Tarsius Pharma, Ltd.
Clinical Protocol GADOT 20/20 Trial

Project:	TRS01
Compound Number / Name:	TRS01
Protocol Number:	GADOT 20/20 NCT04222712
Protocol Title:	A Phase I/IIa Randomized, Double-Masked, Dose-Ranging Study to Evaluate the Safety and Tolerability of TRS01 Eye Drops in Subjects with Active Non-infectious Anterior Uveitis.
Sponsor:	Tarsius Pharma, Ltd. 19 Yahalom St. Zichron Yaacov 30900 Israel
Medical Monitor:	[redacted]

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Investigator Signature Page

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Sponsor:	Tarsius Pharma, Ltd. 19 Yahalom St. Zichron Yaacov 30900 Israel
[redacted]	[redacted]
Contact for Serious Adverse Events:	[redacted]

Investigator Name:

_____

Investigator's Signature:

_____ _____

Date

SYNOPSIS

Sponsor	Tarsius Pharma, Ltd.
Study Title	A Phase I/IIa randomized, double masked, dose-ranging study to evaluate the safety and tolerability of TRS01 eye drops in subjects with active non-infectious anterior uveitis.
Study Objective	The primary objective of the study is to investigate the safety and tolerability of TRS01 [redacted] and [redacted] (w/v) eye drops in subjects with active non-infectious anterior uveitis.
Study Population	The study population will consist of male and female subjects, aged 18 or older, with active non-infectious anterior uveitis requiring initiation of additional topical steroid treatment.
Number of Subjects	Up to 20 subjects that meet the selection criteria will be randomized for treatment in one study eye.
Study eye	The study eye will be identified based on the severity of Anterior Chamber Cells (ACC) at Day 1. The eye with the most severe inflammation (higher ACC grade) will be selected as the study eye. If the ACC score is the same in both eyes, the right eye (OD) will be identified as the study eye. If the fellow eye has concurrent active uveitis at Day 1 or at any time during the study, the investigator can treat the subject's fellow eye per the standard of care. Only the study eye of each subject will be treated with IP.
Investigational Product	TRS01 [redacted] and [redacted] eye drops will be supplied as investigational product (IP).
Route and duration of administration	Study subjects will administer the randomly assigned treatment four times a day (QID) for 4 weeks.
Study Design	This is a Phase I/IIa randomized, double masked, dose-ranging study designed to evaluate the safety and tolerability of TRS01 eye drops ([redacted] in subjects with active non-infectious anterior uveitis. Potential study participants will be required to sign an informed consent document and meet all inclusion/exclusion criteria. Eligible subjects will be randomized to treatment as follows: • [redacted] Once it is determined that all eligibility criteria have been met, subjects will be enrolled and treated with one of two concentrations of TRS01 in a 1:1 ratio. Up to 20 eligible subjects will be enrolled at approximately

	two sites. Study subjects will administer the randomly assigned treatment 4 times a day (QID) for 28 days. All study subjects will return for examination on Week 1, Week 2, Week 3, Week 4, Week 7 and Week 10. Clinical assessments will include the following: • Slit-lamp biomicroscopy • Dilated ophthalmoscopy • Intraocular pressure (IOP) • Best Corrected Visual Acuity (BCVA) • Macular optical coherence tomography (OCT) • Anterior Chamber SD-OCT (if available at the site) • Adverse events (AEs) • Subject-rated ocular pain assessment The Study Visit Schedule and assessments to be performed are described in Appendix 1. Rescue therapy will be offered if one or more of the following rescue criteria are met and a rescue therapy treatment plan is discussed with the Tarsius Medical Officer: • [redacted]

