A Phase 3 Randomized, Active-Controlled, Double-Masked Study to Evaluate the Safety and Efficacy of TRS01 Eye Drops in the Treatment of Subjects with Active Non-infectious Anterior Uveitis including Subjects with Uveitic Glaucoma

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Study Phase:	3
Sponsor:	Tarsier Pharma Ltd. 19 Yahalom Street Zichron Yaacov Israel 3093765
Medical Monitor:	[redacted]

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Protocol Synopsis

Title:	A Phase 3 Randomized, Active-Controlled, Double-Masked Study to Evaluate the Safety and Efficacy of TRS01 Eye Drops in the Treatment of Subjects with Active Non-infectious Anterior Uveitis including Subjects with Uveitic Glaucoma
Phase:	3
Design/Conduct:	Potential study participants will be required to sign an informed consent document and meet all inclusion/exclusion criteria. The main entry criteria are as below: • Subjects who have Active Non-Infectious Anterior Uveitis with an anterior chamber cell (ACC) Grade 2 (6-15 cells) or Grade 3 (16-30 cells) in the study eye. • Subjects must be without treatment for uveitis or be receiving *Stable Medical Therapy* (see definition in Eligibility Criteria section below) and requiring additional treatment in the study eye. Subjects with uveitic glaucoma must also meet <u>at least one</u> of the following criteria in the study eye: [redacted] [redacted] of randomized subjects are planned to meet the criteria for uveitic glaucoma. The enrollment of subjects with uveitic glaucoma will be monitored throughout the study. [redacted] have been randomized that do not meet the criteria for uveitic glaucoma, further enrollment of subjects without uveitic glaucoma will be halted. Once it is determined that all eligibility criteria have been met, subjects will be randomly assigned in a 2:1 ratio, stratified by baseline ACC grade (2 vs. 3) and by uveitic glaucoma diagnosis, to one of two double-masked treatment groups: either TRS01 [redacted] four times per day (QID) or [redacted] QID. The study visit schedule and assessments to be performed at each visit are presented in Schedule of Procedures and Assessments in Appendix 1. **Rescue Therapy** will be considered if one or more of the following rescue criteria in the study eye are met and a rescue therapy treatment plan is discussed with the Medical Monitor (if possible): [redacted]

	[redacted] Note: full details on how rescued subjects will be analyzed are described in the statistical method section of the protocol.
Objective(s):	The primary objective of this study is to evaluate the efficacy and safety of TRS01 [redacted] eye drops compared to [redacted] in subjects with active non-infectious anterior uveitis with or without uveitic glaucoma.
Endpoint(s):	**<u>Primary Endpoint:</u>** [redacted] 1. For Food and Drug Administration (FDA) submission, the proportion of subjects with ACC Grade = 0 (0 cells) on Day 28 in the study eye. 2. For submission to European Medicines Agency (EMA) related countries, the proportion of subjects with ACC Grade = 0 or 1 on Day 28 in the study eye. **<u>Secondary Endpoints:</u>** [redacted] **<u>Powered Key Secondary Efficacy Endpoint</u>:** The powered key secondary endpoint is the change from baseline in ACC Grade on Day 28 in the study eye. [redacted]

	Exploratory endpoints are listed in Section 2.2.3. **Safety Endpoints:** The following safety endpoints will be evaluated and summarized: • Incidence of adverse events (AEs), serious adverse events (SAEs) and complications by severity and relationship to investigational product occurring during the study. • Best corrected visual acuity (BCVA) • Slit-lamp biomicroscopy • Dilated ophthalmoscopy • Change in ocular signs and symptoms including 1) corneal and conjunctival tolerability as assessed by the incidence of ocular treatment-related AEs and 2) intraocular pressure. • Number and percentage who fail to complete the study due to lack of efficacy (need for rescue). • Treatment tolerability by number and percentage of subjects who fail to complete the study due to an AE related to Investigational Product (IP).
Population studied:	The study population will consist of male and female subjects, up to and including 70 years of age (including all pediatric age groups; US only), with active non-infectious anterior uveitis with or without uveitic glaucoma (see Design/Conduct section above) with no treatment or with Stable Medical Therapy (see definition in Eligibility Criteria section below) requiring further treatment in the study eye. **Subjects with Uveitic Glaucoma:** [redacted] of subjects are planned to meet the criteria for uveitic glaucoma. Subjects will be considered to have uveitic glaucoma if they meet at least one of the following: • [redacted] • [redacted] **Pediatric Subject Population:** All pediatric age groups may be included at select sites in the United States (US) only. For further details see Section 4 in the protocol.
Number of subjects:	Approximately 162 subjects: Approximately 108 subjects in the TRS01 [redacted] group and approximately 54 subjects in the [redacted] group.
Number of sites:	Approximately 35 sites in the United States and Europe (EU).
Eligibility criteria:	**Inclusion criteria:** A subject must meet all of the following criteria in order to be eligible for the study: 1. At sites in the US: Male or female up to and including 70 years of age (including all pediatric age groups). At sites in the EU: Male or female between 18 and 70 years of age, inclusive. 2. Able to provide informed consent/assent, or subject's Legally Authorized Representative (LAR) provide consent, follow instructions and complete all required study visits for the duration of the study. 3. Diagnosed with active non-infectious anterior uveitis with anterior chamber cell Grade 2 (6-15 cells) or Grade 3 (16-30 cells) in the study eye that are without any treatment or with Stable Medical Therapy [redacted] requiring further treatment.

4. Have BCVA ≥ 65 letters in the non-study eye using Early Treatment Diabetic Retinopathy Study (ETDRS).
5. Use adequate birth control by men and women, if of reproductive potential and sexually active. If a female subject is currently abstinent, they must agree to use one of the acceptable methods of birth control before they become 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 14 days after the last study visit.
    a. For females of childbearing potential, adequate birth control methods will be defined as hormonal contraceptives or intrauterine device initiated at least 60 days prior to Visit 1, or double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam.
    b. For males with partners who are of child-bearing potential, adequate birth control methods will be defined as double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam or have had a vasectomy for at least 60 days prior to Visit 1.
    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 at least 60 days prior to Visit 1 must be documented, as applicable.

[redacted]

[redacted]

Exclusion criteria:

A subject who meets any of the following criteria is not eligible for the study:

1. Pregnant or breastfeeding females or females with a positive pregnancy test at Visit 1.
2. Have a history of or active significant ocular disease in either eye that, based on the Investigator's judgement, could confound the results of the trial including, but not limited to:
   - [redacted]
3. Uncontrolled intraocular pressure (IOP) (defined as >27mmHg) or narrow angle glaucoma in either eye and/or are at risk of angle closure with dilating. [redacted]
4. Have poor posterior view due to limitation of dilation or media opacity that limits ability to examine the posterior segment.
5. [redacted]
6. Have cancer or melanoma that is actively treated with immunotherapy.
7. Have any clinically significant systemic disease or condition (e.g., hematological, cardiovascular, respiratory, renal 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.

[redacted]

Prohibited Medications and Procedures:	**Medication and Procedures NOT permitted**	**Excluded Timeframe Prior to Visit 1**
	[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]
Investigational product(s):	TRS01 [redacted] and [redacted] will be supplied as investigational product (IP) as a sterile eye drop solution [redacted] packaged in masked 10 mL, sterile, white low-density polyethylene (LDPE) bottles with a standard LDPE controlled dropper tip and white tamper proof caps (high-density polyethylene (HDPE) for TRS01, Polystyrene for prednisolone acetate).
Dosing regimen:	Subjects will be trained to self-administer (or have a caregiver administer) the randomly assigned, masked treatment (either TRS01 [redacted] or [redacted] in the clinic on Visit 1 (Day 1) and then administer one drop QID for 28 days in the study eye. All subjects will return for examination on Day 7, Day 14, Day 21, Day 28, and Day 42.
Assessments/Evaluations:	**Efficacy**: • Subject-Rated Ocular Pain Assessment • Subject-Rated Ocular Photophobia Assessment • Slit-Lamp Biomicroscopy for Assessment of ACC and Flare • Initiation of Rescue Therapy **Safety**: • Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs) • Best Corrected Visual Acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) • Slit-Lamp Biomicroscopy • Intraocular pressure (IOP) by Goldmann applanation tonometry (GAT) • Dilated Ophthalmoscopy • Change in ocular signs/symptoms such as corneal/conjunctival tolerability as assessed by the incidence of ocular treatment-related AEs
Duration of study:	Approximately 6 weeks (42 ± 3 days): 28-day treatment period and 14-day follow-up period.

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1. Introduction

1.1 Background

Uveitis refers to a broad spectrum of ocular inflammatory diseases which are associated with both systemic infectious and non-infectious conditions. Uveitis may affect either the anterior or the posterior segment, or in the case of panuveitis, it can affect the entire eye.

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). Non-infectious uveitis is estimated to be the cause of approximately 30,000 new cases of blindness per year in the United States (Thorne et al., 2016) a number that has not been reduced for the past 30 years (Jiang et al., 1999). Despite available treatment options, prolonged visual loss occurs in two thirds of patients.

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 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 and significant 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 keratic precipitates.

