Clinical Trial Protocol: CYS-005

Protocol Title:	A Phase 3, multi-center, open-label, single-arm clinical trial to assess the long-term safety and tolerability of topical CyclASol® for the treatment of Dry Eye Disease in subjects who completed the clinical trial CYS-004
Protocol Number:	CYS-005
Trial Phase:	3
Investigational Product Name:	CyclASol® 0.1 % Ophthalmic Solution (Cyclosporine A 0.1%)
IND Number:	128163
Indication:	Dry Eye Disease (*keratoconjunctivitis sicca*)
Sponsor:	Novaliq GmbH Im Neuenheimer Feld 515 69120 Heidelberg Germany
Contract Research Organization:	[redacted]
Original Protocol:	27th August 2020
Amendment 1:	10th December 2020

Confidentiality Statement

This protocol contains confidential, proprietary information of [redacted] and Novaliq GmbH. Further dissemination, distribution, or copying of this protocol or its contents is strictly prohibited.

Regulatory Statement

This trial will be performed in compliance with the protocol and in accordance with Good Clinical Practice (International Conference on Harmonisation [ICH], Guidance E6), principles of human subject protection, and applicable country-specific regulatory requirements.

1 SYNOPSIS AND TRIAL CONTACT INFORMATION

1.1 TRIAL CONTACT INFORMATION

SPONSOR PERSONNEL

Scientific Lead:	[redacted]
Clinical Operations:	[redacted]

MEDICAL MONITOR

Medical Monitor	[redacted]

[redacted] PERSONNEL

Clinical Project Manager:	[redacted]
Biostatistician:	[redacted]

1.2 SYNOPSIS

Protocol Title:	A Phase 3, multi-center, open-label, single-arm clinical trial to assess the long-term safety and tolerability of topical CyclASol® for the treatment of Dry Eye Disease in subjects who completed the clinical trial CYS-004
Protocol Number:	CYS-005
Investigational Product:	CyclASol 0.1% Ophthalmic Solution (Cyclosporine A 0.1% solution)
Trial Phase:	3
Trial Objectives:	The primary objective of this trial is to evaluate safety and tolerability of CyclASol during long-term use in subjects with Dry Eye Disease. The secondary objective is to evaluate efficacy of CyclASol during long-term use in subjects with Dry Eye Disease.
Overall Trial Design	
Structure:	Open-label, multi-center, single-arm
Duration:	An individual subject's participation is estimated to be approximately 52 weeks (12 months). The estimated trial duration is 16 months.
Dosage/Dose Regimen:	Subjects who completed the clinical trial CYS-004 and are eligible for participation will receive the following treatment to be administered bilaterally BID for approximately 52 weeks (from Visit 1 to Visit 6): CyclASol 0.1% Ophthalmic Solution (Cyclosporine A 0.1% solution)
Summary of Visit Schedule:	6 onsite-visits over the course of approximately 52 weeks • Visit 1 = Day 1, start of open label treatment (preferably on Day 29 (Visit 3) of CYS-004) • Visit 2 = week 4 ± 2 days, • Visit 3 = week 12 ± 7 days, • Visit 4 = week 26 ± 7 days, • Visit 5 = week 40 ± 7 days, • Visit 6= week 52 ± 7 days / trial exit 7 telephone calls (TC; optionally onsite visits) • TC 1= week 8 follow-up ± 7 days • TC 2 = week 16 follow-up ± 7 days • TC 3 = week 22 follow-up ± 7 days

	• TC 4 = week 30 follow-up ± 7 days • TC 5 = week 36 follow-up ± 7 days • TC 6 = week 44 follow-up ± 7 days • TC 7 = week 48 follow-up ± 7 days
Study Population Characteristics	
Number of Subjects:	Up to [redacted] subjects who completed trial CYS-004 will be enrolled at approximately 13 sites to achieve at least 100 subjects completing [redacted] 52 weeks dosing with respective follow-up visits.
Condition/Disease:	Dry Eye Disease (*keratoconjunctivitis sicca*)
Inclusion Criteria:	**Subjects must:** 1. Have completed the clinical trial CYS-004 2. Have a subject reported history of dry eye disease (DED) [redacted] 3. Have been compliant with trial procedures and application of investigational medicinal product (IMP) in CYS-004 according to investigators assessment of dosing diary; 4. Provide written informed consent; and 5. Be able and willing to follow instructions, including participation in all trial assessments and visits.
Exclusion Criteria:	**Subjects must not:** 1. Have early terminated application of the investigational medicinal product during CYS-004 for any reason; 2. Have any clinically significant slit-lamp findings or ocular conditions at Visit 1 that require prescriptive medical treatment and/or in the opinion of the investigator may interfere with trial parameters; 3. Have a history of herpetic keratitis; 4. Have an ocular or periocular malignancy; 5. Be unwilling to avoid wearing contact lenses during the trial; 6. Have any planned ocular or eyelid surgeries during the trial period; 7. Be a woman who is pregnant, nursing, or planning a pregnancy; 8. Be unwilling to submit a urine pregnancy test at all onsite visits (including early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (i.e. has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is post-menopausal (i.e. without menses for 12 consecutive months);

	9. Be a woman of childbearing potential who is not using an acceptable means of contraception. Acceptable methods of contraception include hormonal contraceptives (i.e. oral, implantable, injectable, or transdermal contraceptives), mechanical contraceptives (i.e. spermicide in conjunction with a barrier such as a diaphragm or a condom), intrauterine devices (IUD), or the surgical sterilization of the partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the trial, she must agree to use adequate birth control as defined above for the remainder of the trial; 10. [redacted] 11. Be currently using an investigational drug or device or have used an investigational drug or device [redacted] 4; 12. [redacted] 13. Have a condition or be in a situation (e.g. language barrier) which the investigator feels may put the subject at significant risk, may confound the trial results, or may interfere with the subject's participation in the trial significantly.
Trial Formulation:	CyclASol 0.1% Ophthalmic Solution (Cyclosporine A 0.1% [redacted])