Safety and Tolerability Outcomes	Assessment of both systemic and ocular adverse events. 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. BCVA using ETDRS 2. Slit-lamp biomicroscopy, specifically evaluation of intraocular anterior inflammation 3. IOP measurement 4. Dilated ophthalmoscopy 5. Safety parameters of interest include a change from baseline to each visit in ocular signs such as corneal/conjunctival tolerability and IOP measurements.
Exploratory Efficacy Measurements	• Anterior chamber cell count by slit-lamp biomicroscopy and by anterior chamber SD-OCT in selected sites. • Anterior chamber flare assessed on slit-lamp biomicroscopy • Change in macular edema by macular OCT • Subject-rated ocular pain assessment
Eligibility Criteria	**Inclusion Criteria** 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) Diagnosed with active non-infectious anterior uveitis requiring an increase or initiation of topical steroids for management of ocular inflammation. An eligible subject must have: [redacted]

[redacted]

5) Use 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 study visit.

   a) For females of childbearing potential, 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 postmenopausal 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 a subject to be eligible they may not:

	• Have any form of infectious uveitis. • Have active retinitis. • Have cancer or melanoma that is actively treated with immunotherapy. • Be pregnant or lactating. • Have been treated with intravitreal or periocular steroids in the study eye within 90 days of Visit 1 or for the duration of the study (including but not limited to Iluvien, Retisert, Ozurdex, etc.). • Have been treated with any intravitreal injection within 30 days prior Visit 1 or for the duration of the study. • Require treatment with any systemic steroids greater than 10 mg/day. • Require topical ocular therapy with steroids more than twice a day (BID) in the study eye. Note: up to 3 additional drops of topical steroids within 7 days prior to Visit 1 is permitted. • Be diagnosed with Fuchs Corneal Dystrophy. • Use any topical ophthalmic medications other than those allowed in the study. • Have any significant ocular disease in addition to the uveitis that may confound the trial results per the Investigator's judgement. • 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. • Use any Cannabidiol products during the trial. • [redacted], narrow angle glaucoma, or glaucoma treated with more than two anti-glaucoma drugs in the study eye. Anti-glaucoma eye drops should be dosed at least 30 minutes before the investigational product dosing. • Have poor posterior view due to dilation or media opacity that limits ability to do OCT, or photography. • 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, or instilling eye drops. • Have had corneal refractive, laser or incisional surgery in the study eye within three months of Visit 1. • Have a known history of alcohol and/or drug abuse. • Have been exposed to an investigational drug or investigational medical device within 60 days prior to Visit 1. • 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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
ACC	Anterior Chamber Cells
AE	Adverse Event
API	Active Pharmaceutical Ingredient
[redacted]	[redacted]
AR	Adverse Reaction
BCVA	Best Corrected Visual Acuity
BID	Twice Daily
°C	Degrees Celsius
CRF	Case Report Form
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IU/L	International Units per Liter
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDPE	Low-density polyethylene
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
µL	Microliter
mmHg	Millimeters of Mercury
mg	Milligram
mL	Milliliter
OCT	Optical Coherence Tomography
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)

Abbreviation/Term	Definition
OTC	Over the counter
OU	Oculus Uterque (both eyes)
PP	Polypropylene
PP	Per Protocol
PRN	As Needed
QID	Four times daily
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SD-OCT	Spectral-Domain Optical Coherence Tomography
US	United States of America
VA	Visual Acuity
w/v	Weight to Volume

1 INTRODUCTION

Uveitis refers to a broad spectrum of ocular inflammatory diseases which are associated with both systemic infectious and non-infectious conditions. 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].

The inflammation associated with uveitis affects the uvea of the eye (iris, ciliary body and choroid) and it 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. Clinically, uveitis manifestations include pain, blurry vision, conjunctival hyperemia, anterior chamber cells, anterior chamber flare, fibrin deposition and corneal endothelial inflammatory precipitates.

Uveitis may affect either the anterior or the posterior segment or in the case of panuveitis, it affects the entire eye. Anterior uveitis, which specifically refers to uveitis in the anterior segment of the eye, is the most common and accounts for approximately 80% of non-infectious uveitis cases in the United States [Thorne et al., 2016].