Topical corticosteroids represent first line treatment for non-infectious anterior uveitis (Kim et al., 2018). The side effects associated with steroid use significantly limit prolonged treatment. The most common adverse effects of ocular steroids are cataracts and elevated intraocular pressure (IOP) which can lead to glaucoma. In an effort to minimize the IOP elevation associated with steroid therapy, immunosuppressants may be used to prevent flare ups of uveitis, and in this case a multidisciplinary team may be utilized including specialists from uveitis, glaucoma, internal medicine, pediatrics and rheumatology.

Anterior uveitis in patients with uveitic glaucoma is a unique disease with a significant unmet medical need, where the current standard of care of topical corticosteroids can treat the inflammation but can also significantly contribute to the progression of glaucoma. Based on the literature, approximately 10% to 30% of patients with uveitis will also have glaucoma, either as a result of the disease itself, as the result of steroid treatment, or a combination of both (Cunningham

et al., 2017; Neri et al., 2004). Uveitic glaucoma is an extremely challenging disease to treat, with a unique pathophysiology, disease course, prognosis, and a significantly more difficult clinical course to manage than anterior uveitis without glaucoma.

Given the limitations of treatment of anterior uveitis with uveitic glaucoma, and the poor results, there is a clear unmet need for an effective anti-inflammatory drug that does not have an IOP-elevating effect or the systemic effects of systemic immunosuppressants.

TRS01 is being developed to serve as a non-steroidal alternative to treat anterior uveitis without having an adverse impact on the intraocular pressure or uveitic glaucoma in these subjects.

1.2 Study Rationale

Based on the novel, unique, active pharmaceutical ingredient (API) called TRS, Tarsier Pharma Ltd. (Tarsier) is developing a novel therapeutic approach for the treatment of ophthalmic inflammatory diseases for both the front and back of the eye. TRS01 is the first lead compound for Tarsier for topical treatment of anterior uveitis including patients with uveitic glaucoma and a subsequent second drug (TRS02) will be developed with the same TRS active pharmaceutical ingredient formulated for intravitreal administration [redacted]

TRS01 is a novel, non-steroidal, topical ophthalmic solution for the treatment of anterior uveitis including patients with uveitic glaucoma that has a unique, dual mechanism of action.

TRS is a [redacted]

TRS Pharmacology

In vitro and in vivo studies conducted with TRS (named TPC in publications) to date have revealed an attractive mechanism of action consisting of inhibition of NF-kB by Toll-like receptor 4 (TLR4), and induction of a shift from inflammatory (M1) macrophages to anti-inflammatory (M2) macrophages.

Both intraocular macrophages and TLR4 play a key role in uveitis formation within the eye (Mérida et al., 2015). Macrophages are abundant in the retina and uvea of the eye. Resident and infiltrated macrophages play relevant roles in uveitis as effectors of innate immunity and inductors

of acquired immunity. Studies have identified that macrophages play a crucial role in experimental autoimmune uveitis (Jiang et al., 1999).

Nonclinical Overview

Nonclinical testing for TRS has been performed to establish the mechanism of action as well as the nonclinical safety and efficacy studies with TRS and TRS01 to support clinical development. Anti-inflammatory activity has been demonstrated in multiple ocular and systemic mice models of inflammation. Additionally, safety and tolerability were observed in the in-vitro studies of TRS and in-vivo toxicology studies of TRS01 in two species.

[redacted]

In summary, the results of the completed nonclinical toxicology/safety studies with TRS and the TRS01 formulation support the clinical evaluation of the safety and efficacy of TRS01 in patients.

Clinical Studies

Two Phase 1/2a randomized, double-masked clinical trials have been completed to explore the safety and efficacy of TRS01 in the treatment of post-operative inflammation after cataract surgery (Tarsius 2020) and in non-infectious uveitis (GADOT 20/20).

Tarsius 2020 was a Phase 1/2a 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 following cataract surgery. The results of this study indicate that TRS01 eye drops [redacted] are safe and well tolerated in subjects with post-surgical inflammation following cataract surgery. [redacted]

GADOT 20/20 was a Phase 1/2a randomized, double-masked, dose-ranging study that evaluated the safety and preliminary efficacy of TRS01 eye drops [redacted] in subjects with active non-infectious anterior uveitis. The results of this study indicate that both doses of TRS01 are safe and well tolerated in subjects with non-infectious anterior uveitis. [redacted]

For additional details on the toxicology studies and the respective safety multiples, please refer to the Investigator's Brochure (IB).

1.3 Risk/Benefit Assessment

1.3.1 Known Potential Risks

[redacted]

1.3.2 Known Potential Benefits

[redacted]

[redacted]

1.3.3 Assessment of Benefits and Risks

TRS01 ophthalmic solution has been demonstrated to be safe and well tolerated. No potential risks have been identified in association with TRS01 during its development. In the two Phase 1/2a studies that have been completed, no dose-limited adverse events have been identified. Continuing with the clinical development program of TRS01 at the selected concentration of [redacted] is justified by the anticipated benefits that may be afforded to subjects with non-infectious anterior uveitis, including subjects with uveitic glaucoma.

1.3.3.1 Risks related to COVID -19

The COVID-19 pandemic may result in additional risks to trial participants, site staff and the robustness of the study data.

To ensure the rights, safety and wellbeing of trial participants, the safety of clinical trial staff and data robustness in case of restrictions due to the pandemic, pragmatic and harmonized actions will be taken to maintain the integrity of the trial. All measurers are compliance with the ICH GCP requirements and the Guidance on The Management of Clinical Trials During the Covid-19 (Coronavirus) Pandemic (version 5). All decisions to adjust clinical trial conduct will be based on continued risk assessment by the sponsor or the investigator. As required by the pandemic situation, the sponsor and/or the investigator will implement measures which prioritize trial participant safety and data validity. In case these objectives conflict, trial participant safety always prevails. Any available information concerning COVID-19 testing or infection status, vaccination, or related adverse events or protocol deviations will be recorded in trial documentation.

2. Study Objectives and Endpoints

2.1 Study Objectives

The primary objective of this study is to evaluate the efficacy and safety of TRS01 [redacted] eye drops compared to [redacted] in subjects with active non-infectious anterior uveitis including subjects with uveitic glaucoma.

2.2 Study Endpoints

2.2.1 Primary Efficacy Endpoint

The study has a single primary efficacy endpoint that differs by region. The following primary endpoint will be analyzed first and only if the null hypothesis is rejected will the secondary endpoints be tested.

For Food and Drug Administration (FDA) submission, the primary endpoint is the proportion of subjects with ACC Grade = 0 (0 cells) on Day 28 in the study eye. For submission to European Medicines Agency (EMA) related countries, the primary endpoint is the proportion of subjects with ACC Grade = 0 (0 cells) or 1 (1-5 cells) on Day 28 in the study eye.

2.2.2 Secondary Efficacy Analyses

[redacted]

The powered key secondary endpoint is the change from baseline in ACC Grade on Day 28.

[redacted]

2.2.3 Exploratory Efficacy Analyses

Exploratory efficacy endpoints include:

2.2.4 Safety Analyses

Safety will be evaluated by AEs, changes from baseline in BCVA and IOP measurements, changes in slit lamp biomicroscopy and dilated ophthalmoscopy, the proportion of subjects who fail to complete the study due to lack of efficacy (need for rescue), and the proportion of subjects who fail to complete the study due to an AE related to IP. Pediatric data will only be summarized if it measured in a manner identical to adult subjects.

3. Study Design

3.1 Overall Design of the Study

This is a Phase 3, multicenter, randomized, active-controlled, double-masked trial designed to evaluate the safety and efficacy of TRS01 eye drops ([redacted]) in the treatment of subjects with active non-infectious anterior uveitis including subjects with uveitic glaucoma.

Approximately 162 subjects will be randomized in this study at approximately 35 sites in the United States (US) and the European Union (EU).

Potential study participants, or their Legally Authorized Representative (LAR), will be required to sign an informed consent document and meet all inclusion/exclusion criteria. The main entry criteria are:

- Subjects who have active non-infectious anterior uveitis with an ACC Grade 2 (6-15 cells) or Grade 3 (16-30 cells) in the study eye.
- Subjects must be without treatment for uveitis or be receiving Stable Medical Therapy (see definition in Inclusion Criteria and Section 5.5.1) and requiring further treatment in the study eye.

Subjects will be considered to have uveitic glaucoma if they meet at least one of the following criteria in the study eye:

- [redacted]
- [redacted]

[redacted] of randomized subjects are planned to meet the criteria for uveitic glaucoma. The enrollment of subjects with uveitic glaucoma will be monitored throughout the study. If [redacted] have been randomized that do not meet the criteria for uveitic glaucoma, further enrollment of subjects without uveitic glaucoma may be halted.

Once it is determined that all eligibility criteria have been met, subjects will be randomly assigned in a 2:1 ratio, stratified by baseline ACC grade (2 vs. 3) and by uveitic glaucoma diagnosis, to one of two double-masked treatment groups: either TRS01 [redacted] (approximately 108 subjects) or [redacted] (approximately 54 subjects).

Study subjects will administer the randomly assigned treatment QID for up to 31 days. All study subjects will return for examination on Week 1, 2, 3 and 4 (Treatment Period) with post-treatment evaluation at Week 6 (Follow-up Period).

Treatment assignments will be masked to Tarsier, study subjects, Investigators, and site staff. In order to prevent unmasking, investigational product will be supplied in identical outer packages and will only be dispensed and collected by [redacted] study personnel.

