Clinical Trial Protocol: CYS-003

Protocol Title:	A Phase 2b/3, multicenter, randomized, double-masked, vehicle-controlled clinical study to assess the efficacy and safety of topical CyclASol® for the treatment of signs and symptoms of Dry Eye Disease
Protocol Number:	CYS-003 / 17-110-0009
Study Phase:	2b / 3
Investigational Product Name:	CyclASol® 0.1 % Ophthalmic Solution (Cyclosporine A 0.1%)
IND/IDE/PMA Number:	128163
Indication:	Dry Eye Disease (*keratoconjunctivitis sicca*)
Investigators:	Multicenter
Sponsor:	Novaliq GmbH Im Neuenheimer Feld 515 69120 Heidelberg Germany
Contract Research Organization:	[redacted]
IRB/IEC:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673 USA

	Date
Original Protocol:	14 September 2017
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Confidentiality Statement

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SYNOPSIS

Protocol Title:	A Phase 2b/3, multicenter, randomized, double-masked, vehicle-controlled clinical study to assess the efficacy and safety of topical CyclASol® for the treatment of signs and symptoms of Dry Eye Disease
Protocol Number:	CYS-003 / 17-110-0009
Investigational Product:	1) CyclASol 0.1% Ophthalmic Solution (Cyclosporine A 0.1% solution) 2) Vehicle Ophthalmic Solution (F4H5)
Study Phase:	2b / 3
Study Objective	The objective of this study is to assess the efficacy, safety, and tolerability of CyclASol 0.1% Ophthalmic Solution in comparison to the vehicle for the treatment of the signs and symptoms of Dry Eye Disease (DED).
Overall Study Design:	
Structure:	This clinical study is multicenter, randomized, double-masked, and vehicle-controlled with a run-in period with artificial tears.
Duration:	An individual subject's participation is estimated to be approximately 14 weeks (approx. 2 weeks screening and 12 weeks treatment period)
Controls:	Vehicle Ophthalmic Solution (F4H5)
Dosage/Dose Regimen:	Subjects eligible to be randomized will receive one of the following treatments to dose with bilaterally BID for approximately 85 days (from Visit 1 to Visit 5). 1) CyclASol 0.1% Ophthalmic Solution (Cyclosporine A 0.1% solution) 2) Vehicle Ophthalmic Solution (F4H5) A 14-day study-run-in period will be used for subject selection before randomization. During this period, all subjects will receive Systane® Balance to dose with bilaterally BID.

Summary of Visit Schedule:	This clinical study involves 6 visits over the course of approximately 14 weeks: • Visit 0, Day -14 ± 2 days, Screening; • Visit 1, Day 1, Baseline/Randomization; • Visit 2, Day 15 ± 1 days, 2-Week Follow-Up; • Visit 3, Day 29 ± 2 days, 4-Week Follow-Up; • Visit 4, Day 57 ± 2 days, 8-Week Follow-Up; and • Visit 5, Day 85 ± 2 days, 12-Week Follow-Up and Study Exit.
Measures Taken to Reduce Bias:	This trial is a multi-center, randomized, double-masked and vehicle-controlled clinical study.
Study Population Characteristics:	
Number of Subjects:	Approximately [redacted] subjects will be screened to enroll at least 316 (158 per treatment arm) subjects at approximately 10 sites.
Condition/Disease:	Dry Eye Disease (*keratoconjunctivitis sicca*)
Inclusion Criteria:	**Each subject must:** a. Be at least 18 years of age; b. Provide written informed consent; c. Have a subject reported history of Dry Eye Disease [redacted]; d. Be currently using (within 30 days before Visit 0) over-the-counter (OTC) eye drops, lubricating gels and/or artificial tears for dry eye symptoms at Visit 0; e. Have an OSDI® score of [redacted] at Visit 0 and Visit 1; f. Have a total corneal fluorescein staining score of [redacted] g. Have a total lissamine green conjunctival score (sum of temporal and nasal regions) [redacted] h. Have an unanesthetized Schirmer's Test score [redacted] i. [redacted] j. Be able and willing to follow instructions and

	participate in all study assessments and visits.
Exclusion Criteria:	**Each subject must not:** a. Have any clinically significant slit-lamp findings at Visit 0 that require prescriptive medical treatment and/or in the opinion of the investigator may interfere with study parameters including trauma, Steven Johnson Syndrome, advanced epithelial basement membrane disease; [redacted] c. Have abnormal lid anatomy (e.g. incomplete eyelid closure, entropion, or ectropion) or abnormal blinking; [redacted] e. Have an ocular or periocular malignancy; [redacted] g. Have a history of herpetic keratitis; h. Have active ocular allergies or ocular allergies that may become active during the study period; i. Be diagnosed with an ongoing ocular or systemic infection (bacterial, viral, or fungal), including a fever, or be undergoing treatment with antibiotics at Visit 0 or Visit 1; j. Have worn contact lenses within 90 days before Visit 0 or anticipate using contact lenses during the study; [redacted]

	l. Have used topical CsA or Lifitegrast within 60 days before Visit 0; [redacted] n. Have had intraocular surgery or ocular laser surgery within 180 days before Visit 0, or have any planned ocular or eyelid surgeries during the study period; o. Be a woman who is pregnant, nursing, or planning a pregnancy; p. Be unwilling to submit a urine pregnancy test at Visit 0 and Visit 5 (or 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); q. 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 study, she must agree to use adequate birth control as defined above for the remainder of the study; r. Have an uncontrolled systemic disease; [redacted]

	[redacted] aa. 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 study results, or may interfere with the subject's participation in the study significantly; or [redacted]
Study Formulations and Formulation Numbers:	1) Systane Balance (run-in) 2) CyclASol 0.1% Ophthalmic Solution (Cyclosporine A 0.1% solution) 3) Vehicle Ophthalmic Solution (F4H5)
Evaluation Criteria:	
Efficacy Measures:	**Primary Efficacy Measures:** The following primary endpoints will be tested in order using hierarchical fixed sequence testing: 1. Change from baseline in total Corneal fluorescein staining (NEI scale) at Day 29 2. Change from baseline in Ocular Surface Disease Index (OSDI) at Day 29 [redacted]

	[redacted]
Safety Measures:	• Visual acuity (VA) • Slit-lamp biomicroscopy • Intraocular pressure (IOP) • Dilated fundoscopy • Systemic and ocular adverse events
[redacted]	[redacted]

General Statistical Methods and Types of Analyses

Hypotheses and Sample Size:

The primary endpoints will be tested in a hierarchical fixed sequence in the following order.

