NOVARTIS

Novartis Research and Development

ECF843 / NCT04391894

Clinical Trial Protocol

A randomized, double-masked, multicenter study to evaluate the safety and efficacy of ECF843 vs Vehicle in subjects with dry eye disease

Document type:	Amended Protocol Version
EUDRACT number:	NA
Version number:	V01 (Clean)
Clinical Trial Phase:	IIb
Release date:	20-Apr-2021

Clinical Trial Protocol Template Version 2.0 dated 01-Aug-2018

[redacted]

Table of contents

[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

µg	microgram
[redacted]	[redacted]
ADR	adverse drug reaction
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BFS	blow-fill-seal
BID	bis in die (twice daily)
CFR	Code of Federal Regulation
CMO	Chief Medical Office
CO	Country Office
CRF	case report/record form (paper or electronic)
CRO	contract research organization
CSR	clinical study report
CTT	clinical trial team
DED	dry eye disease
[redacted]	[redacted]
DRF	dose range finding
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FITC	fluorescein isothiocyanate
F/U	Follow up
GCP	Good Clinical Practice
GCS	Global Clinical Supply
HA	Hyaluronic Acid
hr	hour
IB	Investigator's Brochure
IBI	Inter Blink Interval
ICF	Informed Consent Form
ICH	International Council for Harmonization
[redacted]	[redacted]
IE	Intercurrent event
IEC	Independent Ethics Committee
IL-1	interleukin-1
IMP	investigational medicinal product
IN	Investigator Notification
IOP	intraocular pressure
IRB	Institutional Review Board

[redacted]

IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
[redacted]	[redacted]
IVT	intravitreal injections
J2R	jump to reference
kDa	kilodaltons
LASIK	laser-assisted in situ keratomileusis
LLOQ	lower limit of quantification
LSM	least square mean
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mm	millimeter
MMRM	mixed model repeated measures
NEI	National Eye Institute
[redacted]	[redacted]
PK	pharmacokinetic(s)
PRG4	proteoglycan-4
PRK	photorefractive keratectomy
PRN	pro re nata (as needed)
PRO	patient reported outcomes
QID	quarter in die (four times daily)
QMS	Quality Management System
RDO	Retrieved drop-out
REML	residual/restricted maximum likelihood
RNA	ribonucleic acid
SAE	serious adverse event
SANDE	Symptom Assessment in Dry Eye
SAP	statistical analysis plan
SMQ	standardized MedDRA query
SUSAR	suspected unexpected serious adverse reactions
TBUT	tear breakup time
TFOS DEWS II	Tear Film and Ocular Surface Society Dry Eye Workshop II
TID	ter in die (three times daily)
TNF	tumor necrosis factor
UI	International Unit
US	United States
[redacted]	[redacted]
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a subject feels, functions, or survives
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Discontinuation from study	Point/time when the subject permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the subject permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Subject agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). The action of enrolling one or more subjects.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same subjects under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population level summary for the variable.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a subject's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization	The process of assigning trial subjects to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment

[redacted]

Re-screening	If a subject fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study subjects as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and is used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs when the Subject explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.

[redacted]

Amendment 1 dated 20-Apr-2021

Amendment rationale

The main purpose of this amendment is to update the design of Part 2 of the study in order to remain focused on continued evaluation and development of ECF843.

[redacted]

This amendment also includes clarifications and updates to various aspects of the study.

Changes to the protocol

All changes in Amendment 1 are provided in summary below. However, minor changes such as administrative edits or repetition of a word or concept for consistency, are not listed for every section. These changes are shown in track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Major changes are made to the protocol in the following sections:

- List of abbreviations: updated to include new abbreviations in the amendment
- Glossary of terms: added new terms used in the Amendment 1; updated as per new OneCTP Protocol template Version 4 15-Feb-2021.
- Protocol summary: updated for Purpose and Rationale, Study Design, Study treatment, and Other assessments. Details on the specific changes are described in each individual section below.
- 1.2 Purpose: updated the purpose of Part 2 to reflect an intention to keep the focus on further exploration of the safety and efficacy of ECF843.

[redacted]

- 2.1 Primary Estimands: clarified subject attributes for primary estimands with regards to prohibited/rescue medications and treatment duration.
- 3 Study design: [redacted] updated to a double-masked design for Part 2; clarified that no protocol assessments or solicitation of AEs will be collected between Part 1 and Part 2 which includes specific parameters when an SAE would be captured; clarified that a list of subjects eligible for Part 2 will be discussed between the Investigator and Sponsor; added possibility that if a study site was initiated close to the end of enrollment without sufficient time to recruit subjects, the site may enroll new subjects into Part 2 if approved by Sponsor; amended randomization ratio of ECF843 to Vehicle to 3:1; [redacted]
- 4.1 Rationale for study design: specified that criteria for selection of subjects for primary efficacy analysis are documented in the statistical analysis plan (SAP); [redacted]
- 4.2 Rationale for dose/regimen and duration of treatment: updated to state that no safety concerns have been identified with BID/TID dosing; clarified treatment duration in Part 2.