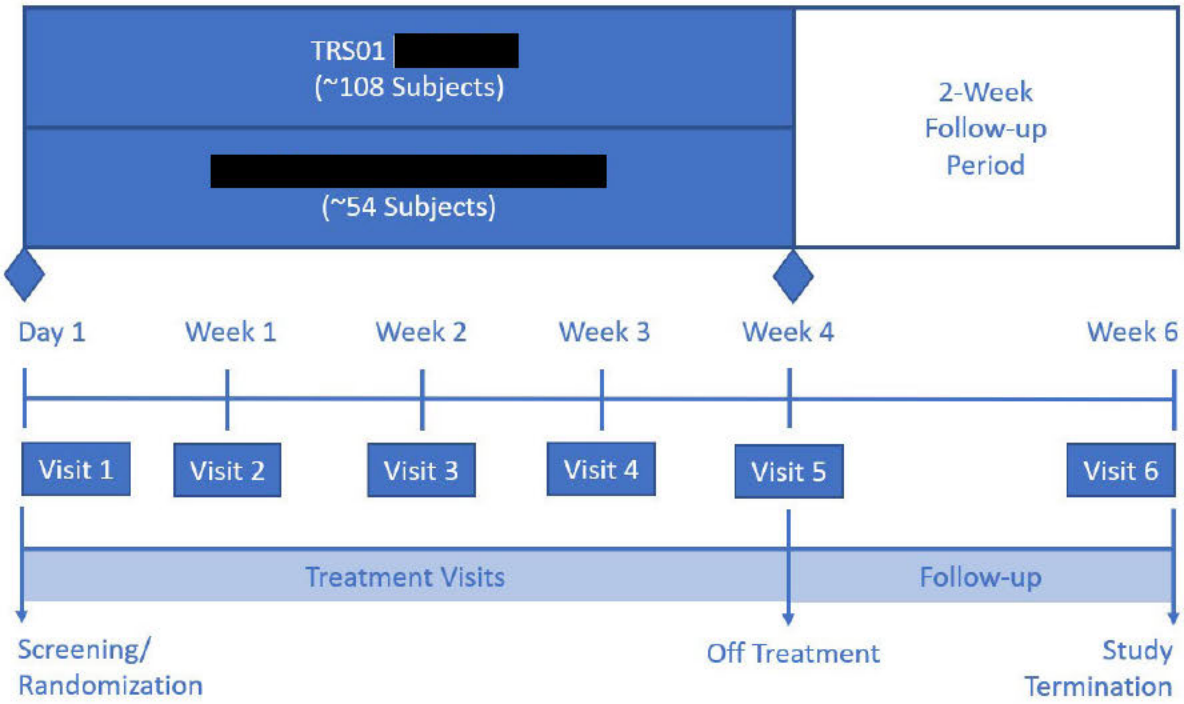
Screening/Randomization Visit: At Visit 1 (Day 1) subjects will be screened for eligibility and randomization to treatment. Subjects who meet all eligibility criteria, including ACC Grade 2 (6-15 cells) or Grade 3 (16-30 cells) in the study eye will be randomized and will initiate dosing with IP in the study eye only. [redacted]

Evaluation Visits: At Visit 2 (Day 7 ±2 days), Visit 3 (Day 14 ±2 days), Visit 4 (Day 21 ±2 days) and Visit 5 (Day 28 ±3 days) subjects will attend clinic visits where efficacy and safety evaluations will be performed. [redacted]

Follow-up Visit: Subjects will return for post-treatment evaluation on Visit 6 (Day 42 ±3 days) and will be exited from the study.

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

Figure 1: Study Schematic



3.2 Rationale for the Study Design

This is a double-masked, active-controlled, [redacted] study in which eligible subjects will be randomized 2:1 to TRS01 [redacted] or the active-control [redacted]

3.3 Dose Justification

The TRS01 dose and dosing regimen selected for this study will be TRS01 [redacted] administered QID to the study eye for 28 days. This is based on the safety demonstrated in the Tarsius 2020 study and the safety and preliminary efficacy demonstrated in the GADOT 20/20, non-infectious anterior uveitis study.

The comparator group was selected as [redacted] administered QID to the study eye for 28 days. QID dosing was chosen to maintain masking [redacted]

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Procedures and Assessments. The end of the study is defined as completion of the last visit or procedure shown in the schedule in the study globally.

4. Study Population

The study population will consist of male and female subjects, up to and including 70 years of age (including all pediatric age groups; US only), with active non-infectious anterior uveitis with or without uveitic glaucoma that are without any treatment or with Stable Medical Therapy (see definition below and in Section 5.5.1) requiring further treatment.

Subjects with Uveitic Glaucoma:

[redacted] of randomized subjects are planned to meet the criteria for uveitic glaucoma. Subjects will be considered to have uveitic glaucoma if they meet <u>at least one</u> of the following criteria in the study eye:

- [redacted]
- [redacted]

Pediatric Subject Population:

Enrollment of pediatric subjects of any age may occur at select sites in the US only. Age-appropriate modifications to the assessments, procedures, and inclusion criteria described herein may be required for pediatric subjects. Requirements for pediatric subjects will be outlined in a separate Pediatric Study Procedure Manual to be provided to the applicable sites.

4.1 Inclusion Criteria

A subject must meet all of the following criteria in order to be eligible for the study:

1. At sites in the US: Male or female up to and including 70 years of age (including all pediatric age groups). At sites in the EU: Male or female between 18 and 70 years of age, inclusive.
2. Able to provide informed consent/assent, or subject's LAR provide consent, follow instructions, and complete all required study visits for the duration of the study.
3. Diagnosed with active non-infectious anterior uveitis with anterior chamber cell Grade 2 (6-15 cells) or Grade 3 (16-30 cells) in the study eye that are without any treatment or with Stable Medical Therapy (as defined below) requiring further treatment.
4. Have BCVA $\geq$ 65 letters in the non-study eye using Early Treatment Diabetic Retinopathy Study (ETDRS).
5. Use adequate birth control by men and women, if of reproductive potential and sexually active. If a female subject is currently abstinent, they must agree to use one of the acceptable methods of birth control before they become 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 14 days after the last study visit.

a. For females of childbearing potential, adequate birth control methods will be defined as hormonal contraceptives or intrauterine device initiated at least 60 days prior to Visit 1, or double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam.
b. For males with partners who are of childbearing potential, adequate birth control methods will be defined as double barrier contraception, i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam or have had a vasectomy for at least 60 days prior to Visit 1.
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 at least 60 days prior to Visit 1 must be documented, as applicable.

Stable Medical Therapy: Permitted Stable Medical Therapy includes the following systemic or topical therapies, for uveitis or other underlying disease or condition:

[redacted]

[redacted]

4.2 Exclusion Criteria

A subject who meets any of the following criteria is not eligible for the study:

1. Pregnant or breastfeeding females or females with a positive pregnancy test at Visit 1.
2. Have a history of or active significant ocular disease in either eye that, based on the Investigator's judgement, could confound the results of the trial including, but not limited to:
   [redacted]
3. Uncontrolled IOP (defined as >27mmHg) or narrow angle glaucoma in either eye and/or are at risk of angle closure with dilating. [redacted]
6. Have cancer or melanoma that is actively treated with immunotherapy.
7. Have any clinically significant systemic disease or condition (e.g., hematological, cardiovascular, respiratory, renal 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.
   [redacted]

12. Use of the following medications and procedures in the study eye are prohibited within the excluded timeframe prior to Visit 1 as defined below (See Table 3: Prohibited Medications and Procedures) and through the end of the study (Visit 6), unless otherwise noted.

Prohibited Medications and Procedures

Medication and Procedures NOT permitted	Excluded Timeframe Prior to Visit 1
[redacted]	[redacted]

4.3 Determination of Study Eye

The study eye will be identified by the investigator from eyes that have ACC Grades 2 or 3 that meet entry criteria. The selection of study eye will allow subjects to be assigned to the appropriate randomization strata according to ACC grade.

[redacted]

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. Minimal information including demography, screen failure details, eligibility criteria, and any adverse event will be recorded.

Participants who do not meet the criteria for participation in the trial at the completion of Visit 1 and are not administered IP may be rescreened. Rescreened participants should be assigned a new subject identification number and all Visit 1 assessments must be repeated, including obtaining of written informed consent.

5. Study Treatment(s) or Intervention(s)

5.1 Investigational Product(s)

The IPs administered during this study will be:

1. TRS01 [redacted]
2. [redacted]

5.1.1 Description

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

[redacted] will be used as the active control. [redacted] is a topical anti-inflammatory agent for ophthalmic use.

Subjects are expected to administer, or have a care provider administer, one drop QID of TRS01 [redacted] or [redacted] in the study eye.

Table 1: Active Investigational Product

Product:	TRS01 [redacted]
Dosage Form:	Ophthalmic solution [redacted]
Unit dose:	[redacted]
Route of administration:	Topical ocular administration
Physical description:	[redacted]
pH	[redacted]
Excipients (Function):	[redacted]
Manufacturer:	[redacted]

	[redacted]

Additional details may be found in the IB.

Table 2: Active Comparator

Product:	[redacted]
Dosage Form:	Ophthalmic [redacted]
Unit dose:	[redacted]
Route of administration:	Topical ocular administration
Physical description:	[redacted]
pH	[redacted]
Excipients (Function):	[redacted]
Manufacturer:	[redacted]

Additional details may be found in the [redacted] package insert.