The statistical hypotheses for the primary endpoint of change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 are as follows:

H_{01}: The difference, between study eyes treated with CyclASol and study eyes treated with vehicle, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 = 0.

H_{A1}: The difference, between study eyes treated with CyclASol and study eyes treated with vehicle, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 ≠ 0, with superiority claimed if the difference is less than 0 (CyclASol minus vehicle).

The statistical hypotheses for the primary endpoint of the change from baseline total OSDI score at Day 29 are as follows:

H_{02}: The difference, between subjects treated with CyclASol and subjects treated with vehicle, in the mean change from baseline total OSDI score at Day 29 = 0.

H_{A2}: The difference, between subjects treated with CyclASol and subjects treated with vehicle, in the mean change from baseline total OSDI score at Day 29 ≠ 0, with superiority claimed if the difference is less than 0 (CyclASol minus vehicle)

One-hundred forty-two (142) intent to treat (ITT) subjects (study eyes) per treatment group yields 90% power to reject H_{01} in favor of H_{A1} and conclude superiority of CyclASol over vehicle in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 assuming a true difference (CyclASol minus vehicle) of -0.85, a common standard deviation of 2.2, and a two-sided alpha = 0.05. Additionally, 142 ITT subjects per treatment group yields 82% power to reject H_{02} in favor of H_{A2} and conclude superiority of CyclASol over vehicle in the mean change from baseline total OSDI score at Day 29 assuming a true difference (CyclASol minus vehicle) of - 5.0, a common standard deviation of 14.5, and a two-sided alpha = 0.05. Accounting for subject discontinuations, 316 total subjects will be enrolled assuming a dropout rate of 10%.

Hierarchical fixed sequence testing will be employed to maintain the type I error rate. The primary analyses will first test the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score between treatments at Day 29. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of CyclASol , then the study will be considered a success; CyclASol will be declared to be superior to vehicle in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29; and the difference in the mean change from baseline total OSDI score between treatments at Day

29 will be tested at the two-sided alpha = 0.05 level.

If in addition to a statistically significant test of the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 in favor of CyclASol, the test of the difference in the mean change from baseline total OSDI score at Day 29 is also statistically significant in favor of CyclASol, then CyclASol will be declared to be superior to vehicle in both the mean change from baseline corneal fluorescein staining (NEI scale) total score and the mean change from baseline total OSDI score at Day 29.

Primary Efficacy Analyses:

The primary comparisons in this study will be between CyclASol versus vehicle at Day 29. The primary efficacy endpoints (e.g. change from baseline in corneal fluorescein staining [total NEI] and OSDI) will be analyzed separately using an ANCOVA model with terms for baseline value, treatment, and the interaction of treatment by baseline value (the interaction term will be maintained in the model only if the p-value for the term is <0.10).

Least squares mean for each treatment group and for the difference between treatment groups will be presented from the model together with two-sided p-values and 95% confidence intervals. In the event that the interaction of treatment by baseline value is significant, estimate and contrast statements will be used to determine the treatment group means and differences at the 25th, 50th, and 75th percentile of the baseline score over treatment groups.

Two-sample t-tests, Wilcoxon rank sum tests and mixed-effect repeated measures analysis comparing treatment groups will be performed as sensitivity analyses.

The primary analysis will use the Full Analysis Set (FAS) with available data per subject. Additional robustness analyses will include repeating the primary analysis on the per protocol set (PPS); the FAS imputing missing data using last observation carried forward (LOCF); the FAS imputing missing data using Markov Chain Monte Carlo (MCMC) multiple imputation methodology under different assumptions of missingness (at random and not at random); and an analysis of trimmed means (Permutt et al., 2017).

[redacted]

[redacted]

Safety Variables

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. 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. Other safety endpoints including visual acuity, slit-lamp biomicroscopy, dilated fundoscopy, and intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized.

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List of Abbreviations

AE	Adverse Event
AIC	Akaike Information Criterion
ANCOVA	Analysis of Covariance
BCVA	Best-Corrected Visual Acuity
BID	Twice Daily
BLQ	Below the Limit of Quantification
CD	Compact Disc
CFR	Code of Federal Regulations
CI	Confidence Interval
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CS	Compound Symmetry
CsA	Cyclosporine A
CV	Curriculum Vitae
DED	Dry Eye Disease
DEWS	(International) Dry Eye Workshop
DHHS	Department of Health and Human Services
EKG	Electrocardiography, Electrocardiogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Information Portability and Accountability Act
IB	Investigators' Brochure
IBI	Inter Blink Interval
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Independent Review Board
[redacted]	[redacted]
ITT	Intent to Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
KCS	Keratoconjunctivitis Sicca
kg	Kilogram
LASIK	Laser-assisted in Situ Keratomileusis
LOCF	Last Observation Carried Forward

logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
µL	Microliter
mm	Millimeter
mmHg	Millimeters of Mercury
[redacted]	[redacted]
NCS	Not Clinically Significant
nd	Not Done
NDA	New Drug Application
NEI	National Eye Institute
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal Anti-inflammatory Drug
OD	Right Eye
OS	Left Eye
OSDI	Ocular Surface Disease Index
OU	Both Eyes
[redacted]	[redacted]
OTC	Over the Counter
PHI	Protected Health Information
PK	Pharmacokinetic
PPS	Per Protocol Set
PRN	As Needed
QD	Once Daily
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SFA	Semifluorinated Alkane
SOP	Standard Operating Procedures
TEAE	Treatment-emergent Adverse Event
TFBUT	Tear Film Break-up Time
TMF	Trial Master File
US	United States
VA	Visual Acuity
VAS	Visual Analog Scale
WHO	World Health Organization