Evaluation Criteria

Endpoint(s):	**Primary Safety Endpoints:** • Ocular and non-ocular adverse events. **Secondary Safety Endpoints:** • Visual acuity (BCVA using EDTRS) • Slit-lamp biomicroscopy • Intraocular pressure (IOP) • Dilated fundoscopy **Prespecified Efficacy Endpoints:** • tCFS score (NEI scale) and CFB at each visit • CFS scores per sub-regions (NEI scale) and CFB at each measured visit • Conjunctival lissamine green staining score by region and total (Oxford scale) and CFB at each measured visit • Visual analogue scale (VAS) scores for Dryness score, frequency of dryness, awareness of dryness, blurred vision, reading problems, fluctuating vision, looking at screens and driving at night and CFB at each measured visit • Ocular Surface Disease Index (OSDI) total, individual and subtotal scores and CFB at each measured visit • Tear Film Break-Up Time (TBUT) and CFB at each measured visit • Unanesthetized Schirmer's Test and CFB at each measured visit. • Proportion of subjects with improvements in tCFS (NEI) score of 1, 2 and 3 units at each measured visit • Proportion of subjects with improvements in cCFS (NEI) score of 1 unit at each measured visit
Other:	• [redacted]

General Statistical Methods and Types of Analyses

Sample Size:

Up to [redacted] subjects will be enrolled in order to ensure that at least 100 evaluable participants complete the week 26 (6-month) treatment period and at least 100 evaluable subjects complete the week 52 (12-month) treatment period.

With 100 subjects completing the 52 weeks [redacted] treatment period, the study will have 95% or greater chance of observing adverse events that occur at a true incident rate of 3.0% or higher. Therefore, with 100 subjects completing 52 weeks [redacted] of treatment, if an adverse event of a specific type is not observed, then with 95% confidence, the true incidence rate of the adverse event is less than 3.0%.

Primary Safety Analyses:

Adverse events (AEs) will be coded using the MedDRA dictionary. An AE is treatment emergent if it occurs or worsens after the first dose of trial treatment.

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class, preferred term, maximal severity, and strongest relationship. Separate summaries will be performed for ocular and non-ocular AEs.

Secondary Safety Analyses:

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by visit using descriptive statistics.

Assessments performed by eye, study eye and fellow eye will be summarized separately. Changes or shifts from baseline (as defined in clinical trial CYS-004) will also be summarized where appropriate.

Exploratory Analyses:

Quantitative prespecified efficacy variables will be summarized descriptively (n, mean, standard deviation, median, min, and max) and analyzed at each measured visit and with change from baseline (as defined in clinical trial CYS-004). Assessments performed by eye, study eye and fellow eye will be summarized separately

Dichotomous secondary efficacy variables will be summarized descriptively (frequency and percentage).

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LIST OF ABBREVIATIONS

AE	Adverse Event
BCVA	Best-Corrected Visual Acuity
BID	Twice Daily
BLQ	Below the Limit of Quantification
CD	Compact Disc
cCFS	Central corneal fluorescein staining
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFS	Corneal fluorescein staining
CI	Confidence Interval
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CsA	Cyclosporine A
DED	Dry Eye Disease
DEWS	(International) Dry Eye Workshop
ECG	Electrocardiography, Electrocardiogram
ET	Early termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
IB	Investigators' Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
IOP	Intraocular Pressure
IRB	Independent Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
µL	Microliter
mm	Millimeter
mmHg	Millimeters of Mercury
NDA	New Drug Application
NEI	National Eye Institute
OD	Right Eye
OS	Left Eye
OSDI	Ocular Surface Disease Index
OU	Both Eyes

SAE	Serious Adverse Event
SAF	Safety Set
SFA	Semifluorinated Alkane
SOP	Standard Operating Procedures
tCFS	Total corneal fluorescein staining
TEAE	Treatment-emergent Adverse Event
TFBUT	Tear Film Break-up Time
US	United States
VA	Visual Acuity
VAS	Visual Analog Scale
WHO	World Health Organization
w/v	Weight per volume
w/w	Weight per weight

2 INTRODUCTION

2.1 Dry Eye Disease (DED)

Dry Eye Disease (DED) is defined by the International Dry Eye Workshop (DEWS) as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Craig et al. 2017). Symptoms of DED such as feeling of dryness, burning, a sandy/gritty sensation, foreign body sensation, pain or itchiness are quite debilitating. In addition, visual function related symptoms such as fluctuating vision with blinking, blurred vision, and difficulty with reading despite perfect visual acuity is an important and underestimated aspect of the disease. In consequence, DED negatively impacts quality of life comparably to other severe diseases (Schiffman et al. 2003), and adverse effects on mental health, such as depression and anxiety, have been observed (Le et al. 2012). DED is a serious disorder that, if left untreated or undertreated, progressively damages the ocular surface and may lead to vision loss due to corneal complications (Lemp et al. 1995).

As many as 5 - 35% of subjects visiting ophthalmic clinics report dry eye symptoms, making it one of the most common conditions seen by ophthalmic specialists (McCarty et al. 1998; Lin et al. 2003). Estimates of the prevalence of dry eye vary considerably, depending on the criteria used to define the disease, but in the United States (US), it has been estimated that as many as 3.2 million women and 1.7 million men over the age of 50 have DED, with a projected 40% increase in the number of patients affected by 2030 (Schaumberg et al. 2002; Schaumberg et al. 2003; Schaumberg et al. 2009) With the aging population in the US and other countries of the developed world, and with increasing use of visual displays / computers, DED is expected to continue to become more prevalent and finding a treatment is becoming more important (Benitez-del-Castillo et al. 2017).