5.1.2 Dosage and Administration

Eligible subjects will be randomized in a 2:1 ratio to receive sterile ophthalmic solution of TRS01 [redacted] or [redacted] respectively, for the 28-day treatment period. All doses will be administered QID as eye drops in the inferior conjunctival fornix of the study eye only.

The randomized IP kit consists of a masked outer box with one dropper bottle of IP each (either one bottle of TRS01 [redacted] or one bottle of [redacted]

[redacted]

5.2 Preparation/Storage/Handling/Accountability

5.2.1 Acquisition and Accountability

Randomized IP kits will be shipped to the investigational sites under sealed conditions. Shipment records will be verified by comparing the shipment inventory sheet to the actual quantity received at the site. Accurate records of receipt and disposition of the investigational product (e.g., dates, quantity, subject number, date dispensed, date returned) must be maintained by the Investigator or their designee.

The used and unused IP kits will be maintained at the site for accountability by the study monitor. After initial receipt, the IP may only be distributed and handled by [redacted] site personnel.

At the end of the study, all used and unused investigational product will be returned to Tarsier (or designee), following approval by Tarsier. All returns of investigational product will be documented. The study monitor (or designee) will verify IP accountability. All IP accountability procedures must be completed before the study is considered complete.

5.2.2 Product Formulation, Appearance, Packaging and Labeling

[redacted]

Each randomized IP kit consists of a masked outer box with one dropper bottle of IP [redacted]

The double-masked labels will minimally contain the following information:

- Sponsor's name and address
- Kit Number
- Required statement(s) per regulatory agency

5.2.3 Product Storage and Stability

TRS01 [redacted] will be received at 35-46°F/2-8°C and will be stored and remain at 35-46°F/2-8°C in a secure, locked, dark, temperature-controlled and monitored, 35-46°F/2-8°C refrigerator with restricted access until time of dispensation. The clinical site staff will maintain an IP temperature log verifying the temperature each business day. [redacted]

[redacted] will be received and stored in accordance with the conditions specified in the package insert and IP Handling Guidelines in a secure, locked, dark, temperature-controlled area with restricted access until time of dispensation. The clinical site staff will maintain an IP temperature log verifying the temperature each business day. [redacted]

5.2.4 Preparation

Neither the TRS01 [redacted] nor the [redacted] will require on site preparation by the investigator.

5.3 Measures to Minimize Bias: Randomization and Blinding

Subjects will be randomized to a treatment assignment. If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data.

A randomization schedule will be generated by a qualified biostatistician independent of the study conduct and project team and maintained in a secure and limited-access location separate from the study Investigator and members of the project team.

In order to prevent unmasking during the study, the IP (either TRS01 [redacted] or [redacted]) will be supplied in identical masked outer boxes identified with kit numbers.

Treatment assignments will be masked to the Sponsor, subjects, investigators and select investigative staff, until completion of the study and the final database is locked. [redacted]

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise and if time permits, the decision to unmask an individual subject's treatment assignment is to be made jointly by the Investigator and Sponsor's medical monitor after consultation with the Sponsor, thus leaving the masking of the remaining subjects intact.

5.4 Treatment Compliance

IP will be administered to the study eye QID for up to 28 ± 3 days. 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 IP administration in a dosing diary, beginning at Day 1 and for the duration of the treatment period.

Compliance with administration of the IP will be assessed at Visits 2, 3, 4 and 5 via review of the subject dosing diary. The subject dosing diary will be formatted to document the daily instillation of the drop. Subjects should be instructed to bring their diary to each study visit during the treatment period to be collected and checked to confirm compliance. Any missed doses will be recorded in the electronic Case Report Form (eCRF). At these visits, subjects will be queried by site staff regarding compliance with the dosing regimen.

Adherence to the dosing protocol will be assessed and verified via review of the subject dosing diary and IP return accountability by the site staff and study monitor.

5.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the case report form are concomitant prescription medications, over-the-counter medications and supplements.

All medications that the subject has taken within 90 days prior to Visit 1 through Visit 6 (or Early Termination Visit) will be recorded. In addition, all Severe Acute Respiratory Syndrome – Coronavirus 2 (SARS-Cov-2) Coronavirus Disease of 2019 (COVID-19) vaccinations received by the subject 90 days prior to Visit 1 or through Visit 6 (or Early Termination Visit) should also be recorded. At each study visit, subjects will be questioned concerning any new medications or changes in their current concomitant medications (CMs) since their previous study visit.

The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication and whether or not the medication was taken due to an adverse event or as rescue therapy will be recorded for each medication. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), version 2021-03 or later, if applicable.

5.5.1 Permitted Medications

Stable Medical Therapy:

Permitted Stable Medical Therapy includes the following systemic or topical therapies, for uveitis or other underlying disease or condition:

[redacted]

Other Permitted Medications:

The following medications are also specifically permitted in the study eye as outlined below:

- Glaucoma medications

[redacted]

5.5.2 Rescue Medication

[redacted]

5.5.2.1 Criteria for Rescue Therapy

Rescue therapy will be considered if one or more of the following rescue criteria in the study eye are met and a rescue therapy treatment plan is discussed with the Medical Monitor (if possible):

[redacted]

Any subject placed on rescue therapy will discontinue use of the IP and continue study participation through Visit 6 (Day 42). The choice of rescue therapy will be at the discretion of the Investigator.

[redacted]

5.5.3 Prohibited Medications and Procedures

The following medications and procedures are not permitted in the study eye for the excluded timeframe prior to Visit 1 as defined below (See Table 3, Prohibited Medications and Procedures) and through the end of the study (Visit 6), unless otherwise noted.

Table 3: Prohibited Medications and Procedures

Medication and Procedures NOT permitted	Excluded Timeframe Prior to Visit 1
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

*[redacted]

6. Study Discontinuation/Participant Withdrawal

6.1 Discontinuation of Study Treatment or Intervention

Investigational Product may be discontinued by a subject at any time. In addition, the Investigator or Sponsor can discontinue a subject from further IP administration for other reasons related to the best interest of the subject. Further, any subject placed on rescue therapy will be instructed to discontinue use of the IP, as outlined in Section 5.5.2.1.

In the event of discontinuation of IP by a subject, the Investigator should make every attempt to have the subject remain in the study for follow up through Visit 6 (Day 42).

6.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Withdrawal of consent
- Study terminated by the Sponsor, US FDA or other regulatory authorities
- Pregnancy
- Significant study treatment/intervention non-compliance
- If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. [redacted] the subject must discontinue use of IP, complete the Visit 6/Early Termination Visit assessments, and be exited from the study.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Participants who sign the informed consent form and are randomized but do not receive the study treatment may be replaced.

Those who sign the informed consent form and are randomized and receive the study treatment and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

In the event of study discontinuation, the Investigator should make every attempt to have the subject complete the Visit 6 (Day 42) assessments as soon as possible. The reason for premature discontinuation should be recorded in the subject chart and entered in the eCRF.

6.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file;
- Should the participant continue to be unreachable before completion of the IP treatment period (Visit 5), he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7. Study Procedures

Written informed consent or assent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained from all participants or the subject's LAR, for subjects under 18 years of age, prior to any study-related procedures being performed. Ophthalmological examination will be performed in both eyes.

[redacted]