1 INTRODUCTION

1.1 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 (DEWS II Definition and Classification 2017). As many as 5 - 35% of patients visiting ophthalmic clinics report dry eye symptoms, making it one of the most common conditions seen by ophthalmic specialists (McCarty CA, *et al*. 1998; Lin PY, *et al*. 2003). Estimates range from 20 million people in the United States (US) being affected with mild to moderate dry eye, to a high of as many as one out of every five Americans. Prevalence is greater in females and the elderly. Schaumberg *et al*. reported prevalence rates ranging from 3.9% in men aged 50–54 years to 7.7% in those 80 years or older, while an increased rate from 5.7% in women younger than 50 years to 9.8% in women >75 years was observed (Schaumberg DA, *et al*. 2003). Prevalence is affected by geographical parameters and appears to be higher in Asian populations. Dry eye can be related to external factors, such as the low humidity of air conditioned offices, winter heating, a dusty or windy outdoor environment, prolonged computer use, or wearing contact lenses, as well as to internal factors, such as hormonal imbalance, autoimmune disease, the presence of many widely prescribed systemic medications, anatomical changes or trauma, and aging. Symptoms result in mildly decreased quality of life at a minimum, and with increasing severity, loss of function and productivity, pain, light sensitivity, and the misery that accompanies significantly impaired vision and decreased quality of life. With the aging population in the United States and other countries of the developed world, and with increasing computer use, DED is expected to continue to become more prevalent and finding a treatment is becoming more important (Schaumberg DA, *et al*. 2009).

1.2 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 disease of the ocular surface such as DED. In the US, CsA eye drops formulated as an emulsion are 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 Commission for the treatment of DED in early 2015.

CyclASol is a clear ophthalmic solution of CsA developed with the goal of avoiding the use of oils, surfactants and preservatives. Potential benefits from the 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

colorless, it has a high vapor pressure and is immiscible with water but has nearly the same refractory index as water. F4H5's physical properties make it an optimal vehicle for topical ocular use. As a result of its high vapor pressure (Krafft MP 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). 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. These dissemination and spreading properties are further thought to improve the local bioavailability.

1.3 Trial Rational

The preclinical profile of CyclASol and of F4H5, the new excipient, has been well characterized. The chronic toxicity studies with F4H5 in rats (oral route) and rabbits (ocular route) estimated NOAELs of 1000 mg/kg/day and 342 mg/kg/day, respectively. These values were 1000-fold and 342-fold above the anticipated clinical dose.

Nonclinical and clinical data suggest that the CyclASol formulation may deliver CsA more rapidly to the target tissues than Restasis. In a murine dry eye model CsA in F4H5 and Restasis were equally effective in reducing corneal staining and, F4H5/CsA was associated with a more rapid therapeutic response and the only treatment that maintained conjunctival goblet cells (Gehlsen 2015).

After successful completion of a Phase 1 safety, tolerability and PK study, a second, multicenter, randomized, double-masked (with an open label comparator - Restasis) phase 2 study investigating the efficacy and safety of CyclASol Ophthalmic Solution (0.05% and 0.1%) in comparison to vehicle in patients with DED was conducted. This was an exploratory Phase 2 study without formal power calculations and no adjustments for multiple comparisons. In this study both CyclASol groups showed consistent improvements in corneal and conjunctival staining compared to the vehicle over the 4-month treatment period. These improvements were already visible after 2 weeks of treatment (Visit 2) and became statistically significant over Restasis at Visit 3 (1 month), which indicates an earlier onset of effect compared to Restasis. The most pronounced effect was seen in the central and inferior area of the cornea, which is particularly important from a patient perspective as it positively influences proper visual function in dry eye patients.

All treatment groups demonstrated improvement in symptoms. In the Ocular Surface Disease Index (OSDI), the vision-related subscale (questions 6 through 9), particularly the question regarding impact on reading, demonstrated a numerically more pronounced effect in CyclASol groups when compared to vehicle.

The CyclASol effect became statistically significant over vehicle (total corneal staining $p<0.1$, central corneal staining $p<0.001$, conjunctival staining $p<0.01$) when using a model-based

analysis. This analysis also suggests a significant CyclASol effect for OSDI as a symptom parameter ($p < 0.01$).

[redacted]

Moreover, both CyclASol concentrations showed excellent safety, tolerability, and comfort profiles. Due to the comparable safety profile but slightly better efficacy of CyclASol 0.1% over CyclASol 0.05%, the higher concentration (CyclASol 0.1%) was chosen for the present study.

Based on these encouraging results the present Phase 2b/3 study was designed to confirm efficacy and safety of CyclASol. Furthermore, additional symptoms shall be explored to learn for further studies.

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

The investigational product (IP) 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 physically, chemically and physiologically inert. 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.

The Phase 2 study showed that CyclASol eye drops are effective in the treatment of signs and symptoms of DED in particular in the sub-population selected for the present study.

In the Phase 1 clinical study with CyclASol the most frequently reported treatment-emergent adverse event TEAE was headache (1 subject [5.6%] after CyclASol and 3 subjects [16.7%] after placebo) and in the Phase 2 clinical study the most frequently reported ocular TEAE (11 subjects [5.3%]) was visual acuity (VA) reduced.

All TEAEs were of mild to moderate intensity. In Phase 1 no subject discontinued the study due to AEs and in Phase 2 three (3) subjects (1.4%) withdrew from study treatment due to an ocular TEAE, two of which were considered at least possibly related to study drug. No deaths were observed in either study. Three (3) treatment-emergent serious adverse events (SAEs) were reported during the Phase 2 study. All SAEs were non-ocular, were considered not-related to study treatment, and had recovered by the end of the study.

Adverse effects resulting from systemic absorption of CsA appear unlikely, because no systemic exposure of CsA could be detected after application of 1 or 2 drops of CyclASol twice daily in neither of the two clinical CyclASol trials, since all plasma concentrations were below the quantification limit (BLQ) (i.e. <0.100 ng/mL).

Adverse effects due to systemic absorption of F4H5 appear very unlikely, as this excipient is very poorly absorbed and did not indicate any potential for toxicity in animal studies. In the two

clinical studies, most samples showed concentrations BLQ, the sporadic samples with measurable F4H5 concentrations were hardly above the BLQ.

In summary, based on the preclinical and clinical data obtained to date, risks to subjects in the planned CYS-003 study are considered very low. Furthermore, the patients randomized in the study will be closely monitored, and current standard ophthalmological safety assessments will be performed during the entire treatment period. The efficacy demonstrated to date supports that CyclASol improves signs and symptoms of DED. In particular corneal and conjunctival staining signs were reduced and symptoms related to visual function showed improvement. CyclASol therefore provides a favorable risk-benefit treatment profile to patients with DED and the CYS-003 study plans to further assess this positive profile.