[redacted]

[redacted]

- 4.4 Purpose and timing of interim analyses/design adaptations: Primary analysis for Part 2 added.
- 4.6 Rationale for Public Health Emergency mitigation procedures: new section added
- 5 Population: clarified that subjects who discontinue the study in Part 1, will not be eligible for Part 2; expanded on eligibility for Part 2 based on subjects who discontinue treatment only or experience treatment related AE/SAEs.
- 5.1 Inclusion criteria: clarified scoring for corneal staining and using an average of 3 consecutive readings for Tear Break-up Time (TBUT).
- 5.2 Exclusion criteria: clarified exclusion #6 regarding corneal scars; [redacted] updated exclusion #22 defining female sterilization to include "bilateral" tubal ligation; clarified that woman are considered not of child bearing potential if they are post-menopausal.
- 6.1 Study treatment: amended for double masked treatment for Part 2.
- 6.1.3 Supply of Study Treatment: section fully deleted.
- 6.1.3 Treatment arms/groups:Treatment arms/groups: [redacted] specified that ECF843 vehicle dosing frequency will be determined from Part 1.
- Table 6-2 Prohibited medication :added Intravitreal injections and Punctal plugs.
- Table 6-3 Blinding levels: added blinding levels for Bioanalytical Team
- 6.4 Treatment blinding: clarified that CTT members/site staff will be unmasked again at the end of Part 2; removed language of open label to subjects and site staff.
- 6.7 Preparation and dispensation: [redacted]; added new paragraph regarding section 4.6 and public health emergency instructional text for IMP delivery to subject

[redacted]

- 7 Informed consent procedures: clarified that subjects will sign the ICF for Part 1 and again for Part 2; added statement about unknown risks to the fetus for women of child bearing potential; listed all informed consents applicable to this study.
- 8 Visit schedule and assessments: re-emphasized that only subjects assigned exclusively to vehicle in Part 1 will be eligible for Part 2; restated that a list of subjects eligible for Part 2 will be discussed between the Investigator and Sponsor; added possibility that if a study site was initiated close to the end of enrollment without sufficient time to recruit subjects, the site may enroll new subjects into Part 2 if approved by Sponsor; clarified that no visits can be skipped; [redacted].
- Table 8-1 Assessment Schedule, Part 1: updated "Patient diary" to be "At home SANDE" and [redacted]. Footnotes updated accordingly.

[redacted]

[redacted]

- 8.1 Screening: expanded on criteria for ability to re-screen with regards to time frames to stabilize chronic medications or use of contact lenses.
- [redacted]
- 9 Study discontinuation and completion: clarified that subjects should not be discontinued after completion of Part 1 unless subject withdraws informed consent or deemed not eligible for Part 2; subjects who discontinue study in Part 1 will not be eligible for Part 2; subjects who discontinue treatment but do not discontinue the study in Part 1, decision for participation in Part 2 will be at discretion of Investigator, with guidance from Sponsor, as needed.
- 9.1.1 Discontinuation of study treatment: added definition and updated to be consistent with Glossary of terms.
- 9.1.2 Discontinuation from study: new section added
- 9.1.3 Withdrawal of informed consent: updated definition of withdrawing informed consent as per new OneCTP Protocol Version 4.
- 10.1.1 Adverse events: updated Eye Drop Comfort Scale to be assessed according to new applicable visits; [redacted]
- 10.1.4 Pregnancy reporting: minor edits to clarify process for pregnancy reporting
- 12.3 Treatments: [redacted].
- 12.4.2 Statistical model, hypothesis, and method of analysis: type I error control changed from 10% to 5%.
- 12.4.3 Handling of intercurrent events of primary estimand: updated primary estimand strategy.
- 12.4.5 Sensitivity analyses for primary estimand: sensitivity analysis dropped.
- 12.4.6 Supplementary analysis: updated supplementary estimand strategy
- [redacted]
- 12.7 Interim Analysis: primary analysis for Part 2 added.
- 12.8 Sample size calculation: sample size adjusted based on updated overall type I error 5%; 95% confidence level provided for updated study design in Part 2.

[redacted]

IRB/ IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs) and Health Authorities.

The changes described in this amended protocol require IRB and Health Authority approval, according to local regulations, prior to implementation.

The changes herein affect the trial specific global model consent form.

[redacted]

Protocol summary

Protocol number	CECF843A2201
Full Title	A randomized, double-masked, multicenter study to evaluate the safety and efficacy of ECF843 vs Vehicle in subjects with dry eye disease
Brief title	A study to assess the safety and efficacy of ECF843 vs Vehicle in subjects with dry eye disease
Sponsor and Clinical Phase	Novartis Phase IIB
Investigation type	Drug; Biological
Study type	Interventional
Purpose and rationale	The purpose of Part 1 of the study is to determine the safety and efficacy of topical ocular ECF843 compared to topical ocular vehicle for the relief of the signs and symptoms associated with moderate to severe dry eye disease (DED). Part 2 of the study is intended to explore additional endpoints and potential areas of differentiation as a treatment for patients with DED.
Primary Objective(s)	The primary objective of the study is to demonstrate superiority of ECF843 versus vehicle for improvement in dry eye related ocular symptoms and ocular surface damage as assessed by change from baseline in Symptom Assessment in Dry Eye (SANDE) score and change from baseline in composite corneal fluorescein staining score
Secondary Objectives	To evaluate the improvement of ECF843 vs vehicle in corneal damage by quadrant as assessed by change from baseline in inferior and central corneal fluorescein staining To evaluate the safety of ECF843 vs Vehicle as assessed by incidence and severity of ocular and non-ocular adverse events
Study design	The study will be conducted in 2 parts: **Part 1** – efficacy and safety of ECF843 vs vehicle, followed by **Part 2** – exploratory assessments of ECF843 vs vehicle. Part 1 uses a double-masked design where subjects will be randomized to receive BID or TID treatment with either ECF843 or vehicle for 56 days. For subjects randomized to ECF843, the maximum drug exposure will be up to 28 days. Part 2 will be initiated only if safety and efficacy of ECF843 during Part 1 is demonstrated. Part 2 also uses a double-masked design of ECF843 versus Vehicle for 84 days after a 2-week vehicle run-in phase.
Population	This study will enroll adult subjects, 18 years of age or older with at least 6 months history of physician diagnosed moderate to severe dry eye disease in both eyes as defined by entry criteria. It is estimated that approximately 800 subjects will need to be screened in Part 1 to have approximately 680 subjects randomized into the 56-day treatment period. For Part 2, it is estimated that up to 200 subjects will need to be screened to randomize up to 160 subjects into the 2 treatment arms.
Key Inclusion criteria	1 Written informed consent must be obtained before any assessment is performed 2 Adult male or female subjects 18 years of age or older 3 Subjects must be able and willing to follow the protocol and required assessments 4 At least 6 months history of physician diagnosed dry eye disease in both eyes 5 Must use, or feel the need to use, artificial tears/gels/lubricants on a regular basis 6 Tear Break-up Time (TBUT) ≤ 5 seconds in at least one eye (average of 3 consecutive TBUT readings) 7 Composite corneal fluorescein staining score ≥ 4 (modified National Eye Institue (NEI) scale) in at least one eye (composite score is the sum score of the 5 regions within a single cornea) 8 PART 1 ONLY: In-office SANDE global ocular discomfort score ≥ 60 (as measured by 100 mm visual analog scale (VAS)