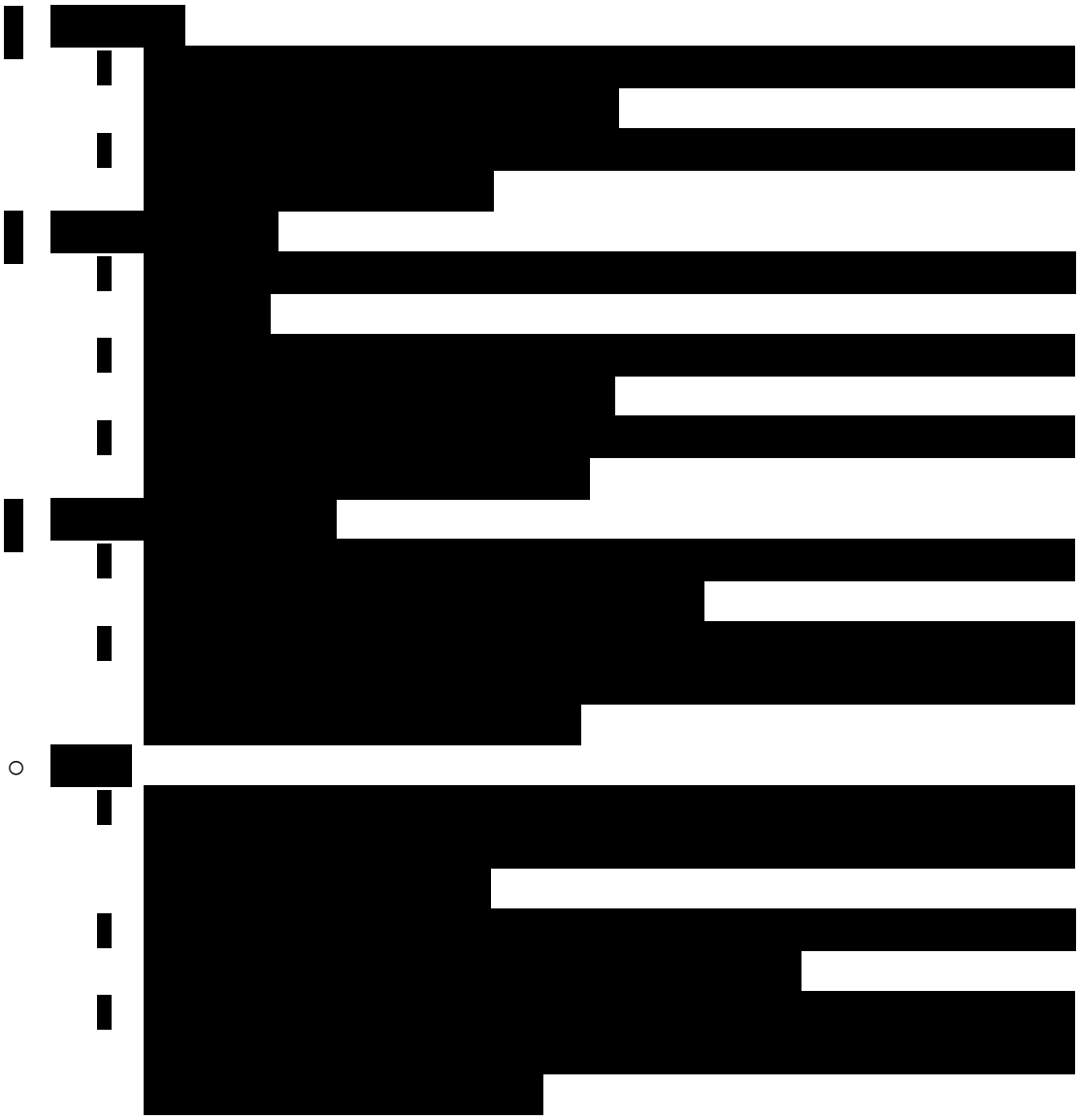
The Schedule of Procedures and Assessments (Appendix 1) lists the procedures that should occur at each study visit. Visit assessments should be performed in the order suggested below. Note: assessments marked with an asterisk (*) may be performed at any time during the visit to accommodate subject and site schedules.

7.1 Visit Descriptions

7.1.1 Screening/Randomization (Visit 1, Day 1)

The visit should be scheduled to occur in the morning, if possible, to allow for QID dosing on Day 1 for randomized subjects. The following procedures will be performed on all participants at the screening/randomization visit:

- Explain the purpose and conduct of the study to the subject, answer the subject's questions, and obtain written informed consent/assent and HIPAA authorization.
- Assign the Subject Identification Number: format will be XXX-001 where XXX represents the site number and the last three digits represent the unique subject number.*
- Obtain the following information: demographics [redacted] CMs, ocular and systemic medical and surgical history (including uveitis disease course).*
- Review study eligibility based on Inclusion/Exclusion criteria.
- Subject-Rated Ocular Pain Assessment. **Note:** Must be performed prior to other assessments.
- Subject-Rated Ocular Photophobia Assessment. **Note:** Must be performed after the Subject-Rated Ocular Pain Assessment.
- Urine pregnancy test (UPT) for all eligible women of child-bearing potential*
- Evaluate uveitis history and collect documentation of test results [redacted]



- ETDRS BCVA
- Slit-lamp Biomicroscopy
- Intraocular Pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Determine if subject is eligible for randomization

For eligible subjects, the following is the process regarding administration of double-masked IP whereby the trained site staff will conduct the following procedures:

- Enter subject information into Interactive Web Randomization System (IWRS) to determine assigned kit number.
- Dispensation of IP and Dosing Diary: The [redacted] site personnel will retrieve the assigned kit, in the masked outer box, and provide to the subject. The subject will be

instructed to self-administer (or have a caregiver administer) the first drop, under the supervision of [redacted] site personnel, prior to leaving the clinic. The subject will be instructed to record this first dose and all subsequent doses in the provided Dosing Diary.

- [redacted] minutes post IP administration the subject will be assessed for any AEs.
- The subject will be instructed to take the bottle, within the masked outer box, home and administer the IP up to three more times (depending on the time of the visit), but approximately every four hours during their waking 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.
- **Note:** Subjects should be reminded to continue on their previous regimen of any permitted medications and that dosing should remain stable throughout the IP treatment period (Note: [redacted]

7.1.2 Visit 2 (Day 7 ± 2 days) - Evaluation

The following procedures will be performed on Visit 2 (Week 1/Day 7):

- Subject-Rated Ocular Pain Assessment. **Note**: Must be performed prior to other assessments.
- Subject-Rated Ocular Photophobia Assessment. **Note**: Must be performed after the Subject-Rated Ocular Pain Assessment.
- Update CMs since last visit*
- Occurrence of AEs since last visit*
- ETDRS BCVA
- Slit-lamp Biomicroscopy. [redacted]
- Intraocular Pressure by Goldmann Applanation Tonometry
- Review and collection of subject's Dosing Diary*
- Dispense new Dosing Diary to subject and emphasize importance of compliance.
- [redacted]

7.1.3 Visit 3 (Day 14 ± 2 days) - Evaluation

The following procedures will be performed at Visit 3 (Week 2/Day 14):

- Subject-Rated Ocular Pain Assessment. **Note**: Must be performed prior to other assessments.

- Subject-Rated Ocular Photophobia Assessment. **Note**: Must be performed after the Subject-Rated Ocular Pain Assessment.
- Update CMs since last visit*
- Occurrence of AEs since last visit*
- ETDRS BCVA
- Slit-lamp Biomicroscopy
  - [redacted]
- Intraocular Pressure by Goldmann Applanation Tonometry
- Review and collection of subject's Dosing Diary*

[redacted]

- Dispense new Dosing Diary to subject and emphasize importance of compliance.

7.1.4 Visit 4 (Day 21 ± 2 days) - Evaluation

The following procedures will be performed on Visit 4 (Week 3/Day 21):

- Subject-Rated Ocular Pain Assessment. **Note**: Must be performed prior to other assessments.
- Subject-Rated Ocular Photophobia Assessment. **Note**: Must be performed after the Subject-Rated Ocular Pain Assessment.
- Update CMs since last visit*
- Occurrence of AEs since last visit*
- ETDRS BCVA
- Slit-lamp Biomicroscopy. [redacted]
- Intraocular Pressure by Goldmann Applanation Tonometry
- Review and collection of subject's Dosing Diary*
- Dispense new Dosing Diary to subject and emphasize importance of compliance.
- [redacted]

7.1.5 Visit 5 (Day 28 ± 3 days) – Evaluation and End of Treatment Period

[redacted]

The following procedures will be performed at Visit 5 (Week 4/Day 28 ±3 days).

- Subject-Rated Ocular Pain Assessment. **Note**: Must be performed prior to other assessments.
- Subject-Rated Ocular Photophobia Assessment. **Note**: Must be performed after the Subject-Rated Ocular Pain Assessment.
- Update CMs since last visit*
- Occurrence of AEs since last visit*
- Urine Pregnancy Test (woman of child-bearing potential)*
- ETDRS BCVA
- Slit-lamp Biomicroscopy. **Note**: wait at least 40 minutes from the time of the last IP administration prior to assessment.
- Intraocular Pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy
- Review and collection of subject's Dosing Diary*
- [redacted]

7.1.6 Visit 6 (Day 42 ± 3 days) – Follow up Visit

The following procedures are to be performed at Visit 6 (Week 6/Day 42):

- Subject-Rated Ocular Pain Assessment. **Note**: Must be performed prior to other assessments.
- Subject-Rated Ocular Photophobia Assessment. **Note**: Must be performed after the Subject-Rated Ocular Pain Assessment.
- Update CMs since last visit*
- Occurrence of AEs since last visit*
- ETDRS BCVA
- Slit-lamp Biomicroscopy
- Intraocular Pressure by Goldmann Applanation Tonometry
- Dilated Ophthalmoscopy

7.1.7 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 (e.g., for treatment of an AE), an unscheduled visit may occur. Unscheduled visits may include but are not limited to, reporting AEs, changes in concomitant medications, or ophthalmic assessments conducted at the discretion of the Investigator.

7.1.8 Early Termination

In the event that a subject exits or is terminated from the study prior to the Follow up visit (Visit 6), every attempt will be made to ensure that all Visit 6 assessments are performed prior to the subject being discharged from the study. In addition to the Visit 6 assessments, the used IP kit (bottle within masked outer box) will be collected by [redacted] site personnel, the subject's dosing diary will be reviewed and collected, and women of child-bearing potential will also have a UPT performed at the early termination visit.

7.1.9 Virtual (Telehealth) Visit

On-site study visits are strongly preferred. Study visits must be conducted on-site, unless prohibited due to an extenuating circumstance such as COVID-19 infection or quarantine of site personnel or trial participant.