The present clinical trial evaluates the treatment of non-infectious anterior uveitis with TRS01.

Topical corticosteroids represent first line treatment for both non-infectious anterior uveitis and postoperative inflammation [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 intraocular pressure (IOP) which can lead to steroid related glaucoma.

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

TRS is the active drug substance of TRS01 which is an [redacted] drug product candidate developed for topical ocular administration (eye drops). Pre-clinical studies have demonstrated the safety and tolerability of TRS01.

[redacted]

The GADOT 20/20 Trial is a Phase I/IIa randomized, double-masked, dose-ranging study to evaluate the safety and tolerability of TRS01 eye drops in subjects with active non-infectious anterior uveitis.

1.1 Description of Investigational Product

TRS01 is formulated as a [redacted] For this trial, dosing volume and dose delivery of TRS01 investigational product (IP) will be supplied as summarized in Table 1. [redacted]

Table 1: TRS01 Dosing Volume and Dose Delivery

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

The IP is a [redacted]

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, Ltd..

TRS01 will be received at [redacted]

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

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

TABLE 2: COMPOSITION OF TRS01 [redacted] AND [redacted] INVESTIGATIONAL PRODUCT

Ingredient	**Ingredient name According to USP**	**Function**	**Concentration (%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]	[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, with active non-infectious anterior uveitis requiring treatment with corticosteroids. Up to 20 subjects that meet the selection criteria will be randomized to two treatment groups.

1.3.1 Determination of Study Eye

[redacted]

2 STUDY OBJECTIVES

The primary objective of the study is to investigate the safety and tolerability of TRS01 [redacted] (w/v) eye drops in subjects with active non-infectious anterior uveitis.

The exploratory objective of the study is to evaluate the preliminary efficacy of TRS01 [redacted] (w/v) eye drops in reducing inflammation is subjects with active non-infectious anterior uveitis.

3 STUDY DESIGN

This is a Phase I/IIa randomized, double-masked, dose-ranging study designed to evaluate the safety and tolerability of TRS01 eye drops [redacted] in subjects with active non-infectious anterior uveitis.

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 adverse events in subjects with inflammation due to active non-infectious anterior uveitis.

1. BCVA
2. Slit-lamp biomicroscopy
3. IOP measurement
4. Dilated ophthalmoscopy
5. Safety parameters of interest include a change from baseline to each visit in ocular signs such as corneal/conjunctival tolerability and IOP measurements.

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. Anterior chamber spectral-domain optical coherence tomography (SD-OCT) will also be conducted at selected sites.
2. Anterior chamber flare assessed on slit-lamp biomicroscopy
3. Change in macular edema by macular OCT
4. Subject-rated ocular pain assessment

3.3 DESCRIPTION OF THE STUDY DESIGN

This is a Phase I/IIa randomized, double-masked, dose-ranging study designed to evaluate the safety and tolerability of TRS01 eye drops [redacted] in subjects with active non-infectious anterior uveitis.

Potential study subjects will be required to sign an informed consent document and meet all inclusion/exclusion criteria.

Eligible subjects will be randomized to treatment as follows:

- [redacted]

Once it is determined that all eligibility criteria have been met subjects will be enrolled and treated with one of two concentrations of TRS01 in a 1:1 ratio. Approximately 20 eligible subjects will be enrolled at approximately two sites.

Study subjects will administer the randomly assigned treatment 4 times a day (QID) for 28 days. All study subjects will return for examination on Weeks 1, 2, 3 and 4 (Treatment Phase) with post-treatment evaluations (Follow-Up Phase) at Weeks 7 and Week 10. Figure 1: Study Schematic summarizes the study phases, anticipated visits and number of subjects at each phase and Appendix 1 summarizes the schedule of assessments from Screening through Week 10.

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.

Randomization is employed as an unbiased method of assigning subjects to two groups in equal allocation (1:1 ratio).