[redacted]

	9 PART 2 ONLY: In office Eye Dryness Score ≥ 40mm (as measured by 100mm VAS scale)
Key Exclusion criteria	1 Ocular infection (bacterial, viral, or fungal) in either eye within 30 days prior to Screening 2 Use of artificial tears, gels, lubricants within 4 hours of conducting assessments at the Screening Visit 3 Use of contact lenses in either eye within 14 days of Screening, and any use of contact lenses for the duration of the study 4 Subjects with uncontrolled ocular rosacea (affecting the eye adnexa), posterior blepharitis or Meibomian gland dysfunction 5 Clinically significant conjunctivochalasis in either eye defined as an excessive redundancy of the conjunctiva that obliterates the inferior tear meniscus and/or rolls over the lower lid margin seen upon routine ocular exam or apparent with normal lid closure 6 Corneal conditions, other than dry eye related corneal epitheliopathies, affecting the corneal structure of either eye 7 Use of Restasis® , Cequa® , or Xiidra® within 30 days of Screening 8 Use of ocular, nasal, inhaled, or systemic corticosteroids within 30 days of Screening (low dose over-the-counter steroid creams applied to the skin are acceptable)
Study treatment	In Part 1, subjects will be screened and assigned to one of the following five masked treatment arms in a ratio of 1:1:1:1:1. • ECF843 0.45 mg/mL TID • ECF843 0.15 mg/mL TID • ECF843 vehicle TID • ECF843 0.15 mg/mL BID • ECF843 vehicle BID In Part 2, following a 2-week run-in phase with vehicle, subjects will be assigned at Visit 2 to one of the following two treatment groups in a ratio of 3:1. • ECF843 (concentration and dosing frequency to be determined from Part 1) • Vehicle (dosing frequency to be determined from Part 1)
Efficacy assessments	The following assessments are included to evaluate the efficacy of ECF843: • Ocular discomfort • Ocular hyperemia • Tear film break-up time • Corneal fluorescein staining • Conjunctival lissamine staining
Key safety assessments	The following assessments are included to evaluate the safety of ECF843: • Corrected Visual Acuity • Slit-Lamp Exam • Intraocular pressure • Fundus exam • Adverse events
Other assessments	The following patient reported outcomes (PRO) will be evaluated: • SANDE (Symptom Assessment in Dry Eye) [redacted]

[redacted]

	[redacted]
Data analysis	The primary objective of Part 1 of the study is to show that at least one ECF843 arm will improve SANDE symptom score and/or composite corneal fluorescein staining score in comparison with its corresponding vehicle (BID or TID) by rejecting the null hypothesis below at a significance level α=0.05 (2-sided). For each of the primary endpoints, mixed model repeated measures (MMRM) will be used with change from baseline at all post-baseline visits on treatment as response variable, and treatment, visit, randomization strata and baseline score as covariate. For secondary endpoints, change from baseline in inferior and central corneal fluorescein staining, summary statistics (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) by treatment arm will be provided. A 95% confidence interval will be provided for the difference between the ECF843 arm vs its corresponding vehicle at each post-baseline visit.
Key words	Dry Eye Disease, lubricin, proteoglycan 4, PRG4

[redacted]

1 Introduction

1.1 Background

Dry Eye Disease (DED, also known as keratoconjunctivitis sicca) is defined as a multifactorial disease characterized by a loss of homeostasis of the tear film and ocular surface, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. This updated, evidence-based definition based on the collective current understanding of DED was published in 2017 as a key outcome from the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) (Craig et al 2017b). DED is a highly prevalent condition with an estimated 344M people affected globally (Craig et al 2017a). Through visual disturbances and chronic ocular pain or discomfort, DED can have a significant impact on a subject's quality of life and economic impact (including treatment costs, absenteeism, and reduced work productivity) (Yu et al 2011, McDonald et al 2016). Despite the many years of research in this area, understanding of DED remains in its infancy highlighting challenges in diagnosis, etiology, and treatment choices.