2 STUDY OBJECTIVES

The objective of this study is to assess the efficacy, safety, and tolerability of CyclASol in comparison to the vehicle for the treatment of the signs and symptoms of (DED).

3 CLINICAL HYPOTHESES

The clinical hypotheses for this study are that CyclASol is superior to vehicle in improving the primary sign and symptom endpoints of DED, as follows:

- Corneal fluorescein staining (NEI Scale) total score at day 29 is more reduced compared to baseline in patients receiving CyclASol than in patients receiving vehicle;
- OSDI total score at day 29 is more reduced compared to baseline in patients receiving CyclASol than in patients receiving vehicle.

4 STUDY DESIGN

4.1 Overall Study Design

This is a Phase 2b/3 multicenter, randomized, double-masked, and vehicle-controlled clinical study to evaluate the efficacy, safety and tolerability of CyclASol 0.1% Ophthalmic Solution in subjects with DED. Approximately 316 subjects of either sex and of any race who are at least 18 years of age with a subject-reported history of dry eye in both eyes and meeting all other study eligibility criteria will be randomized at approximately 10 sites in the US to receive treatment with CyclASol or vehicle in a 1:1 ratio (approx. 158 subjects per treatment arm). This study is composed of two distinct parts: a 14-day run-in period and an 85-day treatment period. During the run-in period, subjects will dose Systane Balance bilaterally BID for approximately two weeks. Eligible patients will thereafter dose the study treatment (CyclASol or vehicle) bilaterally BID for approximately 3 month. A chart illustrating the study's structure is below.

Visit 0 Day -14 ± 2 days Screening	Informed consent (incl. HIPAA) Demographics, medical/medication history & ocular history Review of qualification criteria Urine pregnancy test (as needed) Symptom questionnaires, [redacted] Eye evaluations (Efficacy /Safety) AE query In-office dose of run-in Dispensation of subject diary and run-in to qualified subjects

↓

Approximate 14-Day Run-In Period with Systane Balance

↓

Visit 1 Day 1 Baseline / Randomization	Collection and review of run-in/diary AE query, medical/medication update Review of qualification criteria Symptom questionnaires, [redacted] Eye evaluations (Efficacy /Safety) Randomization In-office dose and drop comfort scale and questionnaire Dispensation of study drug and subject diary

↓

Visit 2 Day 15 ± 1 day 2-Week Follow-Up	Collection and review of study drug/diary AE query, medical/medication update Symptom questionnaires Eye evaluations (Efficacy /Safety) Redispensation of study drug and dispensation of subject diary

↓

Visit 3 Day 29 ± 2 days	Collection and review of study drug/diary AE query, medical/medication update

4-Week Follow-Up	Symptom questionnaires, [redacted] Eye evaluations (Efficacy /Safety) Dispensation of study drug and subject diary

↓

Visit 4 Day 57 ± 2 days 8-Week Follow-Up	Collection and review of study drug/diary AE query, medical/medication update Symptom questionnaires Eye evaluations (Efficacy /Safety) Dispensation of study drug and subject diary

↓

Visit 5 Day 85 ± 2 days 12-Week Follow-Up and Study Exit	Collection and review of study drug/diary AE query medical/medication update and further demographic data Urine pregnancy test (as needed) Symptom questionnaires, reading assessments Eye evaluations (Efficacy /Safety) Study exit

Subjects who terminate early during the treatment period will be asked, if possible, to complete safety assessments before commencing any alternate dry eye therapy. Subjects who are terminated early from the study will not be replaced.

4.2 Participant and Study Completion

An estimated [redacted] subjects will be screened to enroll and randomize at least 316 subjects at approximately 10 sites with 158 subjects per each of the two treatment arms.

The study is planned to start with first patient first visit in October 2017 and is estimated be completed with last subject last visit occurring in June 2018.

4.3 End of Study Definition

The end of the study for an individual patient is defined as that patient's last clinic visit.

The end of the study for the overall trial is defined as the finalization of the Clinical Study Report.

4.4 Justification of Study Design

Based on CYS-002 results Novaliq plans a confirmatory study in DED patients having [redacted] (NEI grading) at baseline. This population responded best in signs and symptoms.

The study will be a randomized, double-masked, vehicle controlled study to demonstrate efficacy and safety of CyclASol after 1-month treatment duration. Vehicle controlled studies are currently the standard for DED studies. Randomization and double masking are state of the art measures to reduce bias. Fast onset of efficacy is important for patients and their compliance to therapies, thus early demonstration of efficacy (e.g. at 1 month) is desired and highly clinically relevant. Moreover, DED is a fluctuating condition with phase-like recurring dry eye complaints that may be linked to seasonal and / or environmental changes (van Setten, *et al*. 2016), thus a primary endpoint assessment at a shorter treatment duration is considered clinically relevant and has a greater potential to capture the true drug effect.

Total corneal fluorescein staining (NEI grading) and total OSDI have been selected as the primary sign endpoint and primary symptom endpoint, respectively. The two primary endpoints will be tested in a sequential order with total corneal fluorescein staining being tested first. Both primary endpoints are well accepted by regulators and clinicians. The hierarchical testing has been selected to protect the α – error. Corneal staining is being tested first as the CYS-002 data for this endpoint is stronger.

4.5 Justification for Dose

The dose for this trial has been selected based on the previous CYS-002 study, which investigated two concentrations of CyclASol (0.05% and 0.1%). Neither the statistical analysis on the total population nor the modelling & simulation analysis identified a clear dose-response for sign or symptoms between the two CyclASol groups. However, there were some trends favoring CyclASol 0.1% over CyclASol 0.05% in symptoms in all subjects and in the target population for the current study (patients having total corneal staining of $\geq$10 at baseline). Moreover, the CsA amount applied with the CyclASol 0.1% is still lower than that of Restasis [redacted] Novaliq intends to pursue the concentration of CyclASol 0.1% for the current pivotal study CYS-003.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

An estimated [redacted] subjects will be screened to enroll and randomize at least 316 subjects at approximately 10 sites with 158 subjects per each of the two treatment arms. Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 1:1 ratio of CyclASol to vehicle.