2.2 Product Rational

Cyclosporine A (CsA), a potent and selective immunosuppressive drug, acts as a regulator of T-cells via inhibition of calcineurin. Due to this mode of action it has been widely studied as topical treatment for T-cell mediated diseases of the ocular surface such as DED. In the US, CsA eye drops formulated as an emulsion have been approved and marketed as Restasis 0.05% for this indication since 2002. In Europe - Ikervis™, a 0.1% CsA emulsion formulation, received a marketing authorization by the European Medicines Agency for the treatment of DED in early 2015. A second CsA containing product, Cequa™, a nano-emulsion was approved in the US in 2018.

CyclASol, in contrast, is a clear ophthalmic solution of CsA developed with the goal of avoiding the use of oils, surfactants and preservatives. Potential benefits from this CyclASol formulation include improved tolerability and efficacy, early onset of efficacy and decreased visual disturbances associated with oily eye drops, emulsions or ointments. Moreover, the multiple dose containers allow for a convenient handling.

For the solubilization of CsA in CyclASol the semifluorinated alkane (SFA) [redacted] F4H5 [redacted] is used as the vehicle. [redacted] F4H5 is colourless, has a high vapor pressure, and is immiscible with water while having nearly the same refractory index. F4H5's physical properties make it an optimal vehicle for topical ocular use. As a result of its high vapor pressure (Krafft et al. 2009), F4H5 dissipates quickly from the ocular surface and consequently does not interact physically with the tear film, as shown in rabbits, where F4H5 had no effect on tear film break-up time (TFBUT) (Agarwal et al. 2019). Due to the low surface tension of F4H5, CyclASol eye drops are of small size, [redacted] potentially reducing pre-corneal clearance. Importantly, the low surface tension of the CyclASol formulation facilitates dissemination of the applied eye drop on the conjunctiva. The dissemination and spreading properties are further thought to improve the local bioavailability.

2.3 Trial Rational

After successful preclinical testing and early clinical testing, a Phase 2b/3 clinical trial (CYS-003, ESSENCE) confirmed the effects and good tolerability seen in the Phase 1 and Phase 2 clinical trials.

CyclASol 0.1% met the primary endpoint showing superiority compared to vehicle in change from baseline in total corneal fluorescein staining (tCFS) at Day 29 with high statistical significance (p=0.0002). Additionally, the CyclASol 0.1% group consistently showed statistically significant improvements over time in total and central corneal and conjunctival staining compared to vehicle. The therapeutic effects observed had an early onset after 14 days of treatment that continued over the 84-day treatment period. CyclASol 0.1% also showed trends of more improvement in the second primary endpoint of change from baseline in total Ocular Surface Disease Index (OSDI©) at Day 29. Additionally, statistically significant and greater improvements in dryness-related symptoms as measured by VAS (Dryness Score) at Day 29 were demonstrated in the CyclASol 0.1% treatment group compared to the vehicle group.

CyclASol 0.1% was safe and comfortable, and showed an excellent tolerability in all clinical trials conducted to date with instillation site reactions as low as 2.5% and a very low drop-out rate due to treatment emergent adverse events (TEAE) of 3 subjects in each CYS-002 in CYS-003.

This phase 3 open label safety extension trial is designed to investigate the long-term safety and tolerability of CyclASol 0.1% BID dosing of subjects completing the 4-weeks treatment trial CYS-004, [redacted].

2.4 Summary of Known and Potential Risks and Benefits to Human Subjects

The investigational medicinal product (IMP) CyclASol 0.1% Ophthalmic Solution contains CsA as active ingredient and its vehicle, which consists of F4H5. CsA is a potent and selective immunosuppressive drug, used routinely for decades as an oral immunomodulator in various indications. CsA containing eye drops have been proven safe over the last 15 years. The excipient F4H5 used in CyclASol is chemically inert, without pharmacologic activity and not undergoing

metabolism in the human body. However, it is not part of any pharmaceutical product approved so far. Therefore, it has been subjected to the same pivotal non-clinical studies as a new active substance with favorable results.

282 subjects have been exposed to CyclASol 0.05% or 0.1% up to 4 months duration in clinical trials to date (clinical trials CYS-001: Phase 1; CYS-002: Phase 2; CYS-003: Phase 2b/3) with a favorable outcome in safety and tolerability.

[redacted]

In summary, based on the preclinical and clinical data obtained to date, risks to subjects in the planned CYS-005 trial are considered very low. Furthermore, the subjects in the trial will be

closely monitored, and current standard ophthalmic safety assessments will be performed during the entire treatment period. The results to date demonstrate the efficacy of CyclASol on signs and symptoms of DED. Treatment with CyclASol therefore provides a favorable benefit-risk profile in subjects with DED, addressing a clinical need that is currently not optimally addressed with available treatment options for DED.

The [redacted] subjects qualifying for participation in CYS-005 will have completed the pivotal clinical trial CYS-004 with four weeks treatment according to protocol and tolerated exposure to IMP (randomized 1:1 to CyclASol or vehicle) well enough to continue treatment for one year. They are experienced in handling the IMP bottle and familiar with all safety and efficacy assessments they will undergo in CYS-005.

This clinical trial CYS-005 is designed to confirm the positive benefit-risk profile for long-term treatment with CyclASol.

3 TRIAL OBJECTIVES

3.1 Primary objective

- The primary objective of this trial is to evaluate safety and tolerability of CyclASol during long-term use in subjects with Dry Eye Disease.

3.2 Secondary objectives

- The secondary objective is to evaluate efficacy of CyclASol during long-term use in subjects with Dry Eye Disease.

4 TRIAL DESIGN

4.1 Overall Trial Design

This is a Phase 3 multicenter, open-label, single-arm clinical trial to evaluate the safety, tolerability and efficacy of CyclASol 0.1% Ophthalmic Solution in subjects with signs and symptoms of DED. [redacted] subjects who completed the clinical trial CYS-004 and meeting all other trial eligibility criteria will be included at approximately 13 sites in the US to receive treatment with CyclASol.

Eligible subjects will dose the IMP (CyclASol) bilaterally BID for approximately 12 months (52 weeks).