Please note the following important points regarding telehealth visits:

- If a trial participant is unable to come to the investigational site for protocol-specified visits, a telehealth visit is permitted (i.e. phone contact or virtual visit).
- The telehealth visit should be completed in accordance with the protocol-specified visit windows.
- The following protocol assessments should be performed during a telehealth visits, if possible:
    - Review and update of Concomitant Medications since last visit
    - Assess for occurrence of Adverse Events since last visit
    - If subject has access to subject-rated assessments (Ocular Pain and Ocular Photophobia), the site staff should review instructions and ensure the subject completes the subject-rated assessments during the telehealth visit.
    - Dosing compliance reminder for Investigational Product and any other permitted stable medical therapy.
    - Assess Dosing Diary for completion and dispense new Dosing Diary
    - Provide any other necessary study reminders, including date of next study visit
- The following protocol assessments will not be performed during a telehealth visit:
    - Best Corrected Visual Acuity Exam, Slit-lamp Biomicroscopy, Intraocular Pressure, Dilated Ophthalmoscopy Exam

8. Study Assessments

The Schedule of Procedures and Assessments (Appendix 1) provides a list of study assessments and evaluations to be performed and the timing of each. Modifications will be implemented for pediatric subjects as detailed in Section 4.

8.1 Efficacy Evaluations

Efficacy assessments will be conducted at the time points indicated on the Schedule of Procedures and Assessments (Appendix 1) and as detailed in the appendices referenced below.

- Subject-Rated Ocular Pain Assessment (Appendix 3)
- Subject-Rated Ocular Photophobia Assessment (Appendix 4)
- Slit-Lamp Biomicroscopy for Assessment of ACC and Flare (Appendix 6)
- Initiation of rescue therapy

8.2 Safety Evaluations

Safety assessments will be performed at the time points indicated on the Schedule of Procedures and Assessments (Appendix 1) and as detailed in the appendices referenced below.

- AE monitoring
- Best Corrected Visual Acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) (Appendix 5)
- Slit-Lamp Biomicroscopy (Appendix 6)
- Intraocular pressure (IOP) by Goldmann applanation tonometry (Appendix 7)
- Dilated Ophthalmoscopy (Appendix 8)
- Change in Ocular Signs/Symptoms such as corneal/conjunctival tolerability as assessed by the incidence of ocular treatment-related AEs

8.2.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Adverse events (AEs) will be monitored throughout the study. Participants and/or participant's LAR or parent (in US sites, if applicable) will be encouraged to report any adverse findings during the study whether or not they are related to IP. These can be collected either in an unsolicited fashion without any prompting or in response to a general question such as: "Have you noticed anything different since you/your child started the study; began the IP, etc.?"

All AEs will be captured on the appropriate eCRF. Information to be collected at minimum includes event description, onset, assessment of severity, relationship to IP, and outcome. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), current version.

SAEs will be followed for outcome information until resolution or stabilization.

Adverse events will be collected for subjects following signing of the informed consent form (ICF) through the end of the study. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. If the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. However, lack of efficacy, uveitis symptoms and the need for rescue therapy in the study eye should not be considered an Adverse Event.

8.2.1.1 Definitions

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening AE,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2.1.2 Classification of Adverse Events

Severity of Adverse Events

The severity of all AEs will be assessed by the Investigator and graded as follows:

- **Mild:** requires minimal or no treatment and do not interfere with the participant's daily activities;

- **Moderate:** results in a low level of inconvenience or concern and may cause some interference with functioning;
- **Severe:** interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. The term "severe" does not necessarily equate to "serious".

Relationship of Adverse Events

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the IP must always be suspect.

- **Unrelated:** no reasonable possibility that the administration of the IP caused the event, no temporal relationship between the IP and event onset, or an alternate etiology has been established;
- **Possibly Related:** some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events);
- **Related:** is known to occur with the IP, is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or is not listed at the specificity or severity that has been observed or is not consistent with the risk information described in the protocol. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB or package insert as occurring with a *class of drugs* (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the IP, but are not specifically mentioned as occurring with the particular IP under investigation.

The Investigator will be responsible for determining whether an AE is unexpected, i.e., if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IP.

8.2.1.3 Adverse Event Reporting Requirements

According to applicable regulations, an Investigator must immediately report within 24 hours to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor (See 21 US Code of Federal Regulations [CFR] 312.64(b)).

According to applicable regulations, the Sponsor must notify all concerned authorities and ECs of

- all SAEs resulting in death no later than seven days after receiving the initial report form the Investigator.
- All SAE meeting the criteria of a SUSAR (Serious Unexpected Suspected Adverse Drug Reaction) no later than seven days after receiving the initial report form the Investigator if it is fatal, and within 15 days in all other cases.

8.2.1.4 Other Events of Interest

Not applicable.

8.2.1.5 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until 30 days after the discontinuation of the study medication.

Any report of pregnancy for any female study subject must be reported within 24 hours to the Sponsor or its delegate using the Pregnancy Report Form. The pregnant female study subject must be withdrawn from the study.

The course and outcome of the pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child should be documented and reported.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to the Sponsor or its delegate using the Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE to the Sponsor or its delegate.

9. Statistical Considerations

Study Design and Objectives:

This study is planned as a prospective, two-arm, double-masked, multi-center, randomized, active-controlled [redacted] study, designed to assess the safety and efficacy of TRS01 [redacted] eye drops in the treatment of active non-infectious anterior uveitis patients including patients with uveitic glaucoma.

If not specified otherwise, continuous measures will be summarized descriptively by the mean, standard deviation, median, minimum, and maximum values. Categorical measures will be summarized by the frequency and percentage of subjects.

[redacted]

9.1 Statistical Hypothesis

[redacted]

9.2 Sample Size Determination

[redacted]

9.3 Analysis Populations

The Full Analysis Set (FAS) consists of all subjects who were randomized who retrospectively met the inclusion criteria for non-infectious uveitis and received at least one dose of double-masked study medication. Subjects will be analyzed in the group to which they were randomized. This set will be used for the analysis of all efficacy endpoints as the primary analysis population.

The Modified Full Analysis Set (mFAS) consists of all subjects who were randomized who retrospectively met the inclusion criteria for non-infectious uveitis and received at least six doses of double-masked study medication. Subjects will be analyzed in the group to which they were randomized. This set will be used as a sensitivity analysis for the primary, powered key secondary, and key secondary endpoints.

The Per Protocol Analysis Set will include all subjects who completed the treatment period in compliance with the protocol and received at least six doses of double-masked study medication, retrospectively met the inclusion criteria for non-infectious uveitis and who followed the protocol without significant deviations. The determination of significant protocol violations will be made prior to locking the final database and unmasking. Subjects will be analyzed in the group to which they were treated. This set will be used for sensitivity analyses of the primary, powered key secondary, and key secondary endpoints.

The Safety Analysis Set will include all subjects who took at least one dose of investigational product as indicated on the dosing record. Subjects will be analyzed in the group according to the

treatment received. All safety variables will be analyzed using the Safety Analysis Set and only observed data will be included (i.e., missing data will remain missing for the safety analysis).

9.4 Statistical Analyses

9.4.1 Baseline Descriptive Analyses

Demographic characteristics including age (years), sex, race, ethnicity, [redacted] and baseline disease characteristics will be summarized by cohort and overall. Medical history (coded using version 24.1 or later of MedDRA), and prior and concomitant medications (coded using version 2021-03 or later of the WHO-DD) will be summarized by cohort and overall.

The numbers of subjects who were enrolled and completed each visit of the study will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, poor compliance, rescue due to lack of efficacy). A list of discontinued subjects, protocol deviations, and subjects excluded from the analysis sets will be provided as well.

Time to study withdrawal due to lack of efficacy will be assessed and presented by Kaplan-Meier curves and may be compared using the Log-Rank test.

9.4.2 Efficacy Analyses

[redacted]

9.4.2.1 Primary Efficacy Analyses

For FDA submission, the primary efficacy analysis is for the proportion of subjects achieving ACC Grade=0 on Day 28 in the study eye. For submission to EMA related countries, the primary efficacy analysis is for the proportion of subjects achieving ACC Grade=0 or 1 on Day 28 in the study eye. The frequency and percentage and two-sided 95% confidence interval of subjects achieving ACC Grade=0 or ACC Grade=0 or 1 at each visit will be presented by treatment group.

[redacted]

[redacted]

9.4.2.2 Secondary Efficacy Analyses

The powered key secondary endpoint is the change from baseline in ACC Grade on Day 28 in the study eye.

[redacted]

[redacted]

9.4.3 Safety Analyses

Safety analyses will be performed on all subjects in the Safety Analysis Set. The assessment of safety will be based on the summary of ocular and non-ocular AEs, BCVA, IOP, treatment tolerability and ophthalmic exams using slit-lamp biomicroscopy and dilated ophthalmoscopy. Summaries will be provided by treatment group, and for ocular assessments separately by study-eye and non-study-eye.

9.4.3.1 Adverse Events

AEs will be coded using MedDRA (most current version) and categorized by system organ class using preferred terms. Separate summaries of AEs related to treatment (as reported by the investigator) and by severity will be presented. The number of deaths and SAEs will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

9.4.3.2 Clinical Laboratory Tests

Laboratory tests including [redacted] (as outlined in Section 7.1.1) will be performed at each site's preferred local laboratory(ies). Test results and date of results will be entered into the eCRF.

9.4.3.3 Other Safety Evaluations

Summary statistics for observed and change from baseline for BCVA and IOP will be presented. Abnormalities in slit-lamp biomicroscopy and dilated ophthalmoscopy will be summarized by frequency and percentage. Treatment tolerability will be compared by summarizing the percent of subjects who fail to complete the study due to an AE related to IP.