To date, very few prescription treatments are available for subjects suffering from chronic DED. In the United States (US), Restasis® (cyclosporine 0.05%) was approved in 2003 to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (dry eye) (Rhee and Mah 2017). No other prescription treatments were approved in the US until 2016 when Xiidra® (lifitegrast 5%) received approval for the treatment of both signs and symptoms of DED (Keating 2017). In 2018, another cyclosporin formulation called Cequa® (cyclosporin 0.09%) was approved in the US for increasing tear production in patients with keratoconjunctivitis sicca (Mandal et al 2019). Ocular adverse events coupled with delayed onset of action with each of these therapies means there remains potential to improve subject satisfaction and address an unmet medical need for new treatments that are safe, effective, and have a more rapid onset of action (O'Neil et al 2019).

Lubricin, also known as Proteoglycan 4 (PRG4), is a mucin-like glycoprotein expressed in areas of high shear stress and friction including the tear film where it binds to and protects tissues of the ocular surface (Samsom et al 2014). Lubricin has been found to be endogenously transcribed, translated, expressed and secreted by the ocular surface epithelia from various species (Schmidt et al 2013, Samsom et al 2014), and lubricin messenger RNA has been detected in lacrimal and Meibomian glands of rabbits (Cheriyan etal2011)

Preliminary unpublished data suggest a deficiency of functional lubricin on the ocular surface of subjects with dry eye disease and those with Sjögren's Syndrome related dry eye compared to normals. Importantly, decreased expression of lubricin has been shown to occur in the presence of inflammatory mediators including some pro-inflammatory cytokines that have been associated with DED such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNFα) (Jones and Flannery 2007). In addition to pro-inflammatory mediators, Cathepsin-S is hypothesized to be involved in the degradation of lubricin. Interestingly, Cathepsin-S activity in human tears was found to be 2-fold higher in subjects with Sjögren's Syndrome compared to subjects with non-Sjögren's DED, and 41-fold higher than in normal controls (Hamm-Alvarez et al 2014). Degradation of lubricin by Cathepsin also resulted in increased

[redacted]

friction in an in vitro ocular surface friction model (Regmi et al 2017). Furthermore, in vitro models also suggest a potential anti-inflammatory effect even though the actual mechanism by which this occurs is not yet understood. Together, these data suggest that lubricin may play a key role in the health of the ocular surface.

rhLubricin is a recombinant human form of endogenously expressed lubricin, and ECF843 refers to the Novartis formulation of rhLubricin. ECF843 is hypothesized to restore the homeostasis on the ocular surface in subjects suffering from DED. The hypothesis that ECF843 will be an effective treatment for the signs and symptoms of DED is based on the results of two small controlled clinical studies comparing the effects of rhLubricin to marketed artificial tear products containing hyaluronic acid (HA) with dosing as frequently as four times per day for up to 28 days. An improvement from baseline in ocular signs and symptoms was observed in both studies, and the effect of rhLubricin within a short time frame could suggest a rapid onset of benefit to subjects.

1.2 Purpose

The purpose of the study is to determine the safety and efficacy of topical ocular ECF843 compared to topical ocular vehicle (Part 1) for the relief of the signs and symptoms associated with moderate to severe DED. The study design includes a component for dose-regimen selection. Part 2 of the study is intended to explore additional endpoints and potential areas of differentiation as a treatment for patients with DED.

This Phase II study will establish the foundation for further development and registration of ECF843.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Part 1:** To demonstrate superiority of ECF843 versus vehicle for improvement in dry eye related ocular symptoms and ocular surface damage	• Change from baseline in Symptom Assessment in Dry Eye (SANDE) score; • Change from baseline in composite corneal fluorescein staining score
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Part 1:** To evaluate the improvement of ECF843 vs vehicle in corneal damage by quadrant	• Change from baseline in inferior and central corneal fluorescein staining
• **Part 1:** To evaluate the safety of ECF843 vs Vehicle	• Incidence and severity of ocular and non-ocular adverse events
[redacted]	

[redacted]

2.1 Primary Estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g premature discontinuation of treatment).

The primary clinical question of interest is: What is the treatment effect of ECF843 versus vehicle on change from baseline in signs and symptoms in subjects with moderate to severe DED, if artificial tears/gels/lubricants and prohibited medications were not used, and treatment was received for the entire study duration?

The justification for the primary estimands is that they will capture the effect of the study drug for the full duration when administered without confounding effects from prohibited medications or artificial tears/gels/lubricants. Further details can be found in Section 12.

The primary estimands are described by the following attributes:

1. Population: subjects with moderate to severe DED. Further details about the population are provided in Section 5.
2. Endpoint: change from baseline in SANDE score and change from baseline in composite corneal fluorescein staining score.
3. Treatment of interest: the randomized treatment (ECF843 or vehicle) if artificial tears/gels/lubricants and prohibitive medications were not used and treatment was received for the entire study duration. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events:

1. Artificial tears/gels/lubricants: Had subjects never used artificial tears/gels/lubricants for occasional rescue and behaved like other subjects who did not take them (hypothetical strategy)
2. Prohibited medications: Had subjects never used prohibited medications and behaved like other subjects who did not take them (hypothetical strategy)
3. Discontinuations from treatment for any reason: had subjects taken the assigned treatment for the entire study duration and behaved like other subjects who did not discontinue treatment (hypothetical strategy)

The summary measure: difference in variable means between ECF843 and vehicle.

Supplementary estimands to the primary estimand are defined in Section 12.

