performed by the Investigator on both eyes to assess ACC.

The following scoring scale for anterior chamber cells will be used:

8.1.2 Flare

The level of flare in the anterior chamber will be assessed by the Investigator at each study visit for both eyes, using slit-lamp biomicroscopy and recorded according to the following scale:

- 0 = None

- 1= Mild (trace to clearly noticeable, visible)
- 2 = Moderate (without plastic aqueous humor)
- 3 = Marked (with plastic aqueous humor)
- 4 = Severe (with fibrin deposits and/or clots)

8.1.3 Subject-Rated Ocular Pain Assessment

In the clinic, subjects will be handed a laminated card on which is printed the Subject-Rated Ocular Pain Assessment. Each subject will be asked to subjectively rate their pain at Visit 3 to 6 based on this scale. This information will be provided to study personnel to enter into the subject's source documentation.

The grading scale for pain to be used will be as follows:

0 = None: Absence of pain.

1 = Minimal: Presence of mild sensation or discomfort typical of post cataract surgery (e.g., diffuse or focal foreign body sensation, mild transient burning or stinging, etc.)

2 = Mild: Mild, tolerable aching of the eye.

3 = Moderate: Moderate or more prolonged aching sufficient to have desire to use over the counter (OTC) analgesics (e.g. acetaminophen).

4 = Moderately Severe: More prolonged aching requiring the use of an OTC analgesic other than acetaminophen.

5 = Severe: Aching or throbbing pain that is not tolerable (e.g. constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics.

9 STATISTICS

9.1 STATISTICAL METHODS

Continuous measures (e.g., age) will be summarized descriptively by the mean, standard deviation, median, minimum and maximum values. Categorical measures will be summarized by the number and percent of subjects.The statistical analyses will be performed in accordance with the Statistical Analysis Plan. All study data will be listed by treatment, subject and visit (as applicable).

9.1.1 Subject Disposition, Demographic and Background Characteristics

Subject disposition, demographic characteristics, and background variables will be summarized by treatment group.

9.1.2 Analysis of Safety

Analysis of safety data will be presented for all subjects. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, most current version) and categorized by system organ class using preferred terms. Treatment emergent AEs will be listed by study group. Treatment related AEs will be tabulated by study group and will be reported by incidence (both number of events and number of subjects) with respect to their intensity and relationship to the IP. Ophthalmoscopy findings will be summarized descriptively. IOP measurements, VA, and slit lamp biomicroscopy will be summarized as safety outcomes.

9.1.3 Analysis of Efficacy

Efficacy measures will be ACC and flare, as well as Subject-rated Ocular Pain Assessment.

Both Investigator-rated ACC and flare data will be assessed as a change from baseline (Visit 3/Day 1) on Days 3, 8 and 15 and a descriptive comparison of the active treatment groups to the vehicle group will be performed.

[redacted]

The Subject-rated Ocular Pain Assessment will be assessed as a change from baseline (Visit 3/Day1) on Days 3, 8 and 15 and a descriptive comparison of the active treatment groups to the vehicle groups will be performed.

9.2 SAMPLE SIZE ESTIMATION

[redacted]

9.3 LEVEL OF SIGNIFICANCE

Level of significance to be outlined in the Statistical Analysis Plan.

9.4 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED, OR SPURIOUS DATA

Any missing, unused, or spurious data will be noted in the final clinical study report.

9.5 PROCEDURE FOR REPORTING DEVIATIONS FROM THE STATISTICAL PLAN

Any deviations from the statistical analysis plan will be described and a justification given in the final clinical study report.

9.6 SUBJECTS TO BE INCLUDED IN THE ANALYSIS

Intent-to-Treat (ITT) Population: The ITT population will include all randomized subjects who took at least 1 dose of investigational product. The Safety Population will include all randomized subjects.

Per Protocol (PP) Population: The PP population is a subset of the ITT population, which will include those subjects who did not have significant protocol deviations. The PP population will be defined and documented by the clinical study team and the biostatistician prior to database lock and unmasking of the subjects.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data and documents (such as tests performed as a requirement for participation in the study and other medical records required to confirm information contained in the case report form such as medical history) to the monitor.