5.2 Study Population Characteristics

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

Each subject must:

a. Be at least 18 years of age;

b. Provide written informed consent;

c. Have a subject reported history of Dry Eye Disease [redacted]

d. Be currently using (within 30 days before Visit 0) over-the-counter (OTC) eye drops, lubricating gels and/or artificial tears for dry eye symptoms at Visit 0;

e. Have an OSDI score of [redacted] at Visit 0 and Visit 1;

f. Have a total corneal fluorescein staining score of [redacted]

g. Have a total lissamine green conjunctival score (sum of temporal and nasal regions) of [redacted]

h. Have an unanesthetized Schirmer's Test score [redacted]

[redacted]

j. Be able and willing to follow instructions and participate in all study assessments and visits.

5.4 Exclusion Criteria

Each subject must not:

a. Have any clinically significant slit-lamp findings at Visit 0 that require prescriptive medical treatment and/or in the opinion of the investigator may interfere with study parameters including trauma, Steven Johnson Syndrome, advanced epithelial basement membrane disease;

[redacted]

[redacted]

c. Have abnormal lid anatomy (e.g. incomplete eyelid closure, entropion, or ectropion) or abnormal blinking;

[redacted]

e. Have an ocular or periocular malignancy;

[redacted]

g. Have a history of herpetic keratitis;

h. Have active ocular allergies or ocular allergies that may become active during the study period;

i. Be diagnosed with an ongoing ocular or systemic infection (bacterial, viral, or fungal), including a fever, or be undergoing treatment with antibiotics at Visit 0 or Visit 1;

j. Have worn contact lenses within 90 days before Visit 0 or anticipate using contact lenses during the study;

[redacted]

l. Have used topical CsA or Lifitegrast within 60 days before Visit 0;

[redacted]

n. Have had intraocular surgery or ocular laser surgery within 180 days before Visit 0, or have any planned ocular or eyelid surgeries during the study period;

o. Be a woman who is pregnant, nursing, or planning a pregnancy;

p. Be unwilling to submit a urine pregnancy test at Visit 0 and Visit 5 (or 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);

q. 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 study, she must agree to use adequate birth control as defined above for the remainder of the study;

r. Have an uncontrolled systemic disease;

[redacted]

aa. 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 study results, or may interfere with the subject's participation in the study significantly; or

[redacted]

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study in particular:

- the occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the investigator and/or sponsor.
- the occurrence of an AE if discontinuation of trial drug is desired or considered necessary by the investigator and/or the subject.
- the occurrence of pregnancy.

Subjects may withdraw consent from the study at any time without reason.

The sponsor and/or the investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.6).

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Variable(s)

Two primary endpoints will be tested in the following order using hierarchical fixed sequence testing:

1. Change from baseline in total corneal fluorescein staining (NEI scale) at Day 29
2. Change from baseline in Ocular Surface Disease Index (OSDI) at Day 29

[redacted]

6.1.4 Criteria for Effectiveness

Hierarchical fixed sequence testing will be employed to maintain the type I error rate. The primary analyses will first test the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score between treatments at Day 29. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of CyclASol, then the study will be considered a success; CyclASol will be declared to be superior to vehicle in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29; and the difference in the mean change from baseline total OSDI score between treatments at Day 29 will be tested at the two-sided alpha = 0.05 level.

If in addition to a statistically significant test of the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 in favor of CyclASol, the test of the difference in the mean change from baseline total OSDI score at Day 29 is also statistically significant in favor of CyclASol, then CyclASol will be declared to be superior to vehicle in both the mean change from baseline corneal fluorescein staining (NEI scale) total score and the mean change from baseline total OSDI score at Day 29.

[redacted]

[redacted]

[redacted]

6.2 Safety Measures

These evaluations will be performed in an effort to ensure subject safety throughout the trial:

- Change in visual acuity from baseline at Visit 1 to Visits 2, 3, 4, and 5;
- Change in slit-lamp biomicroscopy findings from Visit 1 to Visits 2, 3, 4, and 5;
- Change in intraocular pressure from Visit 0 to Visit 3 and 5;
- Change in dilated fundoscopy findings from Visit 0 to Visit 5.
- Systemic and ocular AEs

[redacted]

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment(s)/ Formulation(s)/ Medical Device Composition or Design

Run-In

- Systane Balance Lubricant Eye Drops

Randomized Study Treatments

- CyclASol 0.1% Ophthalmic Solution
- Vehicle Ophthalmic Solution (F4H5)

7.1.2 Description of for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s).

- At the end of Visit 0, qualified subjects will receive the run-in medication (Systane Balance). Their first dose of run-in will be in-office. They will then be instructed to dose at home BID up to and including the morning of Visit 1. Subjects will be instructed to dose in the morning and in the evening at bedtime. Subjects will record in the subject's diary that their doses were taken.

- Study drug will be provided to sites as subject kits containing 3 bottles of CyclASol 0.1% Ophthalmic Solution or Vehicle Ophthalmic Solution.

- At Visit 1, used/unused run-in will be collected from subjects. At the end of Visit 1, qualified subjects will be randomized and the first dose of study drug will be administered in the study center. The subject will receive the first bottle out of the assigned subject kit for dosing BID. Subjects will record in their diary that their doses were taken. A bottle should not be used after 30 days after opening; based on the use of visit windows for a subject this may be prolonged at the discretion of the Investigator.

- At Visit 2, used/unused study drug will be collected from subjects for drug accountability. If the bottle is still intact and contains sufficient liquid it will be returned to the subject with instructions to continue to dose BID. If the bottle is not intact or there is insufficient liquid in the bottle, the subject will be dispensed a new bottle to continue BID dosing. Subjects will record in their diary that their doses were taken. A bottle should not be used after 30 days after opening; based on the use of visit windows for a subject this may be prolonged at the discretion of the Investigator.

- At Visit 3 used/unused study drug will be collected from subjects for drug accountability. Subjects will receive their bottle from the same subject kit with instructions to continue to dose BID. The site must ensure that the study drug supply given to the subject is taken from the correct kit that was previously assigned to that subject. Subjects will record in their diary that their doses were taken. A bottle should not be used after 30 days after opening; based on the use of visit windows for a subject this may be prolonged at the discretion of the Investigator.