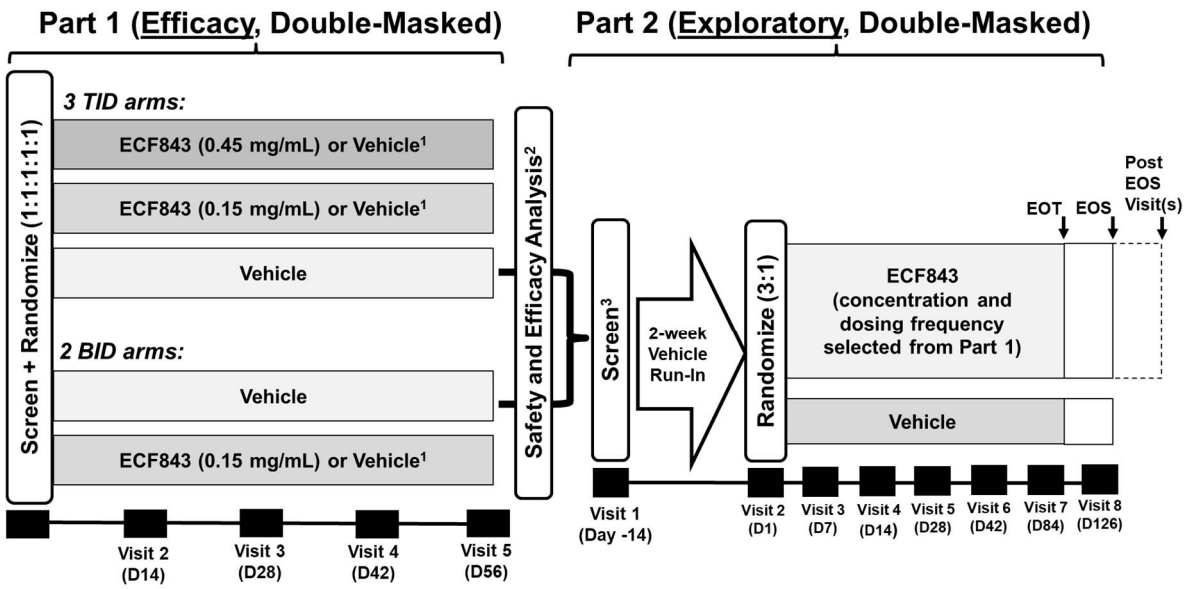
2.2 Secondary Estimands

Not applicable.

[redacted]

3 Study design

Figure 3-1 Study Design



The study will be conducted in 2 parts: **Part 1** – efficacy and safety of ECF843 vs vehicle, followed by **Part 2** – additional exploratory assessments of ECF843 vs Vehicle. Both parts of the study include a double-masked study design, with randomization stratified for subjects with Sjogren's Syndrome.

In Part 1 subjects will be randomized to receive twice daily (BID) or three times daily (TID) treatment with either ECF843 or vehicle for 56 days. For subjects randomized to ECF843, the maximum drug exposure will be up to 28 days. At some point during Part 1, all subjects will receive vehicle. The study will be conducted in a way that neither the Investigator nor the subject are aware of the criteria for qualification into the primary efficacy analysis, nor the period(s) during which vehicle treatment is assigned. There will be a database lock after all subjects have completed their participation in Part 1 of the study. The data will be analyzed to determine the efficacy and safety of ECF843 vs vehicle and selection of the optimal concentration and posology. Part 1 must be fully completed prior to initiating Part 2. Part 2 will be initiated only if safety and efficacy of ECF843 during Part 1 is demonstrated.

Between the end of the subject's participation in Part 1 and the beginning of participation in Part 2, subjects will be treated as needed and according to Investigator judgement, and no protocol assessments or proactive solicitation of adverse events will be collected. If a subject spontaneously reports a serious adverse event (SAE) within 30 days of completing Part 1, those events will be captured as stated in Section 10.1.3.

Only subjects assigned exclusively to vehicle treatment in Part 1 may be eligible to participate in Part 2 of the study. A list of subjects eligible for screening in Part 2 of the study will be discussed between the Investigator and the Sponsor prior to initiating screening visits. In the

event a study site was initiated close to the end of enrollment and did not have sufficient time to begin recruiting subjects, the site may enroll subjects into Part 2 of the study if approved by the Sponsor.

Subjects will again be asked to sign the informed consent form (ICF) in order to participate in Part 2, and will be re-screened to determine continued eligibility. If the subject meets all entry criteria, the subject may be randomized to receive either ECF843, at the concentration and posology selected from Part 1, or Vehicle at the same selected posology at a 3:1 ratio for 84 days of treatment. Enrollment for Part 2 of the study will be discussed between the Investigator and the Sponsor prior to initiating screening visits.

[redacted]

4 Rationale

4.1 Rationale for study design

Part 1 of the study is a double-masked, randomized, parallel design which includes two concentrations and two posologies in order to evaluate the difference in efficacy based on concentration and frequency of dosing. Because administration of vehicle does provide benefit to subjects and shows some efficacy in many dry eye clinical studies, there is not a true placebo (e.g., a treatment that has no effect on the disease being studied). Therefore, it is important to compare active to vehicle at the same frequency of dosing. To address this, there are two vehicle arms: one for comparison of BID active vs vehicle and one for TID active vs vehicle.

The primary objectives for Part 1 of the study are based on the assessment of ocular symptoms (via an at home daily electronic diary using the SANDE VAS symptom scores) and ocular surface damage assessed by the degree of corneal fluorescein staining. These are well established endpoints that are recognized as key parameters to define severity of the dry eye disease state, as well as improvement in the disease severity after treatment.