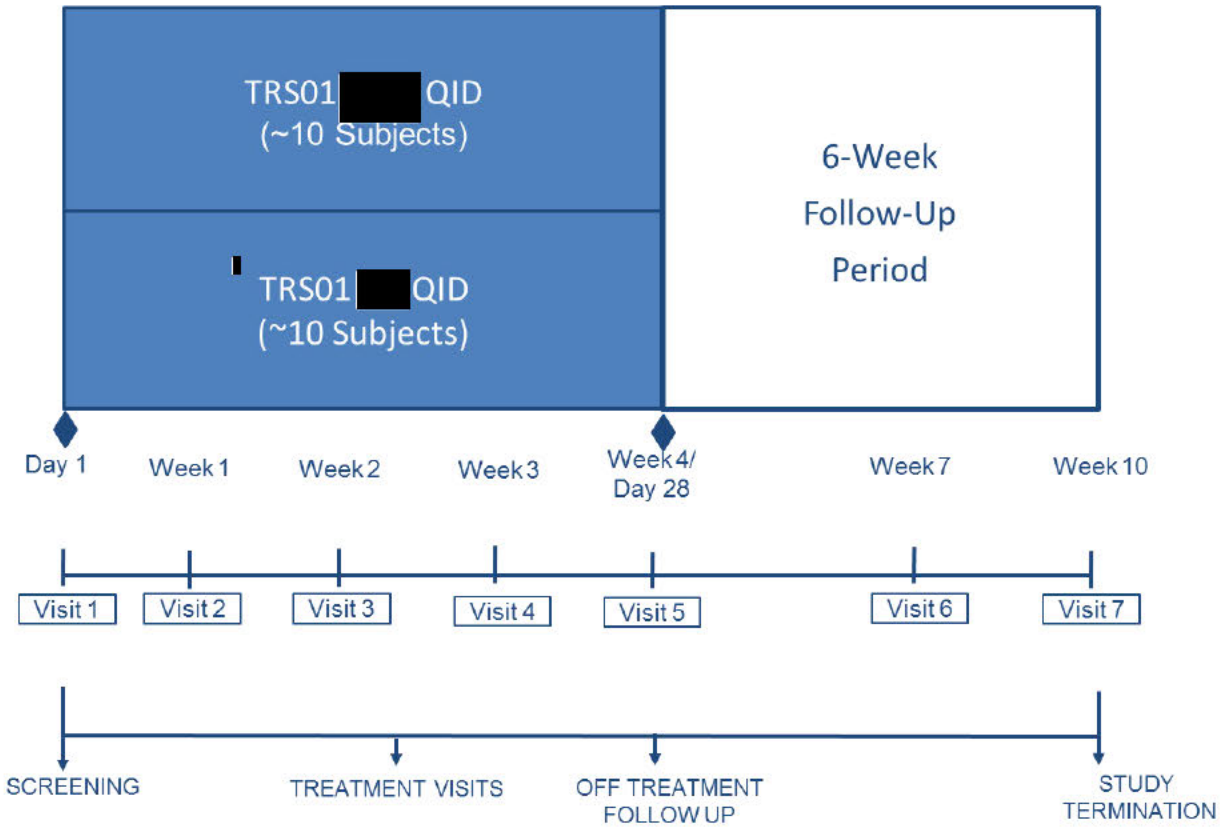
Visits:

1. Visit 1/Day 1 – Screening/Randomization: Initial screening for eligibility and randomization to treatment. Subjects who meet the qualification criteria with anterior chamber cells Grade [redacted] 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.
    1.1. [redacted] post first dose, AEs, if any, will be recorded. Subjects will be given one bottle of IP and instructed to dose at the remaining time points for that day (midday, afternoon, and evening if appropriate) and to begin dosing four times a day on the following day and onward.
2. Visit 2/Week 1 – Evaluation [redacted].
3. Visit 3/Week 2 – Evaluation [redacted].
4. Visit 4/Week 3 – Evaluation [redacted].
5. Visit 5/Week 4 – Conclusion of 28 days of dosing/treatment phase, [redacted].
6. Visit 6/Week 7 – Evaluation
7. Visit 7/Week 10 – Evaluation and study completion.