4.2 End of Trial Definition

The “end of the trial” for an individual subject is defined as that subject’s last visit as specified in the Schedule of Assessments.

The “end of the trial” for the overall trial is defined as completion of the last visit or procedure as specified in Schedule of Assessments for all subjects in the trial.

4.3 Visit Description

Subjects will be required to sign an Informed Consent before completing any trial related procedure. All examination procedures are listed in Section 8.4 and in the Schedule of Assessments. For consistency and to avoid interference, they should be performed in the respective order as listed. Trial Drug Dispensation is described in Section 7.1.4.

Visit 1

The results of assessments at Visit 3 (Day 29) in study CYS-004 (final visit) will be taken as Day 1 data for CYS-005. Further data/assessments to be captured will be the CYS-005 Informed Consent, Inclusion/Exclusion Criteria to determine CYS-005 eligibility, and IMP dispensation. [redacted] Each subject will be given a dosing diary to record that their doses were taken. Study staff will help the subject to understand how to use the dosing diary and when the remaining doses should be taken. Subjects will be instructed to take their first dose at home. If needed, at the discretion of the Investigator and/or request of the subject, self-dosing can occur at this visit under staff supervision for instruction purposes.

Visits 2-6

Subjects will return to the clinic on week 4 ± 2 days (Visit 2), week 12 ± 7 days (Visit 3), week 26 ± 7 days (Visit 4), week 40 ± 7 days (Visit 5) and week 52 ± 7 days (Visit 6) to investigate ocular and non-ocular safety and tolerability of IMP and assess signs and symptoms of dry eye disease. At those visits all used and unused trial medication should be returned to the clinic. [redacted] The dosing diary will be collected during each visit and checked for compliance. Subjects will be discharged from the trial after all Visit 6 assessments have been completed.

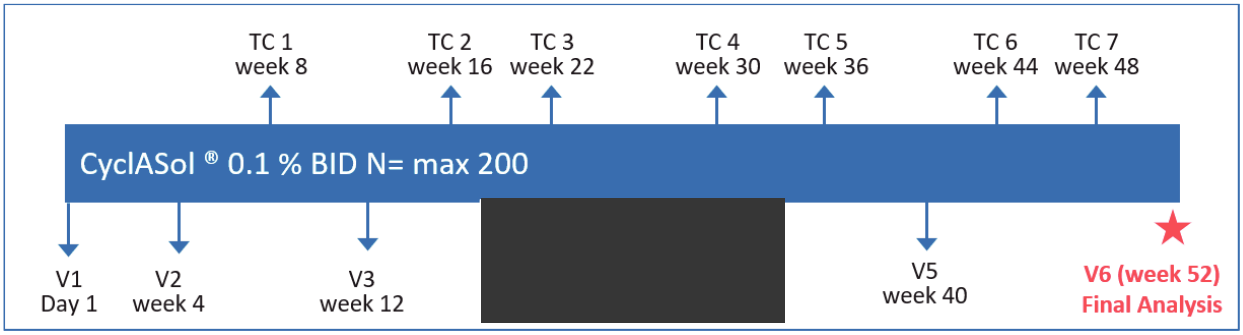
Interim Telephone Calls

In order to keep a monthly contact with the subjects, interim telephone calls on a monthly basis will be performed asking about the subject's well-being with non-leading AE questioning, BID dosing, issues with IMP and any changes in medical history or concomitant treatments.

Early Termination (ET)

Subjects who terminate early during the treatment period will be asked to complete all assessments as indicated at Visit 6 on the schedule of assessments prior to commencement of any alternative dry eye therapy (if considered possible). Dosing diary and trial medication will be collected. Subjects who are terminated early from the trial will not be replaced.

4.4 Trial Flow



4.5 Enrollment and Treatment Assignment

Subjects will keep the assigned unique subject number as allocated in clinical trial CYS-004. If all inclusion and none of the exclusion criteria are met at Visit 1, [redacted] qualifying subjects will be included in CYS-005. [redacted]

Each subject will spend approximately 52 weeks in the trial. The total duration of the trial from "first subject in" to "last subject out" is expected to be approximately 16 months.

4.6 Justification of Trial Design

This trial is designed as an open-label, single-arm extension trial to clinical trial CYS-004 to investigate long-term safety and tolerability of 52 weeks treatment with CyclASol 0.1% BID in at least 100 subjects. [redacted]

An open-label design is deemed adequate as there are no eye-drops available acting purely as placebo in DED, thus influencing the background incidence of AEs in this indication. In addition, the vehicle F4H5 previously used as control in clinical trials with CyclASol 0.1% is as well part of the CyclASol formulation.

4.7 Justification for Dose

The CyclASol 0.1% BID dosing regimen was selected for the first pivotal trial CYS-003 based on results of CYS-002. The trial CYS-004 is designed to replicate the efficacy and safety results of CYS-003 with the same dosing regimen, consequently the open label extension trial CYS-005 will use the same dose and schedule of application.

5 TRIAL POPULATION

5.1 Number of Subjects (approximate)

[redacted] subjects who completed the clinical trial CYS-004 will be enrolled at approximately 13 sites to achieve at least 100 subjects completing [redacted] and 52 weeks (12 months) dosing with respective safety and tolerability assessments.

5.2 Trial Population Characteristics

Subjects who completed trial CYS-004, have been compliant with CYS-004 trial procedures and application of IMP may be invited to enroll into trial CYS-005.

All subjects must be at least 18 years of age, of either sex, and of any race. Furthermore, subjects must have a subject-reported history of dry eye in both eyes and meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Subjects will be eligible to participate in this trial if they **meet all** following criteria:

1. Have completed the clinical trial CYS-004;
2. Have a subject reported history of DED [redacted]
3. Have been compliant with trial procedures and application of investigational medicinal product (IMP) in CYS-004 according to investigators assessment of dosing diary;
4. Provide written informed consent; and
5. Be able and willing to follow instructions, including participation in all trial assessments and visits.