The active and vehicle test articles are presented in identical packaging to ensure no bias to the study results due to knowledge of the treatment assignment. There is an additional level of masking which includes the selection of subjects that will be included in the primary efficacy analysis of the study. The criteria for selection of these subjects is pre-defined and documented in the statistical analysis plan (SAP) but is not disclosed to the Investigator nor the subject to avoid the selection bias and regression effects that have been observed in many historical dry eye studies. The criteria for selection of subjects into the primary analysis are within the guidelines of the stated entry criteria for the study in order to protect against any unintended risk to the subject. In order to preserve this level of masking, and to allow for exploration of differences in treatment outcomes between the population of subjects who are selected vs those that are not, all subjects will remain in the study for the full treatment period.

[redacted]

Part 2

Part 2 of the study is an exploratory, double-masked, randomized parallel assessment of ECF843 vs Vehicle. [redacted]

Due to different medications being approved in various countries, the comparison is being done to vehicle rather than an active comparator in order to help inform hypotheses for areas where ECF843 may be differentiated from other currently available treatments, and that warrant further evaluation in future studies.

4.2 Rationale for dose/regimen and duration of treatment

The planned doses and posologies of ECF843 eye drops are [redacted] BID or TID, and [redacted] TID, based on an estimated maximum average drop size of [redacted] and solution concentration of 0.15 mg/mL and 0.45 mg/mL, respectively. Previous clinical studies LUB0114MD and LUB0115MD, evaluating 0.15 mg/mL rhLubricin eye drops QID and BID/PRN, respectively, demonstrated the efficacy and tolerability/safety of rhLubricin in subjects with DED. The additional dose level of 0.45 mg/mL is included to further assess the dose/response relationship. Test concentrations included in this study are based on the lowest and highest feasible doses that can be reproducibly manufactured while adhering to formulation specifications.

There are no animal models and limited *in vitro* models to justify the selection of dose. In *in vitro* testing using a cartilage-glass friction assay with 14 different concentrations of rhLubricin ranging from 0-300 µg/mL, maximum lubrication was observed at concentrations of 50 µg/mL or higher (Gleghorn et al 2009). Lubrication is a surrogate for potency of formulated ECF843, and the potential effect that may be observed in the clinical assessments.

Supportive nonclinical ocular pharmacokinetic (PK) data are limited to studies in rats and dogs. Compared to rats, dogs have a blink rate and eye size closer to humans. In the rat studies, fluorescein isothiocyanate (FITC)-labeled lubricin was administered topically and tear and ocular surface fluorescence measured for 10 minutes (Dompe Study MIR 027/15 in vivo, PR&DS 090/14 in vivo). ECF843 was rapidly cleared from the ocular surface with [redacted]). In the dog study, animals received a single bilateral topical ocular dose of 0.15 mg/mL or 0.45 mg/mL unlabeled ECF843 followed by collection of tear and ocular tissues at time points up to 6 hours for PK. The tear results confirmed the rapid clearance of ECF843 observed in the rat study, although there were quantifiable levels at [redacted] Half-life could not be determined due to the limited quantifiable data available. ECF843 was not detected in ocular tissues, indicating negligible absorption, although these data do not discount the possible presence of ECF843 on the ocular surface below the sensitivity of the ECF843 assay.

The previously observed efficacy in humans with 0.15 mg/mL BID implies that the effect persists beyond the detectable presence of ECF843 on the eye, and despite the rapid ocular

[redacted]

clearance observed in rat and dogs. The target ocular ECF843 concentration is unknown; however, studies are in progress to obtain definitive concentrations of endogenous lubricin in human tears and conjunctiva (via impression cytology), which could possibly be used as target concentrations in modeling.

Clinical Study CECF843A2201 will evaluate and compare ECF843 dosed BID and TID, and is based on BID previously demonstrating a positive effect in humans. TID could further enhance residence time of ECF843 and result in better efficacy. No safety concerns have been identified which would preclude BID or TID dosing in this study.

ECF843 eye drops at doses of 0.15 mg/mL and 0.45 mg/mL BID/TID is expected to be safe and well tolerated, based on previous human studies and ocular toxicology assessments in monkeys, administered ECF843 eye drops for 3 months at up to 0.45 mg/mL 4 times per day [redacted] With regard to systemic exposure and safety, the molecular size of ECF843 at approximately 450 kilodaltons (kDa) makes it unlikely that ECF843 will be systemically bioavailable. This has so far been confirmed in the dose range finding (DRF) toxicology study in which monkeys were administered ECF843 eye drops up to 0.45 mg/mL 6 times per day for 7 days, and where ECF843 was non-quantifiable (< LLOQ of 100 ng/mL) in the serum at 0.5, 1, 3 and 6 hrs post-dose on Day 7.

Due to the mechanism of action of ECF843 and consistent with other DED studies, the duration of dosing in Parts 1 and 2 should be sufficient to detect if any pharmacological effect can be observed. To date there have been two clinical studies conducted with a rhLubricin formulation which included up to 28 days of QID dosing. Additionally, the 84 day assessment period in Part 2 is consistent with other currently approved pharmacological treatments for patients with DED. The lengths of treatment in Part 1 and Part 2 are both supported by toxicology testing since only subjects who had received vehicle during Part 1 of the study may enter Part 2.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Part 1 and Part 2 of the study are vehicle-controlled in order to assess whether ECF843 demonstrates a pharmacological effect that is superior to administering the same formulation without the active ingredient (rhLubricin). A vehicle control is standard in dry eye studies for product registration by the US Food and Drug Administration (FDA), and has been confirmed through the FDA Pre-Investigational New Drug (pre-IND) Application meeting as being an appropriate control.