9.5 Interim Analysis

[redacted]

[redacted]

9.6 Subgroup Analyses

Subgroup analysis of the primary and powered secondary endpoint and key secondary efficacy endpoints may be performed to assess a potential differential effect of the treatment across different subgroups. The following sub-groups may be considered:

- Demographic and subjects' characteristics data [redacted]
- Baseline ACC Grade 2 versus Grade 3;
- Subjects with and without uveitic glaucoma;
- [redacted]
- Compliant versus non-compliant subjects;
- Region (US vs OUS);
- Subjects with and without stable medical therapy.

9.7 Exploratory Analyses

[redacted]

9.8 Missing or Unused Data

[redacted]

[redacted]

Safety analyses will use observed data only.

9.9 Pooling

Subgroup analysis of the primary efficacy endpoints by region (US vs. OUS) will be used to evaluate the poolability of the results. [redacted]

9.10 Tabulation of Individual Participant Data

All data collected in this study will be presented in individual subject data listings for all subjects.

9.11 Data Safety Monitoring Committee

[redacted]

10. Supporting Documentation and Operational Considerations

10.1 Regulatory Issues, Ethical Concerns, and Study Oversight

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent Documents

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to any procedures being done specifically for the study.

10.1.1.2 Consent Procedures and Documentation

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

For participants who are unable to provide legal consent, their legally acceptable representative will be fully informed of the risks and requirements of the study and, during the study, they will be given any new information that may affect their decision to continue the potential subject's participation. They will be told that their consent for the participation of the potential subject in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects will be enrolled whose legally acceptable representatives are fully able to understand the potential risks and benefits of the study and provide their consent voluntarily.

When referring to the signing of the ICF, the terms legal guardian and legally authorized representative refer to the legally appointed guardian with authority to authorize participation in research. If the subject is <18 years of age (US only), his or her parent(s) (preferably both parents, if available) or legally authorized representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments.

Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies and local regulations. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally authorized representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause or at Sponsor's discretion for any reason. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) Sponsor and regulatory authorities as applicable. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/EC and/or FDA.

10.1.3 Confidentiality and Privacy

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

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

The Study Monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product will be able to inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (i.e., office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at [redacted] This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by [redacted] research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at [redacted]

10.1.4 Clinical Monitoring

[redacted] will conduct the clinical monitoring for this study for sites in the US and EU, respectively. A clinical Monitoring Plan (MP) is to be used, which will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed and the distribution of monitoring reports.

In exceptional circumstances, such as the COVID-19 pandemic, the conditions under which site visits are conducted may change in order to meet local and government regulations. In addition to planned study procedures, the sites may take additional measures to ensure the safety of patients and site staff, such as establishing phone contact prior to study visits, requesting additional information about the patients' health conditions at the time of visits in order to determine whether

there is a risk that they are infected (e.g. by questionnaire), additional physical examinations, and the requirement to wear personal protective equipment (e.g. face mask, gloves). Remote monitoring visits may only be conducted to the extent that data safety and privacy are not jeopardized.

Should any of the additional measures related to COVID-19 constitute a substantial amendment to the study protocol, they will only be implemented after having received approval by Competent Authorities and concerned Ethics Committees.

10.1.5 Quality Assurance and Quality Control

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

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements (e.g., GLP, Good Manufacturing Practice [GMP]).

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

10.1.6 Data Handling and Record Keeping

10.1.6.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site's Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to insure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into [redacted], a 21 CFR Part 11-compliant electronic data capture system provided by [redacted] The data

system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

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. When applicable, all personal data will be collected and processed in compliance with the European Union General Data Protection Regulation – GDPR (Regulation n. 2016/679). As per the definitions of GDPR, Tarsier Pharma is considered the sole Data Controller in this study, whereas [redacted] assume the role of Data Processor.

10.1.6.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of major deviations, corrective actions are to be developed by the site and implemented promptly. Details concerning minor, major and critical protocol deviations will be outlined in the Clinical Management Plan (CMP).

It is the responsibility of the site's Investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to the IRB (as applicable), the Contract Research Organization (CRO) and/or Sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.8 Publication and Data Sharing 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 the Sponsor.

11. References

1. Cunningham ET, Zierhut M. (2017) Uveitic Ocular Hypertension and Glaucoma. Ocular Immunology & Inflammation 25(6): 737–739.

2. Jiang HR, Lumsden L, and Forester JV. (1999) Macrophages and dendritic cells in IRBP-induced experimental autoimmune uveoretinitis in B10RIII mice. Investigative Ophthalmology Visual Science. 40 (13) 3177–3185.

3. Kim T, Sall K, Holland EJ, Brazzell RK, Coultas S, Gupta PK. Safety and efficacy of twice daily administration of KPI-121 1% for ocular inflammation and pain following cataract surgery. Clin Ophthalmol. 2018 Dec 27;13:69-86.

4. Mérida S, Palacios E, Navea A, Bosch-Morell F. Macrophages and uveitis in experimental animal models. Mediators of Inflamm. 2015; 2015:671417.

5. Neri P, Azuara-Blanco A, Forrester JV. Incidence of glaucoma in patients with uveitis. J Glaucoma. 2004 Dec;13(6):461-5.

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7. Sheppard J, Garg S, Lievens C, et al. Iontophoretic dexamethasone phosphate compared to topical prednisolone acetate 1% for noninfectious anterior segment uveitis . Am J Ophthalmol. 2020 211:76–86.

8. 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 Nov1;134(11):1237-1245.

9. Guidance on The Management of Clinical Trials During the Covid-19 (Coronavirus) Pandemic (version 5).

12. Appendix

12.1 Appendix 1: Schedule of Procedures and Assessments

	Treatment Period					Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6/ET[1]**
Week		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**
Study Day (window)	**Day 1**	**Day 7 (± 2)**	**Day 14 (± 2)**	**Day 21 (± 2)**	**Day 28 (± 3)[7]**	**Day 42 (± 3)**
Informed consent/assent	X					
Medical, Surgical and Ophthalmic History	X					
Demographics [redacted]	X					
Inclusion/Exclusion criteria	X					
Concomitant medications	X	X	X	X	X	X
Urine pregnancy test	X				X	X[1]
Subject-rated Ocular Pain Assessment[2]	X	X	X	X	X	X
Subject-rated Photophobia Assessment[3]	X	X	X	X	X	X
ETDRS BCVA	X	X	X	X	X	X
Slit-lamp biomicroscopy[4]	X	X	X	X	X	X
Intraocular pressure	X	X	X	X	X	X
Dilated ophthalmoscopy	X				X	X
Laboratory Tests [redacted]	X					
Randomization[5]	X					
Adverse events assessment[6]	X	X	X	X	X	X
[redacted]	[redacted]		[redacted]			
[redacted]			[redacted]		[redacted]	[redacted]
Dispense Diary	X	X	X	X		
Review and Collect Diary		X	X	X	X	X[1]

[1]Visit 6 is also the Early Termination visit. To be performed in addition to the Visit 6 assessments, if Visit 6 is an Early Termination Visit.
[2]The Subject-Rated Ocular Pain Assessment must be performed prior to any other assessments.
[3]The Subject-Rated Photophobia Assessment must be performed after the Ocular Pain Assessment.
[redacted]
[5]Randomization performed if subject meets all Inclusion/Exclusion criteria, including ACC grade 2 or 3.
[redacted]

12.2 Appendix 2: Abbreviations and Definition of Terms

ACC	Anterior Chamber Cell(s)
ACF	Anterior Chamber Flare
AE	Adverse Event
[redacted]	[redacted]
API	Active Pharmaceutical Ingredient
BCVA	Best Corrected Visual Acuity
CFR	US Code of Federal Regulations
CI	Confidence Interval
CM(s)	Concomitant Medication(s)
[redacted]	[redacted]
CMP	Clinical Management Plan
COVID-19	Coronavirus Disease of 2019
CP	Conditional Power
CRO	Contract Research Organization
CS	Clinically Significant
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FDA	US Food and Drug Administration

[redacted]	[redacted]
GAT	Goldmann Applanation Tonometry
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High-density Polyethylene
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
IB	Investigator's Brochure
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IgG	Immunoglobulin G
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Randomization System
LAR	Legally Authorized Representative
LDPE	Low-Density Polyethylene
M1	Inflammatory Macrophages
M2	Anti-Inflammatory Macrophages

[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MP	Monitoring Plan
NCS	Non-Clinically Significant
NSAID	Nonsteroidal Anti-Inflammatory Drug
OD	Right Eye
OS	Left Eye
OTC	Over the Counter
OUS	Outside of United States
PI	Principal Investigator
[redacted]	[redacted]
PRN	As Needed
QC	Quality Control
[redacted]	[redacted]
QID	Four Times Per Day
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARs-Cov-2	Severe Acute Respiratory Syndrome – Coronavirus 2
SOP	Standard Operating Procedure
[redacted]	[redacted]
[redacted]	[redacted]
TLR4	Toll-Like Receptor 4

[redacted]	[redacted]
UPT	Urine Pregnancy Test
US	United States
VA	Visual Acuity
WHO-DD	World Health Organization Drug Dictionary

12.3 Appendix 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 for each eye 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.