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).

A schematic of the study design is below in Figure 1: Study Schematic.

Figure 1: Study Schematic



3.3.1 Investigational product kit

[redacted]

The subject dosing diary is formatted to document the daily applications of the drop. Subjects should be instructed to bring their diary to Visit 2, 3, 4 and 5 as it will be collected and checked to confirm compliance.

[redacted]

3.3.2 Treatments administered

Eligible subjects for GADOT 20/20 Trial will be randomized in a 1:1 ratio to receive [redacted] of TRS01[redacted] or TRS01[redacted] for the 28-day Treatment Period. All doses will be administered as eye drops in the inferior conjunctival fornix.

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 [redacted] and to dose approximately every four hours during the day (example: first dose - morning, second dose - midday, third dose - afternoon and fourth dose - evening). 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 two doses of TRS01 will be supplied in identical packages identified with kit numbers.

[redacted]

The first dose will be administered under the supervision of an unmasked staff member and will serve as confirmation that the subject can adequately administer the IP. 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

Individuals of either gender or any race will be eligible for study participation at Visit 1 (Screening and Randomization) 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. Diagnosed with active non-infectious anterior uveitis requiring an increase or initiation of topical steroids for management of ocular inflammation.

An eligible subject must have:

[redacted]

4. [redacted]
5. Use 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 study visit.
    a. For females of child-bearing potential, 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 post-menopausal 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 a subject to be eligible at Visit 1 (Screening and Randomization) they may not:

1. Have any form of infectious uveitis.
2. Have active retinitis.
3. Have cancer or melanoma that is actively treated with immunotherapy.
4. Be pregnant or lactating.
5. Have been treated with intravitreal or periocular steroids in the study eye within 90 days prior to Visit 1 or for the duration of the study (including but not limited to Iluvien, Retisert, Ozurdex, etc.).
6. Have been treated with any intravitreal injection within 30 days prior to Visit 1 or for the duration of the study.
7. Require treatment with any systemic steroids greater than 10 mg/day.
8. Require topical ocular therapy with steroids more than BID in the study eye. Note: up to 3 additional drops of topical steroids within 7 days prior to Visit 1 is permitted.
9. Be diagnosed with Fuchs Corneal Dystrophy.
10. Use any topical ophthalmic medications other than those allowed in the study.
11. Have any significant ocular disease in addition to the uveitis that may confound the trial results per the Investigator's judgement.
12. 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.
13. Use any Cannabidiol products during the trial.
14. [redacted], narrow angle glaucoma or glaucoma treated with more than two anti-glaucoma drugs in the study eye. Anti-glaucoma eye drops should be dosed at least 30 minutes before the investigational product dosing.
15. Have poor posterior view due to dilation or media opacity that limits ability to do OCT,

or photography.

16. 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, or instilling eye drops.
17. Have had corneal refractive, laser or incisional surgery in the study eye within three months of the Visit 1.
18. Have a known history of alcohol and/or drug abuse.
19. Have been exposed to an investigational drug or investigational medical device within 60 days prior to Visit 1.
20. 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.

4.2.1 Masking and Randomization Methodology

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

Randomization will occur after subjects meet all eligibility requirements at Screening Day 1/Visit 1. Each subject will be assigned a unique subject number.

Each kit package [redacted] will contain a kit number that can be later correlated to the subject number and treatment assignment at the site. [redacted]

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; sponsor, 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 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.

4.3 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:** The same investigator in each site must assess and score anterior chamber cells and flare across all study visits for subjects.