5.4 Exclusion Criteria

Subjects will not be eligible to participate in this trial **if any** of the following criteria apply**:**

Subjects must not:

1. Have early terminated application of the investigational medicinal product during CYS-004 for any reason;
2. Have any clinically significant slit-lamp findings or ocular conditions at Visit 1 that require prescriptive medical treatment and/or in the opinion of the investigator may interfere with trial parameters;
3. Have a history of herpetic keratitis;
4. Have an ocular or periocular malignancy;
5. Be unwilling to avoid wearing contact lenses during the trial;

6. Have any planned ocular or eyelid surgeries during the trial period;
7. Be a woman who is pregnant, nursing, or planning a pregnancy;
8. Be unwilling to submit a urine pregnancy test at all onsite visits (including early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (i.e. has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is post-menopausal (i.e. without menses for 12 consecutive months);
9. Be a woman of childbearing potential who is not using an acceptable means of contraception. Acceptable methods of contraception include hormonal contraceptives (i.e. oral, implantable, injectable, or transdermal contraceptives), mechanical contraceptives (i.e. spermicide in conjunction with a barrier such as a diaphragm or a condom), intrauterine devices (IUD), or the surgical sterilization of the partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the trial, she must agree to use adequate birth control as defined above for the remainder of the trial;
10. [redacted]
11. [redacted]
12. [redacted]
13. Have a condition or be in a situation (e.g. language barrier) which the investigator feels may put the subject at significant risk, may confound the trial results, or may interfere with the subject's participation in the trial significantly.

5.5 Subject/ Trial Withdrawal Criteria

Subjects are free to discontinue their participation in the trial at any time without giving their reasons.

A subject **must be** discontinued from the trial for any of the following reasons:

- If at any time during the trial the Investigator determines that a subject's safety has been compromised;
- Occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety;
- If discontinuation is considered necessary by the investigator and/or sponsor;
- Occurrence of AEs that present an unacceptable consequence or risk to the subject in the judgment of the investigator, sponsor, or the medical monitor;
- Occurrence of pregnancy;
- Withdrawal of subject`s consent.

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case a subject has to be withdrawn from the trial, the sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned or the subject´s health has reached a stable condition.

Subjects who are withdrawn from the trial after dosing will not be replaced.

In case of premature withdrawal from the trial, the processes outlined in Section 8.4.2 should be followed. In any case, the appropriate electronic Case Report Form (eCRF) section including the reason for discontinuation as defined in Section 8.6.2 must be completed.

The trial **can be** prematurely discontinued as described in Section 8.7.

6 TRIAL PARAMETERS

6.1 Safety Endpoints

6.1.1 Primary Safety Endpoint

- Ocular and non-ocular adverse events.

6.1.2 Secondary Safety Endpoints:

- Visual acuity and CFB at each measured post-baseline visit (BCVA using EDTRS)
- Slit-lamp biomicroscopy findings and CFB at each measured post-baseline visit
- Intraocular pressure and CFB at each measured post-baseline visit
- Dilated fundoscopy findings and CFB at each measured post-baseline visit

6.2 Efficacy Endpoints

6.2.1 Prespecified Efficacy Endpoints

- tCFS score (NEI scale) and CFB at each visit
- CFS scores per sub-regions (NEI scale) and CFB at each measured visit
- Conjunctival lissamine green staining score by region and total (Oxford scale) and CFB at each measured visit
- Visual analogue scale (VAS) scores for Dryness score, frequency of dryness, awareness of dryness, blurred vision, reading problems, fluctuating vision, looking at screens and driving at night and CFB at each measured visit
- Ocular Surface Disease Index (OSDI) total, individual and subtotal scores and CFB at each measured visit
- Tear Film Break-Up Time (TBUT) and CFB at each measured visit
- Unanesthetized Schirmer's Test and CFB at each measured visit
- Proportion of subjects with improvements in tCFS (NEI) score of 1, 2 and 3 units at each measured visit
- Proportion of subjects with improvements in cCFS (NEI) score of 1 unit at each measured visit

[redacted]

[redacted]

[redacted]

7 TRIAL MATERIALS

7.1 Investigational Medicinal Product

7.1.1 IMP/ Formulation

Table 1. Active Investigational Medicinal Product

	Investigational Product
Product name:	CyclASol
Chemical name:	Cyclosporine A 0.1% [redacted]
Dosage form:	[redacted]
Unit dose:	[redacted]
Route of administration:	Topical ocular administration
Physical description:	Colorless and clear ophthalmic solution
Excipients:	[redacted]
Manufacturer:	[redacted]

7.1.2 Labeling and Packaging of IMP

IMP will be labelled according to the legal requirements and packaged into individual subject kits, [redacted] The subject should note bottle number and the day of opening in the diary.

As per the Code of Federal Regulations 21 part 312, section 312.6, the labels for the IMP shall be comprised of:

- Protocol number
- Investigational new drug statement
- Lot number
- Storage conditions
- Name and address of the sponsor

7.1.3 IMP Storage

The IMP must be stored in a secure area accessible only to the investigator or pharmacist and his/her designees. [redacted].

7.1.4 IMP Dispensation

[redacted]

At Visit 2 (for visual inspection only), Visit 3, Visit 4, Visit 5 and Visit 6 used/unused IMP and diaries will be collected from subjects for drug accountability.

7.1.5 Instructions for Use and Administration

Subjects will be instructed to instill one drop in each lower eyelid two times daily (in the morning and in the evening at bedtime). Subjects will be instructed to use a second drop only if the first drop misses the eye. Subjects will receive detailed written instructions how to store and dose IMP, and how to complete their diary.

Subjects will be instructed to immediately contact the site if there is any problem with the IMP (e.g. if the bottle was dropped or lost).

7.2 IMP Accountability

The investigator must keep an accurate accounting of IMP received from the supplier by maintaining a detailed inventory via IRT. This includes the amount of IMP received by the site,

amount dispensed to subjects, amount of IMP returned to the investigator by the subjects, and the amount returned to the sponsor or designee upon the completion of the trial.