- At Visit 4 used/unused study drug will be collected from subjects for drug accountability. Subjects will be dispensed the third bottle from the same subject kit with instructions to continue to dose BID. The site must ensure that the study drug supply given to the subject is taken from the correct kit that was previously assigned to that subject. Subjects will record in their diary that their doses were taken. A bottle should not be used after 30 days after opening; based on the use of visit windows for a subject this may be prolonged at the discretion of the Investigator.

- At Visit 5 used/unused study drug will be collected from subjects for drug accountability.

- Subjects will be instructed to use run-in (at Visit 1) or study drug on the day of visits (Visit 2, 3, 4, and 5) at least 2 hours prior to the start of the visit.

- Subjects will be instructed to immediately contact the site if there is any problem with the study drug (e.g. if the bottle was dropped or lost). In case the subject needs a replacement, the next bottle from the kit will be dispensed. If no bottle remains in the kit, a new kit will be assigned to the subject using the IWRS.

7.1.3 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 before bed). 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 dose and complete their diary.

7.2 Other Study Supplies

Schirmer's test strips, sodium fluorescein, lissamine green, lissamine strips, Fluress, Tropicamide, InflammaDry.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in sections 5.2, 5.3, and 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Before a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or study-related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent (and/or assent) using an informed consent form. The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board (IRB).

8.1.3 Washout Intervals

Prohibiteed medications and treatments are listed in the Exclusion Criteria (Section 5.4) with their respective washout intervals.

8.1.4 Procedures for Final Study Entry

To qualify for Final Study Entry, each subject must meet all of the Inclusion Criteria (Section 5.3) and none of the Exclusion Criteria (Section 5.4).

8.1.5 Methods for Assignment to Treatment Groups:

Before the initiation of study run-in at Visit 0, each subject who provides written and informed consent will be assigned to a screening number. All screening numbers will be assingned in strict numerical sequence at a site and no numbers will be skipped or omitted. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 0 and Visit 1 will be assigned a randomization number at the end of Visit 1. The IWRS will be used to assign all randomization numbers.

Randomization and kit numbers will be assigned automatically to each subject by strata as they are entered into the IWRS. [redacted]

[redacted]

The site staff will dispense from this kit medication required until the next visit. Both the randomization number and the dispensed study drug kit number will be recorded on the subject's source document and electronic Case Report Form (eCRF). The rest of the kit will remain at the site and the site ensures that the same subject will receive study medication from the respective kit at his/her next visit. The sponsor, investigators, and study staff will be masked during the randomization process and throughout the study.

8.2 Concurrent Therapies

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

Concurrent enrollment in another investigational drug or medical device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Disallowed medications and treatments are listed in the Exclusion Criteria (Section 5.4). All medications and treatments that were not allowed prior to

study are also not allowed during the study, in particular no other dry eye treatment shall be used during the course of the study such as artificial tears (other than run-in medication), gels, ointments shall be used during the course of the study. Physical treatments such as lid scrubs, lid wipes, warm compresses must be kept stable. Hypochlorous acid wipes are not allowed.

8.2.2 Escape Medications

Not applicable.

[redacted]

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objective(s)

The procedures outlined in this section will performed as described in Appendix 2.

Visit 0 (Day -14 ± 2 days): Screening

- Informed consent / HIPAA
- Medical/medication history and demographic data
- Urine pregnancy test for females of childbearing potential
- Ocular Surface Disease Index (OSDI)
- [redacted]
- Visual acuity (ETDRS)
- Slit-lamp biomicroscopy
- [redacted]
- Fluorescein staining (NEI scale)
- [redacted]
- Intraocular pressure
- Dilated fundoscopy
- Review of qualification criteria
- In-office instillation of run-in drops to qualified subjects
- Dispensation of subject diary and run-in for bilateral, BID dosing until Visit 1 as described in Section 7.1.3
- Adverse event query

- Qualified subjects are scheduled for Visit 1

Visit 1 (Day 1): Baseline / Randomization

- Collection and review of run-in and diary
  - Calculate subject compliance as described in Section 8.5
  - Ask subject if he/she dosed with run-in the morning of Visit 1 and, if applicable, record the time of the dose
- Medical/medication history update
- Adverse event query
- OSDI
- [redacted]
- Visual acuity
- Slit-lamp biomicroscopy
- [redacted]
- Fluorescein staining (NEI scale)
- [redacted]
- Review of qualification criteria
- Randomization
- In-office instillation of randomized study drug
- [redacted]
- Dispensation of subject diary and randomized study drug for bilateral, BID dosing until Visit 2 as described in Section 7.1.3
- Adverse event query
- Randomized subjects are scheduled for Visit 2

Visit 2 (Day 15 ± 1): 2-Week Follow-Up

- Collection and review of study drug and subject diary
- [redacted]
- Medical/medication history update
- Adverse event query

- OSDI
- Visual acuity
- Slit-lamp biomicroscopy
- Fluorescein staining (NEI scale)
- Dispensation of subject diary and randomized study drug for bilateral, BID dosing until Visit 3 as described in Section 7.1.3
- Adverse event query
- Schedule for Visit 3

Visit 3 (Day 29 ± 2): 4-Week Follow-Up

- Collection and review of study drug and subject diary;
- Medical/medication history update
- Adverse event query
- OSDI
- Visual acuity
- Slit-lamp biomicroscopy
- Fluorescein staining (NEI scale)
- Intraocular pressure
- Dispensation of subject diary and randomized study drug for bilateral, BID dosing until Visit 4 as described in Section 7.1.3
- Adverse event query
- Schedule for Visit 4

Visit 4 (Day 57 ± 2): 8-Week Follow-Up

- Collection and review of study drug and subject diary
- Medical/medication history update
- Adverse event query
- OSDI
- Visual acuity
- Slit-lamp biomicroscopy
- Fluorescein staining (NEI scale)
- Dispensation of subject diary and randomized study drug for bilateral, BID dosing until Visit 5 as described in Section 7.1.3
- Adverse event query
- Schedule for Visit 5

Visit 5 (Day 85 ± 2): 12-Week Follow-Up and Study Exit

- Collection and review of study drug and subject diary
- Medical/medication history update, and further demographic data
- Urine pregnancy test for females of childbearing potential
- Adverse event query
- OSDI
- Visual acuity
- Slit-lamp biomicroscopy

- [redacted]
- Fluorescein staining (NEI scale)
- [redacted]
- Intraocular pressure
- Dilated fundoscopy
- Adverse event query
- Study exit

8.3.2 Early Termination/Discontinuations

If a subject is discontinued from the study before Visit 5 (Day 85 ± 2 days), then all safety evaluations that are to be performed at Visit 5 should be performed and the demographic data [redacted] should be obtained on the day of early termination/discontinuation or at the discretion of the investigator.