5.1.1 Visit 1: Screening/Randomization: Day 1

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

- 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)
- Subject-Rated Ocular Pain Assessment – prior to other assessments
- BCVA
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Anterior Chamber SD-OCT (study eye only) in selected sites
- Macular OCT (study eye only)
- Randomization: subjects that meet eligibility criteria should be randomized to one of the treatment groups through the Interactive Web Response System (IWRS).
- 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.
- [redacted] minutes post IP administration the subject will be assessed for AEs in both eyes. If any AEs are reported at Visit 1 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 up to three more times depending on the time of the visit, but approximately every 4

hours. 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 treatment period.

- Subjects should be reminded to continue on their previous medication regimen and that the dosing should remain stable throughout the IP treatment period (Note: changes to the dosing of cycloplegic medications during the study is permitted). The subjects should also be reminded to wait 10 minutes between dosing IP and their other medications.

5.1.2 Visit 2: Week 1/Day 7 (±2 days) Treatment Evaluation

This visit will occur no more than 9 days and no less than 5 days after Visit 1 and the following will be performed/assessed (in both eyes, unless otherwise noted):

- Subject-Rated Ocular Pain Assessment – prior to any other assessments
- Concomitant medication update
- Occurrence of any AEs since the last visit
- BCVA
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Anterior Chamber SD-OCT (study eye only) in selected sites only
- [redacted]
- Review of subject's Dosing Diary by unmasked personnel
- [redacted]

5.1.3 Visit 3: Week 2/Day 14 (±2 days) Treatment Evaluation

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
- Occurrence of any AE's since last visit
- Concomitant medication update
- BCVA
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy

- Anterior Chamber SD-OCT (study eye only) in selected sites only
- [redacted]
- Review subject's Dosing Diary by unmasked personnel
- [redacted]

5.1.4 Visit 4: Week 3/Day 21 (±2 days) Treatment Evaluation

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
- Occurrence of any AE's since last visit
- Concomitant medication update
- BCVA
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Anterior Chamber OCT (study eye only) in selected sites only
- [redacted]
- Review subject's Dosing Diary by unmasked personnel
- [redacted]
- [redacted]

5.1.5 Visit 5: Week 4/ Day 28 (±2 days) Evaluation and End of Study Treatment

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

- Subject-Rated Ocular Pain Assessment – prior to other assessments
- Occurrence of any AE's since last visit
- Concomitant Medications
- Urine pregnancy test (if female of child-bearing potential)
- BCVA
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Anterior Chamber SD-OCT (study eye only) in selected sites only
- Macular OCT (study eye only)
- [redacted]
- Review subject's Dosing Diary by unmasked personnel

5.1.6 Visit 6: Week 7/Day 49 (± 3 days) Follow-up Period:

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
- Concomitant medication update
- Occurrence of any AEs since the last visit
- BCVA
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Anterior Chamber SD-OCT (study eye only) in selected sites only

5.1.7 Visit 7: Week 10/Day 70 (± 3 days) Follow-up Period

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

- Subject-Rated Ocular Pain Assessment – prior to other assessments
- Occurrence of any AE's since last visit
- Concomitant Medications
- BCVA
- Slit-lamp biomicroscopy
- Intraocular pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Anterior Chamber SD-OCT (study eye only) in selected sites only
- Macular OCT (study eye only)

5.1.8 Unscheduled Visits

If at any time during the study, outside of the above scheduled visits, the subject requests or the investigator determines the subject should be assessed for treatment 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.):

- BCVA
- 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 and/or 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 Visit 7 (Week 10).

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 7 (Week 10) will be asked to complete all procedures outlined in Visit 7 (Week 10).

Female subjects of child-bearing potential will also have a UPT performed at the early termination visit. Termination of the study may also occur as determined by the Sponsor, FDA, or other regulatory authorities.

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

Subjects on therapy for their uveitis will not be asked to stop their usual medications, rather they will add TRS01 QID to their current regimen. 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 Director 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 IP and continue study participation through Visit 7.