Investigational trial medication orders, records of receipts, dispensing records, and inventory forms will be examined and reconciled by designated site personnel. At each visit, subjects will return all bottles to designated site personnel for accountability purposes. Accountability will be ascertained by performing reconciliation between the amount of IMP cartons (kits and their components) sent to the site, the amount used and unused at the time of reconciliation. No investigative drugs or kits will be discarded prior to full accountability by sponsor's monitor.

7.3 IMP Handling and Disposal

Unless otherwise directed, at the end of the trial all returned used and unused IMP must be shipped from the clinical site to the depot for disposal of medications.
Note: The medications should not be disposed prior to full accountability by the sponsor's designated monitor.

The clinical site will provide a copy of all completed drug disposition forms to the sponsor after the completion of the trial.

7.4 Other Trial Supplies

Diaries, questionnaires, VAS rulers, Schirmer's test strips, sodium fluorescein, lissamine strips, Fluress, Tropicamide, Urine pregnancy test.

8 TRIAL METHODS AND PROCEDURES

8.1 Concurrent Medications and Therapies

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the Investigator. If there is any question as to whether the medication may interfere, the Investigator should contact the Medical Monitor or Sponsor. Whenever possible and indicated, medications should be administered in dosages that remain constant throughout the study duration.

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

[redacted]

8.2 Prohibited Treatments

Disallowed treatments are listed in the Exclusion Criteria (Section 5.4). [redacted]

[redacted]

8.3 Restrictions and Prohibitions

[redacted]

8.4 Examination Procedures

8.4.1 Procedures to be Performed at Each Trial Visit with Regard to Trial Objective(s)

The procedures outlined in this section will performed as described in Appendix 1: Schedule of Assessments.

Visit 1 (Day 1):

Assessments and procedures from Visit 3 of clinical trial CYS-004:

- *At the beginning of the visit the subject will be asked about the time of last dose.* [redacted]
- *Medical/medication history update*
- *Urine pregnancy test for females of childbearing potential*
- *Non-leading AE questioning*
- [redacted]
- [redacted]
- *Visual acuity*
- *Slit-lamp biomicroscopy*
- [redacted]
- *Fluorescein staining (NEI scale)*
- *Lissamine green staining (Oxford scale)*
- [redacted]
- *Intraocular pressure*
- *Dilated fundoscopy*

CYS-005 specific assessments

- Informed consent / HIPAA
- Review of qualification criteria
- [redacted]
- Non-leading AE questioning
- Subjects are scheduled for Visit 2

Visit 2 (Week 4 ± 2 days)

- At the beginning of the visit the subject will be asked about the time of last dose. [redacted].
- Collection and review of IMP and subject diary
  - [redacted]
  - [redacted]
- Medical/Medication history update/Non-leading AE questioning
- Urine pregnancy test for females of childbearing potential
- [redacted]
- [redacted]
- Visual acuity
- Slit-lamp biomicroscopy
- [redacted]
- Fluorescein staining (NEI scale)
- Lissamine green staining (Oxford scale)
- [redacted]
- [redacted]
- Intraocular pressure
- [redacted]
- Non-leading AE questioning
- Schedule for Visit 3

Visit 3 (week 12 ± 7 days), Visit 4 (week 26 ± 7 days), Visit 5 (week 40 ± 7 days)

- At the beginning of the visit the subject will be asked about the time of last dose. [redacted]
- Collection and review of IMP and subject diary;
  - [redacted]
  - [redacted]
- Medical/Medication history update/ Non-leading AE questioning
- Urine pregnancy test for females of childbearing potential
- [redacted]
- [redacted]
- Visual acuity

- Slit-lamp biomicroscopy
- [redacted]
- Fluorescein staining (NEI scale)
- Lissamine green staining (Oxford scale)
- [redacted]
- Intraocular pressure
- Dilated fundoscopy
- [redacted]
- Non-leading AE questioning
- Subjects are scheduled for next Visit

Visit 6 (week 52 ± 7 days) or ET

- At the beginning of the visit the subject will be asked about the time of last dose. [redacted]
- Collection and review of IMP and subject diary;
  - [redacted]
  - [redacted]
- Medical/Medication history update/ Non-leading AE questioning
- Urine pregnancy test for females of childbearing potential
- [redacted]
- Visual acuity
- Slit-lamp biomicroscopy
- [redacted]
- Fluorescein staining (NEI scale)
- Lissamine green staining (Oxford scale)
- [redacted]
- Intraocular pressure
- Dilated fundoscopy
- Non-leading AE questioning
- Trial exit

TC 1-7 (Weeks 8/ 16/ 22/ 30/ 36/ 44/ 48 ± 7 days)

- Medical/Medication History Update
- Non-leading AE questioning
- Confirm dosing as instructed

8.4.2 Early Termination/Discontinuations

Data from subjects discontinuing after dosing will be captured completely in the eCRF including Early Termination Visit and reason for discontinuation.

If a dosed subject is discontinued from the trial before Visit 6 and is not willing to perform all subsequent visits and assessments, all evaluations of Visit 6 (at least all safety related evaluations) should be performed at Early Termination Visit on the day of early termination/discontinuation or at the discretion of the investigator.

8.4.3 Unscheduled Visits

An unscheduled visit may be performed during the course of the trial to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any unscheduled visit procedure listed in the eCRF that is not performed should be indicated as "not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp biomicroscopy
- Visual acuity
- Intraocular pressure
- Urine pregnancy test (for women of childbearing potential)
- Dilated fundoscopy
- Assessment of AEs
- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgement of the investigator

8.5 Compliance with Dosing/Protocol Deviations

Subjects will be instructed on the proper use and storage of the IMP at Visits 1, 2, 3, 4 and 5 and provided with written instructions. Subject diaries and IMP will be collected at each visit from Visit 2 up to and including Visit 6 to assess subject compliance with the protocol.