4.4 Purpose and timing of interim analyses/design adaptations

For Part 1, the primary analysis will be performed after all subjects in Part 1 have completed or discontinued from randomized treatment. The data will be analyzed to determine the efficacy and safety of ECF843 vs vehicle and to select the concentration and posology for Part 2. Part 2 will be initiated only if efficacy and safety of ECF843 vs vehicle from Part 1 are demonstrated. For Part 2, the primary analysis will be performed after all subjects in Part 2 have completed or discontinued from 12 weeks of treatment. The data will be used to explore the efficacy and safety of ECF843 vs vehicle after 12 weeks of treatment.

Refer to Section 12 (Data Analysis and Statistical Methods) for further details.

[redacted]

4.5 Risks and benefits

ECF843 is a formulation of a recombinant human lubricin. Lubricin is transcribed, translated, and expressed by ocular surface tissues to reduce friction and protect the ocular surface. Additional evidence suggests lubricin may confer a potential anti-inflammatory effect. Lubricin is hypothesized to play a key role in ocular surface health and may restore homeostasis on the ocular surface in subjects suffering from DED. Because current choices for prescription treatments are limited and generally are associated with ocular adverse events and/or delayed onset of action, ECF843 may provide a novel treatment option and address a significant unmet medical need for subjects with moderate to severe DED.

Limited clinical experience exists with the investigational treatment in this study. Two clinical studies (LUB0114MD and LUB0115MD) have been conducted using a different formulation of rhLubricin, with one of the studies including up to 28 days of exposure with four times a day (QID) dosing. Both studies demonstrated clinical efficacy based on improvements in ocular signs and symptoms of dry eye disease. No serious adverse events (SAEs) or deaths reported in either study, and no adverse drug reactions (ADRs) were identified based on the safety data from these two studies.

The risk to subjects in this current study may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Because lubricin is an endogenous protein expressed on the ocular surface, the likelihood of hypersensitivity reactions is low. Evaluation of subject serum samples for detection of anti-ECF843 antibody formation will be performed in Part 2 of the study.

Subjects will undergo certain ophthalmological procedures which are common in dry eye practice (e.g., corneal fluorescein staining, slit-lamp biomicroscopy, fundus examination) during this study. Any subject demonstrating a potential hypersensitivity reaction to the investigational medicinal product (IMP) will cease use of the IMP and receive appropriate care. To minimize any discomfort and risks, the study and associated procedures will be carried out by experienced study staff under the supervision of a Principal Investigator who is experienced in managing subjects with dry eye. Although subjects may receive vehicle instead of active drug for part or all of the study, the inclusion of a vehicle control is not considered a major risk in a dry eye study since vehicle itself can provide some benefit to subjects.

Women of child bearing potential should be informed that taking the investigational drug may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

Given the minimal systemic exposure after topical ocular administration, and the lack of safety findings in clinical studies conducted to date, the foreseeable risks associated with ECF843 are considered very low compared to the anticipated benefit to subjects with DED. There may be risks associated with the use of ECF843 which are unknown at this time.

[redacted]

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure subjectsafety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

This study will enroll adult subjects, 18 years of age or older with at least 6 months history of physician diagnosed moderate to severe dry eye disease in both eyes as defined by entry criteria.

It is estimated that approximately 800 subjects will need to be screened in Part 1 to have approximately 680 subjects randomized into the 56-day treatment period. Enrollment in the study will remain open until a sufficient number of evaluable subjects is achieved in Part 1.

For Part 2, it is estimated that up to 200 subjects will need to be screened to randomize up to 160 subjects into the 2 treatment arms.

Subjects discontinuing the study after randomization in either Part 1 or Part 2 will not be replaced, and subjects who discontinue the study in Part 1 will no longer be eligible for Part 2.

For subjects who discontinue treatment but do not discontinue the study during Part 1, or for subjects who experience a treatment related adverse event (AE) or serious adverse event (SAE), eligibility for Part 2 will be dependent on the reasons for treatment discontinuation or nature of the AE/SAE. The decision for participation in Part 2 will be at the discretion of the Investigator, with guidance from the Sponsor as needed.

The following inclusion/exclusion criteria apply to screening of subjects in Part 1, as well as screening and baseline in Part 2.

5.1 Inclusion criteria

Subjects eligible for inclusion in Part 1 must meet all of the following criteria at the Screening Visit (i.e., Visit 1).

Subjects eligible for inclusion in Part 2 must meet all of the following criteria at the Screening Visits (i.e., Visit 1) and Baseline Visit (i.e., Visit 2).

1. Written informed consent must be obtained before any assessment is performed
2. Adult male or female subjects 18 years of age or older
3. Subjects must be able and willing to follow the protocol and required assessments
4. At least 6 months history of physician diagnosed dry eye disease in both eyes
5. Must use, or feel the need to use, artificial tears/gels/lubricants on a regular basis
6. Tear Break-up Time (TBUT) $\leq$ 5 seconds in at least one eye (average of 3 consecutive TBUT readings)
7. Composite corneal fluorescein staining score $\geq$ 4 (modified National Eye Institute (NEI) scale) in at least one eye (composite score is the sum score of the 5 regions within a single cornea)

[redacted]

8. **PART 1 ONLY:** In office SANDE global ocular discomfort score ≥ 60 (as measured by 100 mm Visual Analog Scale (VAS)
9. **PART 2 ONLY:** In office Eye Dryness Score ≥ 40mm (as measured by 100mm VAS scale)
10. Schirmer score ≥ 1 and ≤ 10 mm after 5 minutes in at least one eye
11. Subjects with Sjögren's Syndrome must have dry eye (same inclusion criteria as above) associated with a confirmed diagnosis of primary or secondary Sjögren's Syndrome (e.g., diagnosis supported by lab results, positive biopsy, etc., which may be obtained by any qualified physician including rheumatologist, etc).