[redacted] Subjects on rescue therapy due to lack of efficacy should not be withdrawn from the study, but rather followed through the end of the study.

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 first).

The following medications are also specifically permitted during the trial:

- Glaucoma eye drops with the exclusion of Prostaglandins. Note: subjects may be treated with up to two glaucoma eye drops in the study eye. Anti-glaucoma eye drops should be [redacted] before the investigational product dosing.
- Mydriatic agents
- Use of PRN artificial tears up to twice a day
- [redacted]

[redacted]

The above medications, if used at the onset of the trial, must not be discontinued during the course of the trial and the dosing and regimen should remain stable through Visit 5 (end of IP treatment period).

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 (above the permitted dosages outlined in the eligibility criteria and in Section 6.2) that would have a therapeutic effect on inflammation in the anterior segment, other than the IP (e.g., systemic treatment with an immunosuppressant agent, ocular injection of steroids, 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.

The addition or increase in 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.

6.4 MEDICATIONS NOT PERMITTED

Use of the following medications are not permitted either during the study or for the timeframes, frequency or dose levels defined here:

1. Intravitreal or periocular steroids in the study eye within 90 days of Visit 1.
2. Any intravitreal injection within 30 days of Visit 1.
3. Topical ocular therapy with steroids more than BID in the study eye, throughout the IP treatment period.
4. Treatment with systemic steroids >10mg/day, throughout the IP treatment period.
5. Any topical ophthalmic medications (either eye) other than medications specifically allowed as part of the trial, throughout the IP treatment period. 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. Further, changes in the dosing of cycloplegics as needed during the study is allowed.
6. Other investigational drugs or or investigational medical device within 60 days prior to Visit 1.

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 reported adverse 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 3.

TABLE 3: 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.
Intraocular pressure	The IOP measurements will be performed by Goldmann applanation tonometry with a single measurement. IOP pressure recorded in mmHg (e.g., 18 mmHg). IOP measurements will be performed at all study visits,
Dilated Ophthalmoscopy: *Vitreous haze, retina vessels, macula, optic nerve, cup/disc ratio.*	The status of the macula, vessels 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 all visits.
BCVA	The visual acuity test is used via a standardized ETDRS chart.

These ocular safety measures will be summarized using descriptive statistics. For continuous ocular safety measures, changes from Baseline (Day 1/Visit 1) variables will also be summarized descriptively. Safety parameters of interest include a change from baseline to each visit in ocular signs such as corneal/conjunctival tolerability, IOP measurements.

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 causesloss 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 rescue criteria are met and a rescue therapy treatment plan is discussed with the Tarsius Medical Officer:

- If visual acuity in the study eye decreases by >2 lines compared to baseline, which in the opinion of the investigator, is due to non-infectious anterior uveitis.
- [redacted]

If rescue therapy is initiated, the subject will be instructed to discontinue IP. The choice of rescue therapy will be at the discretion of the Investigator. 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.

Any medication administered on Visit 5 (Day 28) after the subject has exited the study will not be considered as rescue therapy.

If possible, during the visit where rescue therapy is initiated, Macular OCT should be performed for the study eye.

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 uveitis status.
- 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 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. At select sites, anterior chamber SD-OCT automated quantification of anterior chamber cells may also be used as a secondary measure of anterior chamber inflammation [Sharma et al., 2015].

8.1 EFFICACY VARIABLES

Efficacy of TRS01 will be assessed by evaluation of anterior chamber inflammation by Investigator assessment with slit-lamp biomicroscopy, and may also be assessed by anterior chamber SD-OCT automated quantification of anterior chamber cells at select sites.

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

8.1.1 Anterior Chamber Cells

Note: The same investigator in each site must assess and score anterior chamber cells and flare across all study visits for an individual subject.