[redacted]

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or Study Operations manual requirements. The noncompliance may be on the part of the subject, the PI, or

study staff. As a result of deviations, corrective actions may need to be developed by the study staff and implemented promptly.

These practices are consistent with PI and Sponsor obligations in ICH GCP guidelines:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3 and 4.5.4
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2

All deviations from the protocol must be addressed in study subject source documents and promptly reported to the IRB according to their requirements.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the trial.

8.6.2 Discontinued Subjects

Notification of a subject's discontinuation and the reason for discontinuation will be made to [redacted] and/or trial sponsor and will be clearly documented on the eCRF as:

- Adverse Events
- Protocol violations
- Lack of efficacy
- Administrative reasons (e.g., inability to continue, lost to follow up)
- Sponsor termination of trial
- Subject choice (e.g. withdrawal of consent)
- Other

Discontinuations that are the direct result of SARS-CoV-2 (COVID-19) will be classified separately and clearly documented in the eCRF. A separate field will be completed to denote a COVID-19 related discontinuation and the specific reason will be documented utilizing the above noted list of subcategories.

Subjects must be discontinued as outlined in Section 5.5.

Subjects, who discontinue for any reason after dosing will not be replaced.

8.7 Trial Termination

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, e.g. due to:

  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions
    or
  - Other unfavorable safety findings.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the sponsor's IMP.
- Terminated or suspended upon request of Health Authorities

Health Authorities and Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

8.8 Trial Duration

An individual subject's participation will involve six visits and 7 phone calls over approximately a 52-week period. After the trial, subjects will be treated according to the standard of care at the discretion of the treating physician. The total duration of the trial from "first subject in" to "last subject out" is expected to be 16 months.

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered IMP-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical (investigational) product, whether or not related to the medical (investigational) product.

Resolved AEs and AE that are ongoing after Visit 3 (Day 29) in the CYS-004 trial, and prior to IMP administration at Visit 1 of CYS-005, will not be considered Adverse Events in CYS-005. These events will be considered medical history and will be transferred to CYS-005 database accordingly. If there is a worsening or reoccurring of such medical history after administration of the IMP, this should be considered a new AE and reported.

Worsening of DED will be considered an AE only if the dry eye status of the subject exceeds their previous experiences with the condition. This will be determined by the subject and the investigator.

A clinically relevant worsening of visual acuity from Visit 0 of CYS-004, [redacted] will be considered an AE.

IMP includes the investigational drug under evaluation and any other medications required by the protocol given during any stage of the trial.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to IMP, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon non-leading questioning.

AEs (both elicited and observed) will be monitored from the time of Informed Consent and throughout the trial. All AEs will be promptly reviewed by the investigator for accuracy and completeness. All AEs will be documented on the appropriate source document and eCRF.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to investigational product or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

Severity is not the same as "seriousness", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning (see Section 9.2). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.1.2 Relationship to Investigational Product

The relationship of each AE to the IMP should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the investigational product caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the investigational product caused the AE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. Types of evidence that would suggest a causal relationship between the IMP and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IMP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IMP exposure, but is otherwise uncommon in the population exposed to the IMP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the trial population independent of drug therapy) that indicates those events occur more frequently in the IMP-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IMP. CyclASol contains the active ingredient CsA and the vehicle F4H5 and has been tested in three clinical studies up to now, AEs of those have been listed in the Investigator's Brochure. Therefore, the following definition will be used:

- *Unexpected*: An AE that is not listed in the investigator's brochure (IB) in the Adverse Reaction Section at the specificity or severity that has been observed.
- *Expected*: An AE that is listed in the investigator's brochure (IB) in the Adverse Reaction Section at the specificity and severity that has been observed.
- *Not Applicable*: Any AE that is unrelated to the IMP.

The Investigator should initially classify the expectedness of an AE, but the final classification is subject to the sponsor's determination.

9.1.4 Outcome

The outcome of any AE will be determined and recorded using the following categories:

- Recovered/Resolved
- Recovering/Resolving

- Not Recovered/Not Resolved
- Recovered/Resolved with Sequelae
- Lost to Follow-up
- Fatal
- Unknown

9.1.5 Period of Observation

For the purpose of this study, the period of observation for collection of adverse events extends from the time the patient gives informed consent until the end of the Visit 6 at (Week 52 ± 1) or Early Termination.

If the investigator detects a Serious Adverse Event (Section 9.2) in a study patient after the end of the period of observation this should be reported to the Sponsor only if the investigator considers the event related to prior study treatment or procedures. The investigator should contact the sponsor to determine how the adverse event should be documented and reported.

9.2 Serious Adverse Events

An AE 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;
  - Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;
  - Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.
  - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect;
- Medically important.
  - Note: Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to [redacted], Novaliq, [redacted] and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of their relationship to the IMP, must be immediately reported (i.e. within a maximum 24 HOURS after becoming aware of the event). All information relevant to the SAE must be recorded on the appropriate SAE report forms. The investigator is obligated to pursue and obtain information requested by [redacted] and/or Novaliq in addition to that information reported on the case report form. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify [redacted] and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide [redacted] and the trial sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IMP; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

External safety service provider	[redacted]
Email:	[redacted]
Fax:	[redacted]

Contact information for Medical Monitor:

Medical Monitor:	[redacted]
Office Telephone:	[redacted]
Alternative Telephone (24-hr line):	[redacted]
Fax:	[redacted]

9.3.2 Reporting a Suspected Unexpected Serious Adverse Reaction

All SAE that are 'suspected reactions' and 'unexpected' are to be reported to the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

9.4 Procedures for Unmasking of IMP

All subjects, investigators, and trial personnel involved with the conduct of the trial will be unmasked as this is a single-arm and open label extension trial.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF page with the status noted.