11 QUALITY CONTROL

The progress of the study will be monitored by on-site, written, e-mail, and telephone communications between personnel at the study center and the sponsor (or designated monitor). The Investigator will allow Tarsius Pharma, Ltd. monitors or designee to inspect all CRFs; subject records (source documents); signed informed consent forms; records of investigational product receipt, storage, and disposition; and regulatory files related to the study.

12 ETHICS

12.1 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

The clinical study protocol, protocol amendments, ICF, and all other appropriate study-related documents will be reviewed and approved by an appropriate Independent Ethics Committee (IEC) according to local laws and regulations for study sites outside the United States (US), or Institutional Review Board (IRB) constituted in accordance with US Title 21 Code of Federal Regulations Part 56 for sites in the US. A copy of the letter indicating EC/IRB approval will be provided to Tarsius Pharma, Ltd. (Tarsius) prior to study initiation or implementation of each relevant protocol amendment.

13 AMENDMENTS TO THE PROTOCOL

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor (or its representative). The written amendment must be reviewed and approved by the Sponsor and submitted to the IRB for approval.

Amendments specifically involving change to trial design, risk to subject, increase of dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the appropriate IRB. The amendment will be submitted formally to regulatory authorities by the Sponsor as applicable, after IRB approval and specifically when an increase of dosing or subject exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

14 DATA HANDLING AND RECORDKEEPING

All procedures for the handling and analysis of data will be conducted using GCP and will meet ICH guidelines and US FDA regulations, for sites in the US, for the handling and analysis of data for clinical trials. All personal data will be collected and processed in compliance with the requirements arising out of the European General Data Protection Regulation – GDPR (Regulation n. 2016/679) and French regulation MR001 2018-153 3 May 2018

14.1 DATA QUALITY CONTROL AND REPORTING

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and monitor(s) for resolution. The study database will be updated in accordance with the resolved query reports. All changes to the study database will be documented.

14.2 RECORDS RETENTION

The study center will retain all records related to the study in accordance with local and ICH GCP guidelines.

15 PUBLICATION POLICY

The institution and Investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of Tarsius Pharma.

16 APPENDICES

Appendix 1: Schedule of Assessments

	Visit 1	Visit 2	Visit 3		Visit 4	Visit 5	Visit 6/ET[8]
Assessment schedule:	Screening	Surgery	Treatment Period				
	(-30) to (-1) days	Day 0	Day 1 – 1-day post-surgery		Day 3 ±1	Day 8 ±1	Day 15 ±1
			Pre[1]	**Post[2]**			
Signed and dated Informed Consent	x						
Medical & Ophthalmic History	x						
Demographics including Iris color	x						
Inclusion/exclusion criteria	x		x				
Concomitant Medications	x	x	x		x	x	x
Urine pregnancy test[3]	x						x
Randomization criteria			x				
Subject-Rated Ocular Pain Assessment[4]			x		x	x	x
Snellen Distance Visual Acuity (VA) by Pinhole Method	x		x		x	x	x
Slit-lamp biomicroscopy[5]	x		x		x	x	x
Intraocular pressure	x		x		x	x	x
Dilated ophthalmoscopy	x						x
Self administration eye drop assessment	x						
[redacted]			[redacted]		[redacted]	[redacted]	[redacted]
Adverse events Assessment (AEs)[7]	x	x	x	x	x	x	x
Dispense investigational product			x			x	
Collect investigational product and compliance						x	x

1. Visit 3/Day 1 prior to randomization
2. 40 min ± 10 min post first administration of investigational product
3. Required for female subjects of childbearing potential
4. The Subject-Rated Ocular Pain Assessment must be performed prior to any other assessments

5. The same investigator must assess and score anterior chamber cells and flare at Visit 3, Visit 4, Visit 5 and Visit 6 for an individual subject.
6. May be conducted at select sites, on study eye only
7. Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs but will be recorded
8. Visit 6 is also the Early Termination visit

17 REFERENCES

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