8.1.1.1 Slit-lamp biomicroscopy

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

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

[redacted]

8.1.1.2 Spectral- Domain Optical Coherence Tomography

Anterior chamber SD-OCT imaging will be performed for the study eye on Visit 1/Day 1 after randomization (before first drop administration) and at each subsequent study visit, at select sites. [redacted]

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:

- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

8.1.3 Macular OCT

Both the average center subfield thickness and the macular volume will be evaluated on site by the investigator. Macular OCT will be performed for the study eye at Visit 1, Visit 5 and Visit 7 at select sites. Macular OCT should also be performed for the study eye at the visit where a subject is placed on rescue therapy.

8.1.4 Best Corrected Visual Acuity

BCVA will be assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) charts either retro-illuminated or frontally illuminated at a distance of 4 meters. Visual acuity will be measured with spectacle or pinhole correction at all study visits. The BCVA score and Snellen equivalent will both be recorded.

8.1.5 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 every visit 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 (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, iris color, 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 add in version once finalized) 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 assessments will be summarized as safety outcomes.

9.1.3 Analysis of Efficacy

Efficacy measures will be ACC and flare.

Both Investigator-rated ACC and flare data will be assessed as a change from baseline (Visit 1/Day 1) Weeks 1 through 4 and a descriptive comparison of the two active treatment groups will be performed.

If available, anterior chamber SD-OCT cell data will be assessed as a change from baseline (Visit 1/Day 1) on Weeks 1 through 4 and a descriptive comparison of the two active treatment groups will be performed.

Changes in subject-rated ocular pain assessment on Weeks 1 through 4 will be evaluated via a descriptive comparison between the two active treatment groups.

9.2 SAMPLE SIZE ESTIMATION

This is a Phase I/IIa clinical study to evaluate the safety and tolerability of TRS01 with the sample size of up to 20 randomized subjects, across approximately 2 sites, as proposed by Tarsius. No formal sample size estimation was undertaken as this trial is exploratory in nature.

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. 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.

14.1 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	Visit 7/ ET[1]
Assessment schedule:	Treatment Period					Follow-up Period	
	Day 1	Week 1 Day 7 ±1 day	Week 2 Day 14 ±2 day	Week 3 Day 21 ±2 day	Week 4 Day 28 ±2 day[7]	Week 7 Day 49 ±3 days	Week 10 Day 70 ±3 days
Signed and dated Informed Consent	x						
Medical & Ophthalmic History	x						
Demographics including Iris color	x						
Inclusion/exclusion criteria	x						
Concomitant Medications	x	x	x	x	x	x	x
Urine pregnancy test	x				x		
Subject-rated Ocular Pain Assessment[2]	x	x	x	x	x	x	x
BCVA	x	x	x	x	x	x	x
Slit-lamp biomicroscopy[3]	x	x	x	x	x	x	x
Intraocular pressure	x	x	x	x	x	x	x
Dilated ophthalmoscopy	x	x	x	x	x	x	x
Randomization	x						
Anterior Chamber SD-OCT[4]	x	x	x	x	x	x	x
Macular OCT[4,5]	x				x		x
Adverse events Assessment (AEs)[6]	x	x	x	x	x	x	x
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		

1.Visit 7 is also the Early Termination visit; 2.The Subject-Rated Ocular Pain Assessment must be performed prior to any other assessments; 3. The same investigator must assess and score anterior chamber cells and flare across all study visits for an individual subject.; 4.May be conducted at select sites, on study eye only; 5. Macular OCT should also be performed for the study eye at the visit where a subject is placed on rescue therapy. 6. At Visit 1, 40 min ± 10 min post first administration of investigational product. 7. [redacted]

17 REFERENCES

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4. Sharma S, et al. Automated Analysis of Anterior Chamber Inflammation by Spectral-Domain Optical Coherence Tomography. Ophthalmology. 2015 Jul;122(7):1464-70.
5. Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, Ganguli A. Prevalence of Noninfectious Uveitis in the United States: A Claims-Based Analysis. JAMA Ophthalmol. 2016; 1;134(11):1237-1245.