12.4 Appendix 4: Subject-Rated Ocular Photophobia Assessment

Subjects will be asked to subjectively rate their photophobia for each eye at each visit by placing a vertical mark on the horizontal line to indicate the level of discomfort. 0 corresponds to "No Symptom" and 100 corresponds to "Severe Symptoms".

Subject Instructions: Please review the symptom below. After your review, please rate how your eye feels for the symptom (0-100) by placing a single vertical mark that represents how your symptom feels at this moment.

0 = No Symptom and 100 = Severe Symptom

Photophobia (sensitivity to light)

0 **50** **100**

|_____|

12.5 Appendix 5: BCVA

Visual Acuity (VA) testing should precede any examination requiring contact with the eye or instillation of drops to dilate or anesthetize the eye for examination, as is detailed in the order of assessments for each visit in Section 7.1. Visual acuity testing will be performed using a pinhole occluder. The subject may use a pinhole occluder over their current spectacle distance correction, if needed. The technique used should remain consistent at all study visits.

BCVA must be assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) charts either retro-illuminated or frontally illuminated (60-watt bulb or well-lit room) at a distance of 4 meters. It is recommended that Original Series ETDRS Chart 1 is used for testing the right eye (OD) and Original Series ETDRS Chart 2 is used for testing the left eye (OS). In order to provide standardized and well-controlled assessments of visual acuity during the study, the same lighting conditions must be used consistently throughout the study.

The subject should be positioned according to the elevation of the chart (either seated or standing) so that the chart is at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter instead of the number. The subject should be asked to read slowly, about 1 letter per second, to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response. If the subject changes a response before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart; the subject should be encouraged to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted.

If less than 20 letters are read with either eye at 4 meters, the eye(s) with reduced acuity is tested at 1 meter. Ask the subject to read from the top left-hand corner as above. Continue to the last letter of each row until the subject makes 3 mistakes on a given row despite guessing or until the subject reaches the end of the sixth row on the chart.

BCVA scoring:

- At the end of the test, count the number of circled letters for each row and then add them together for that eye at the bottom of the column.
- If BCVA was tested at 4 meters only (testing at 1 meter was not required), then add 30 to the number of letters read correctly at 4 meters to get the letter score.
- If testing at 1 meter was required, the letter score is the sum of the letters read correctly at 4 meters and 1 meter.

12.6 Appendix 6: Slit-lamp Biomicroscopy

The slit-lamp biomicroscopy exam will be performed to examine eye structures for each eye at each study visit. Areas assessed will include the following: anterior chamber, eyelids, conjunctiva, cornea, iris, pupils, lashes and lens. [redacted]

It should be performed with a slit lamp (halogen illumination system or similar is required) using a beam width and intensity that provide optimal evaluation of the anterior segment.

This procedure will be performed in the same manner for all subjects observed at the Investigator's site. The site will record all ABNORMAL findings in the source document and the Investigator will evaluate the ABNORMAL findings as Non-Clinically Significant (NCS) or Clinically Significant (CS). CS and NCS ABNORMAL findings will be recorded in the source documentation. However, only ABNORMAL CS descriptions will be captured in the eCRF.

The scoring scales below will be used:

Anterior Chamber Cells (ACC)	0 = No cells seen 1 = 1 - 5 cells 2 = 6 - 15 cells 3 = 16 - 30 cells 4 = greater than 30 cells
Anterior Chamber Flare (ACF)	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)
Eyelid • Eyelid Hyperemia • Eyelid Edema	0 = None 1 = Mild 2 = Moderate 3 = Severe
Conjunctiva • Hyperemia • Edema (Chemosis) • Conjunctival Discharge/Exudate	0 = None 1 = Mild 2 = Moderate 3 = Severe
Cornea • Corneal Edema	0 = None 1 = Mild 2 = Moderate 3 = Severe

Iris	0 = Normal 1 = Abnormal
Pupil	0 = Normal 1 = Abnormal
Lashes	0 = Normal 1 = Abnormal
Lens	0 = Normal 1 = Abnormal

12.7 Appendix 7: Intraocular Pressure by Goldmann Applanation Tonometry

The IOP measurements will be performed by Goldmann applanation tonometry with a single measurement recorded in mmHg (e.g., 18 mmHg) for each eye. IOP measurements will be performed at all study visits.

12.8 Appendix 8: Dilated Ophthalmoscopy

Dilated ophthalmoscopy will include assessment of the retina for any abnormal findings, optic nerve head for pallor and cupping (cup to disc ratio). The status of the vitreous (including haze), retina (including vessels), macula, optic nerve will be determined as Normal or Abnormal. The cup to disc ratio will be recorded with two decimal points (e.g., 0.80). After the Ophthalmoscopy procedure, the Investigator will determine if findings are within normal limits or are abnormal. For abnormal findings at Visit 1, the Investigator will determine whether or not the abnormality would exclude the subject from study participation. The dilated ophthalmoscopy exam will be conducted for each eye at Visit 1, Visit 5 and Visit 6/Early Termination.

12.9 Appendix 9: Investigator Agreement

A Phase 3 Randomized, Active-Controlled, Double-Masked Study to Evaluate the Safety and Efficacy of TRS01 Eye Drops in the Treatment of Subjects with Active Non-infectious Anterior Uveitis including Subjects with Uveitic Glaucoma

Version No.: 3.0

Issue Date: 06May2022

I have read the clinical study protocol and understand it. I agree to conduct the study as outlined in this document and in accordance with Good Clinical Practice Guidelines, all local and federal requirements and regulations, and in compliance with those precepts set forth in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

Further, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Investigator:

Name (printed)	Signature	Date

12.10 Appendix 10: Compliance Statement

The study will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and as stipulated in the Declaration of Helsinki (2013) with respect to the use of human subjects in clinical studies and investigations.

The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) Sponsor, funding agency and documented approval from the Institutional Review Board or Local Ethics Committee (IRB/EC), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

Sponsor's Representative(s):

[redacted]

Medical Monitor(s):

[redacted]

TRS4Vision Protocol Clarification Memo #3

To: Principal Investigators and Site Staff

From: [redacted]

Date: August 17, 2022

Re: **TRS4Vision: A Phase 3 Randomized, Active-Controlled, Double-Masked Study to Evaluate the Safety and Efficacy of TRS01 Eye Drops in the Treatment of Subjects with Active Non-infectious Anterior Uveitis including Subjects with Uveitic Glaucoma**

The above-referenced TRS4Vision Protocol, Version 3.0, Amendment 02 (dated 06May2022) has been modified as outlined below.

These modifications have been made in order to assist clinical sites in recruiting eligible patients and to allow flexibility in visit scheduling for patients who do not require an in-person clinic visit at Week 2 (Visit 3).

Summary of Changes:

Change From	**Change To**
Section 4.: Inclusion Criteria #1	
Rationale: To extend the upper age range of eligible subjects in the US to 75 years of age.	
1. At sites in the US: Male or female up to and including 70 years of age (including all pediatric age groups). At sites in the EU: Male or female between 18 and 70 years of age, inclusive.	1. At sites in the US: Male or female up to and including **75** years of age (including all pediatric age groups). At sites in the EU: Male or female between 18 and 70 years of age, inclusive.
Section 7.1.9: Virtual (Telehealth) Visit	
Rationale: For subjects whose inflammation is stable or improved at Visit 2 (Week 1), the Visit 3 (Week 2) visit may be conducted as a virtual (telehealth visit), if needed.	
On-site study visits are strongly preferred. Study visits must be conducted on-site, unless prohibited due to an extenuating circumstance such as COVID-19 infection or quarantine of site personnel or trial participant. Please note the following important points regarding telehealth visits:	On-site study visits are strongly preferred, **except in the circumstances outlined below**. Study visits must be conducted on-site, unless prohibited due to an extenuating circumstance such as COVID-19 infection or quarantine of site personnel or trial participant. **Additionally, Visit 3 (Week 2) is not required to be conducted on-site for subjects whose**

	inflammation at Week 1 was stable or improved compared to baseline (Day 1) and who experienced no possibly related or related Adverse Events as of the Week 1 visit. For these subjects, Visit 3 may instead be conducted as a virtual visit, if needed.
Section 7.1.2: Visit 2 (Day 7 ± 2 days)	
Rationale: For subjects whose inflammation is stable or improved at the Visit 2 (Week 1) visit, the Visit 3 (Week 2) visit may be conducted as a virtual (telehealth visit), if needed. ➢ In this case, the diary card and [redacted] as outlined below.	
• Dispense new Dosing Diary to subject and emphasize importance of compliance. [redacted]	• Dispense **two** new Dosing Diaries **(Visit 2 and Visit 3 diary cards**) to subject and emphasize importance of compliance. [redacted]
Section 7.1.3: Visit 4 (Day 21 ± 2 days)	
Rationale: For subjects whose inflammation is stable or improved at the Visit 2 (Week 1) visit, the Visit 3 (Week 2) visit may be conducted as a virtual (telehealth visit), if needed. [redacted]	
•Review and collection of subject's Dosing Diary	•Review and collection of subject's Dosing Diary [redacted]

Section 5.5.3: Prohibited Medications and Procedures

These clarifications will be incorporated into the protocol should any future protocol amendments be required.

The original signed copy should be retained in your study files and a signed copy returned to [redacted]

[redacted]

17 August 2022
Date

Signature of Principal Investigator:

Name (printed) Signature Date