Adverse events (both elicited and observed) will be monitored throughout the study. All AEs will be promptly reviewed by the investigator for accuracy and completeness. All AEs will be documented on the appropriate eCRF.

If a female has a positive pregnancy test during the study, then the investigator will notify [redacted] immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to [redacted].

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

An unscheduled visit may be performed during the course of the study 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;

- VA;
- IOP;
- Urine pregnancy test (for women of childbearing potential);
- Dilated fundoscopy;
- Assessment of AEs;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgement of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on the proper use and storage of the study drug at Visits 0, 1, 2, 3, and 4, and provided with written instructions. Subject diaries and study drug will be collected at each visit from Visit 1 up to and including Visit 5 to assess subject compliance with the protocol.

[redacted]

8.6 Subject Disposition

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to:

- AEs;
- Protocol violations;
- Lack of efficacy;
- Administrative reasons (e.g., inability to continue, lost to follow up);
- Sponsor termination of study;
- Pregnancy;
- Other

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the investigator.

Notification of a subject discontinuation and the reason for discontinuation will be made to [redacted] and/or study sponsor and will be clearly documented on the eCRF.

Discontinued subjects will not be replaced.

8.7 Study Termination

The study may be stopped at any time by the investigator, the sponsor, and/or [redacted] with appropriate notification.

The whole trial may be discontinued prematurely in the event of any of new information leading to unfavorable risk-benefit judgment of the IP, 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 IP.
- Health Authorities and IECs/ IRBs will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

8.8 Study Duration

An individual subject's participation will involve 6 visits over approximately a 14-week period. If applicable and as needed, after the study, subjects will be treated according to the standard of care by the discretion of the investigator / treating physician.

8.9 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug/device accountability, and ensure the study 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 study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, sponsor quality assurance 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 giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

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 drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug or the run-in medication, without any judgment about causality.

If there is a worsening of a medical condition that was present prior to the administration of the study drug, this should also be considered a new AE and reported. Any medical condition present prior to the administration of the study drug that remains unchanged or improved should not be recorded as an AE at subsequent visits.

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 significant visual acuity decrease [redacted] from baseline (Visit 0) will be considered an AE.

Study drug includes the investigational drug under evaluation and any comparator drug, vehicle, or any other medications required by the protocol given during any stage of the study.

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

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 patient/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.

9.1.2 Relationship to Investigational Product

The relationship of each AE to the investigational product 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 investigational product and the AE. Types of evidence that would suggest a causal relationship between the investigational product and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (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 study population independent of drug therapy) that indicates those events occur more frequently in the IP-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 study drug. CyclASol contains the active ingredient CsA and the vehicle F4H5 and has been tested in two 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 study drug.

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

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 patient 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.

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 patient or 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] the study sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AE that are 'suspected' and 'unexpected' are to be reported to [redacted] the study sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the investigational product, 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 case report forms. The investigator is obligated to pursue and obtain information requested by [redacted] and/or the sponsor 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 study 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 investigational product; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

[redacted]

9.4 Procedures for Unmasking (if applicable)

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), [redacted] and/or the study sponsor should be notified before unmasking study drug. [redacted] and/or the study sponsor must be informed immediately about any unmasking event.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact [redacted] and/or the medical monitor prior to unmasking the identity of the IP, if possible. [redacted] will ask the site to complete and send them the Unmasking Request Form. [redacted] will notify Novaliq and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject using IWRS. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File (TMF). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject, must be noted in the subject's study file.

Unmasked subjects will be discontinued from the study.

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 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/Unanticipated Report Form must be completed and faxed to [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.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis population will be considered:

- Full Analysis Set (FAS) – The FAS includes all randomized subjects who received at least one dose of investigation product. The primary analysis will be performed on the FAS. Subjects in the FAS will be analyzed as randomized.

- Per Protocol Set (PPS) – The PPS includes subjects in the FAS who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PPS will be analyzed using observed data only for efficacy variables. Subjects in the PPS will be analyzed as treated.

- Safety Set (SAF) – The SAF includes all randomized subjects who have received at least one dose of the investigational product. The SAF will be analyzed for all safety assessments. Subjects in the SAF will be analyzed as treated.

The statistical analysis of safety data will be performed for the SAF. The analysis of baseline and efficacy data will be performed for the FAS. The primary efficacy analyses will also be performed on the PPS as sensitivity analyses.

10.2 Statistical Hypotheses

The primary endpoints will be tested in a hierarchical fixed sequence in the following order.

The statistical hypotheses for the primary endpoint of change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 are as follows:

H_{01}: The difference, between study eyes treated with CyclASol and study eyes treated with vehicle, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 = 0.

H_{A1}: The difference, between study eyes treated with CyclASol and study eyes treated with vehicle, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 $\neq$ 0, with superiority claimed if the difference is less than 0 (CyclASol minus vehicle).

The statistical hypotheses for the primary endpoint of the change from baseline total OSDI score at Day 29 are as follows:

H_{02}: The difference, between subjects treated with CyclASol and subjects treated with vehicle, in the mean change from baseline total OSDI score at Day 29 = 0.

H_{A2}: The difference, between subjects treated with CyclASol and subjects treated with vehicle, in the mean change from baseline total OSDI score at Day 29 ≠ 0, with superiority claimed if the difference is less than 0 (CyclASol minus vehicle).

Hierarchical fixed sequence testing will be employed to maintain the type I error rate. The primary analyses will first test the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score between treatments at Day 29. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of CyclASol, then the study will be considered a success; CyclASol will be declared to be superior to vehicle in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29; and the difference in the mean change from baseline total OSDI score between treatments at Day 29 will be tested at the two-sided alpha = 0.05 level.

If in addition to a statistically significant test of the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 in favor of CyclASol, the test of the difference in the mean change from baseline total OSDI score at Day 29 is also statistically significant in favor of CyclASol, then CyclASol will be declared to be superior to vehicle in both the mean change from baseline corneal fluorescein staining (NEI scale) total score and the mean change from baseline total OSDI score at Day 29.