If the investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE Report Form must be completed and e-mailed/faxed [redacted] within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

9.6 Procedures for Reporting Pregnancies

Pregnancy in itself is not considered an AE or SAE (unless there is a suspicion that an IMP may have interfered with the effectiveness of a contraceptive medication), but it is an important medical event that must be followed up. Any pregnancy that occurs during the clinical trial where the fetus could have been exposed to IMP must be followed through the outcome of the pregnancy.

It is the responsibility of the Investigator to obtain the outcome and condition of the infant information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

If a subject or Investigator suspects that the subject may be pregnant prior to IMP administration, the IMP must be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the subject must not receive IMP and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving IMP treatment, the IMP must immediately be withheld until the result of pregnancy testing is known.

If a female has a positive pregnancy test during the trial, then the investigator must report the pregnancy and the outcome of the pregnancy to [redacted] within 24 hours of learning about the pregnancy.

A Pregnancy Reporting Form will be completed by the trial site's principal investigator and sent to [redacted] via the SAE Fax number or e-mail (see Section 9.3). [redacted] will forward the documentation to the medical monitor, [redacted] project manager and the sponsor for review.

At the completion of the pregnancy, the Pregnancy Outcome Form is to be submitted to [redacted] via the SAE contact details. [redacted] will manage the query and reconciliation process until the pregnancy documentation is complete.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis population will be considered:

- Safety Set (SAF) – The SAF includes all enrolled subjects who received at least one dose of the IMP. The SAF will be analyzed for all assessments.

The statistical analysis of baseline, primary and secondary endpoint data will be performed for the SAF.

10.2 Statistical Hypotheses

There are no formal hypotheses to be tested in this open-label safety extension trial.

10.3 Sample Size

[redacted] subjects will be enrolled in order to ensure that at least 100 evaluable participants complete [redacted] the 52 weeks (12-month) treatment period.

With 100 subjects completing the 52 weeks [redacted] treatment period, the study will have 95% or greater chance of observing adverse events that occur at a true incident rate of 3.0% or higher. Therefore, with 100 subjects completing 52 weeks [redacted] of treatment, if an adverse event of a specific type is not observed, then with 95% confidence, the true incidence rate of the adverse event is less than 3.0%.

10.4 Statistical Analysis

10.4.1 General Considerations

Quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The dichotomous variables will be summarized using counts and percentages.

Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

For the purpose of summarization, medical history, concurrent therapies, and AEs will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

Baseline measures are defined as the measure prior to the administration of IMP as defined in clinical trial CYS-004. CFB will be calculated as Visit CYS-005– Baseline CYS-004.

Summaries will be presented separately for subjects treated with CyclASol in CYS-004 and subjects treated with vehicle in CYS-004 as well as overall.

10.4.2 Unit of Analysis

For efficacy endpoints, the unit of analysis will be the "study eye" which was determined during CYS-004. This information is transferred to the CYS-005 trial.

10.4.3 Missing Data

The primary analysis will be completed with available data per subject from the Safety Set (SAF).

10.4.4 Primary Safety Analyses

All safety analyses will be performed on the Safety Population.

Dosing information will be summarized overall subjects and listed for each subject will be listed. Discontinuation of treatment will be summarized by treatment received. The primary reason for trial drug discontinuation will also be summarized by treatment received.

Adverse events (AEs) will be coded using the MedDRA dictionary. An AE is treatment emergent if it occurs or worsens after the first dose of trial treatment in clinical trial CYS-005.

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class, preferred term, maximal severity, and strongest relationship. Separate summaries will be performed for ocular and non-ocular AEs.

Concomitant medications will be coded using the most recent version of WHO-Drug Dictionary and summarized by treatment group.

10.4.5 Secondary Safety Analyses

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) and dilated fundoscopy will be summarized by visit using descriptive statistics. Changes or shifts from baseline (as defined in clinical trial CYS-004) will also be summarized where appropriate. Assessments performed by eye will be summarized separately for study eye and fellow eye.

10.4.6 Exploratory Analyses

The analysis of the prespecified efficacy endpoints and other endpoints will use the SAF with available data per subject.

Quantitative efficacy variables will be summarized descriptively (n, mean, standard deviation, median, min, and max) and analyzed similarly to the primary endpoint at each measured visit and CFB. Assessments performed by eye will be summarized separately for study eye and fellow eye.

Dichotomous secondary efficacy variables will be summarized descriptively (frequency and percentage).

[redacted]

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This trial will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of investigational products in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any trial specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to performing any trial specific procedures and assessments.

All informed consent/assent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the

governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the trial as well as those currently enrolled in the trial.

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11.1.2 Institutional Review Board (IRB) Approval

This trial is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103).

Only an IRB/IEC approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal trial subject data collected and processed for the purposes of this trial should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of [redacted] drug safety, the sponsor, the IRB/IEC approving this trial, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the trial subject's original medical and trial records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the investigational product may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

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

11.4.1 Retention of Documentation

All trial related correspondence, subject records, consent forms, record of the distribution and use of all investigational products and copies of case report forms should be maintained on file for at least two 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 two years

have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator must notify the sponsor prior to destroying trial documentation even after the above-mentioned time has passed.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

All subject data will be captured in the subject source documents which will be transcribed to the eCRFs. The investigator is responsible for ensuring that trial data is completely and accurately recorded on each subject's eCRF, source document, and all trial-related materials. All trial data should also be attributable, legible, contemporaneous, and original. Recorded data should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff that have been trained on the system and have access to the system. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the trial and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each investigator site to be maintained on file by the investigator.

11.6 Monitoring and Quality Assurance

During the course of the trial a clinical research associate (CRA) will make routine site visits to review protocol compliance, assess IMP accountability, and ensure the trial is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the trial monitoring will be outlined in a monitoring plan.

Domestic and foreign regulatory authorities, [redacted] and quality assurance, sponsor and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out with consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

11.7 Handling of Biological Samples

Not applicable.

11.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the trial. Authorship will be established before writing the manuscript. The trial sponsor will have the final decision regarding authorship, manuscript and publication.

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