10.3 Sample Size

One-hundred forty-two (142) ITT subjects (study eyes) per treatment group yields 90% power to reject H_{01} in favor of H_{A1} and conclude superiority of CyclASol over vehicle in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 assuming a true difference (CyclASol minus vehicle) of -0.85, a common standard deviation of 2.2, and a two-sided alpha = 0.05. Additionally, 142 ITT subjects per treatment group yields 82% power to reject H_{02} in favor of H_{A2} and conclude superiority of CyclASol over vehicle in the mean change from baseline total OSDI score at Day 29 assuming a true difference (CyclASol minus vehicle) of -5.0, a common standard deviation of 14.5, and a two-sided alpha = 0.05. Accounting for subject discontinuations, 316 total subjects will be enrolled [redacted].

For justification of clinical relevance of selected differences see Section 6.1.4.

10.4 Statistical Analysis

10.4.1 General Considerations

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

All summaries will be presented by treatment group. 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 is defined as the last non-missing measure prior to administration of study drug and change from baseline will be calculated as Visit – Baseline.

10.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the "study eye" as defined by the following:

10.4.3 Missing Data

The primary analysis will use the FAS with available data per subject. Additional robustness analyses will include repeating the primary analysis on the PPS; the FAS imputing missing data using LOCF; the FAS imputing missing data using Markov Chain Monte Carlo (MCMC) multiple imputation methodology under different assumptions of missingness (at random and not at random); and an analysis of trimmed means (Permutt et al., 2017).

No secondary efficacy endpoints or safety endpoints will be imputed.

10.4.4 Multiplicity Considerations

Fixed sequence testing will be employed to maintain the type I error rate. The primary analyses will first test the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score between treatments at Day 29. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of CyclASol, then the study will be considered a success; CyclASol will be declared to be superior to vehicle in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29; and the difference in the mean change from baseline total OSDI score between treatments at Day 29 will be tested at the two-sided alpha = 0.05 level.

If in addition to a statistically significant test of the difference in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 in favor of CyclASol, the test of the difference in the mean change from baseline total OSDI score at Day 29 is also statistically significant in favor of CyclASol, then CyclASol will be declared to be superior to vehicle in both the mean change from baseline corneal fluorescein staining (NEI scale) total score and the mean change from baseline total OSDI score at Day 29.

10.4.5 Primary Efficacy Analyses

The primary comparisons in this study will be between CyclASol versus vehicle at Day 29. The primary efficacy endpoints (e.g. change from baseline in corneal fluorescein staining [total NEI] and OSDI) will be analyzed separately using an ANCOVA model with terms for baseline value, treatment, and the interaction of treatment by baseline value (the interaction term will be maintained in the model only if the p-value for the term is <0.10).

Least squares mean for each treatment group and for the difference between treatment groups will be presented from the model together with two-sided p-values and 95% confidence intervals. In the event that the interaction of treatment by baseline value is significant, estimate and contrast statements will be used to determine the treatment group means and differences at the 25th, 50th, and 75th percentile of the baseline score over treatment groups.

Two-sample t-tests and Wilcoxon rank sum tests comparing treatment groups will be performed as sensitivity analyses. A mixed-effect repeated measures model will also be used as an additional sensitivity analysis of mean scores and mean changes from baseline at each visit. This model will include treatment, visit, and the interaction between treatment and visit as fixed effects, and subject as a random effect. An unstructured covariance matrix will initially be used to model the covariance among repeated measures; however, if the model fails to converge using this covariance structure, either heterogeneous TOEPLITZ, homogeneous TOEPLITZ, or CS (compound symmetry) will be implemented according to the Akaike information criterion with a correction for finite sample sizes (AICc). As an additional sensitivity analysis, a mixed-effect repeated measures model will be used with the covariance matrix selected from unstructured, heterogeneous TOEPLITZ, homogeneous TOEPLITZ and CS according to AICc.

[redacted]

[redacted]

[redacted]

[redacted]

10.4.8 Safety Variables

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it 1) occurs after the first dose of randomized study treatment or 2) if it is present prior to receipt of randomized study treatment but worsens in severity or increases in frequency after the first dose of randomized study treatment. Furthermore, frequencies will be given of subjects with TEAEs 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; by system organ class and preferred term for SAEs; and by system organ class, preferred term, and day of onset. Separate analyses will be performed for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit lamp biomicroscopy, intraocular pressure (IOP) and dilated fundoscopy, will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. [redacted]

10.4.9 Interim Analyses

No interim analyses are planned for this study.

10.5 Additional Analyses

[redacted]

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

This study 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 study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

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 [redacted] prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by [redacted] and/or study sponsor and provided in writing by [redacted] and/or study sponsor prior to the consent process.

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

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

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study 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] the sponsor, the IRB approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study 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 study 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 study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and EKGs. The investigator's copy of the eCRFs serves as the investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, patient 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.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study 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 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

11.5.1 Labeling/Packaging

For the run-in period, 1 bottle of Systane Balance will be dispensed for two weeks of BID dosing.

Investigational drug will be packaged and labeled into clinical kits. Study drug will be provided as subjects' kits containing 3 bottles of CyclASol 0.1% Ophthalmic Solution or Vehicle Ophthalmic Solution. The required medication until the next visit will be dispensed to the subject (see Section 7.1.2 for details). The kit with remaining medication will be kept at the site.

11.5.2 Storage of Study Drug

The study drug must be stored in a secure area accessible only to the investigator and his/her designees. The study drug will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

Study drug must be stored at room temperature and must not be refrigerated, protected from light, and secured at the investigational site in a locked container. Subjects should be instructed to store study drug in the same manner at home. A bottle should not be used after 30 days after opening; based on the use of visit windows for a subject this may be prolonged at the discretion of the Investigator.

11.5.3 Accountability of Study Drug

The study drug is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects properly qualified under this protocol to receive study drug.

The investigator must keep an accurate accounting of study drug received from the supplier. This includes the amount of study drug dispensed to subjects, amount of study drug returned to the investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study drug.

11.5.4 Return or Disposal of Study Drug

All study drug will be returned to the sponsor or their designee. The return and disposal of study drug will be specified in writing.

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

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum 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 and randomized 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. Only AE data will be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study 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.

11.7 Handling of Biological Specimens

Not Applicable.

11.8 Publications

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

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