5.2 Exclusion criteria

Subjects meeting any of the following exclusion criteria at the Screening Visit in Part 1 are not eligible for participation in the study.

Subjects meeting any of the following exclusion criteria at the Screening and Baseline Visits in Part 2 are not eligible for participation in Part 2 of the study.

1. Ocular infection (bacterial, viral, or fungal) in either eye within 30 days prior to Screening
2. Use of artificial tears, gels, lubricants within 4 hours of conducting assessments at the Screening Visit
3. Use of contact lenses in either eye within 14 days of Screening, and any use of contact lenses for the duration of the study
4. Subjects with **uncontrolled** ocular rosacea (affecting the eye adnexa), posterior blepharitis or Meibomian gland dysfunction

   NOTE: Controlled is defined as a stable condition, not as an asymptomatic condition. If the subject is doing lid scrubs and/or warm compresses to control these conditions, they must continue with their normal regimen. However, subjects must have been utilizing these therapies for at least 30 days prior to Screening, no new regimens added during the course of the study, and no current regimens discontinued during the study.
5. Clinically significant conjunctivochalasis in either eye defined as an excessive redundancy of the conjunctiva that obliterates the inferior tear meniscus and/or rolls over the lower lid margin seen upon routine ocular exam or apparent with normal lid closure
6. Corneal conditions, other than dry eye related corneal epitheliopathies, affecting the corneal structure of either eye including but not limited to:
   - Clinically significant corneal dystrophies defined as affecting the structure of the corneal surface, affecting best-corrected visual acuity, or is an actively changing or unstable condition
   - Corneal scars with residual corneal surface irregularity
   - Pterygia that extend > 2mm onto the corneal surface, or are elevated rather than flat, or show concentrated staining
   - Keratoconus
7. Any history of ocular herpes simplex virus or herpes zoster virus infection, or other severe ocular conditions such as graft versus host disease, Stephen's Johnson Syndrome, sarcoidosis

[redacted]

8. Currently active, or history of ocular allergies during the time of year the subject will be participating in the study
9. History of hypersensitivity to ECF843, staining reagents (fluorescein sodium or lissamine), or their excipients.
10. Subjects with current punctal plugs or punctal cauterization or occlusion
11. Chronic medications (both over the counter and prescription) that have not been stable for at least 30 days prior to Screening. Subjects who have any anticipated change in their chronic medication regimen are excluded until the new regimen has been stable for at least 30 days.

    NOTE: chronic refers to medications taken on a specific regimen which includes medications that may not be taken daily (e.g., bisphosphonates given once per month). Pro re nata (PRN) medications such as low dose acetaminophen (e.g., Tylenol) and over the counter Non Steroidal Anti Inflammatory Drugs (NSAIDs) are not excluded.
12. Use of Restasis®, Cequa®, or Xiidra® within 30 days prior to Screening
13. Medical device use to treat meibomian gland dysfunction (e.g., LipiFlow, Intense Pulse Light Therapy, or similar) within 3 months prior to Screening
14. Use of ocular, nasal, inhaled, or systemic corticosteroids within 30 days of Screening (low dose over-the-counter steroid creams applied to the skin are acceptable), or any use during the duration of study participation
15. Any history of corneal refractive surgery (e.g., laser-assisted in situ keratomileusis [LASIK], photorefractive keratectomy [PRK], etc)
16. Any intraocular surgery including cataract surgery within 6 months prior to Screening
17. Chronic systemic disease that was diagnosed within the last 30 days or that has not been stable for at least 30 days prior to the Screening
18. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
19. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
20. Subjects demonstrating any medical condition (systemic or ophthalmic) that may, in the opinion of the Investigator, preclude the safe administration of test article or safe participation in this study, or potentially impact the outcome of the study
21. Pregnant or nursing (lactating) women
22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of investigational drug. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

[redacted]

- Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same contraceptive for a minimum of 3 months before taking investigational drug. Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential.

6 Treatment

6.1 Study treatment

Part 1

Subjects will receive double-masked treatment for 56 days.

Part 2

Subjects will receive double-masked treatment for 84 days after a 14-day ECF843 vehicle run-in period.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
ECF843 0.15 mg/ml	Liquid as drops single-dose ophthalmic	Topical ocular	Double masked	Global
ECF843 0.45 mg/ml	Liquid as drops single-dose ophthalmic	Topical ocular	Double masked	Global
ECF843 Vehicle	Liquid as drops single-dose ophthalmic	Topical ocular	Double masked	Global

[redacted]

ECF843 active and vehicle will be packed as double masked kits. Each kit will consist of a carton containing 6 aluminum foil pouches to protect the product from light, and each pouch will contain 3 blow-fill-seal (BFS) containers for single use. IRT will instruct on the number of kits to be dispensed. A sufficient number of kits will be dispensed per visit to cover the required treatment period between visits.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

In Part 1, subjects will be screened and assigned to one of the following five masked treatment arms/groups in a ratio of 1:1:1:1:1.

- ECF843 0.45 mg/mL TID or vehicle
- ECF843 0.15 mg/mL TID or vehicle
- ECF843 vehicle TID
- ECF843 0.15 mg/mL BID or vehicle
- ECF843 vehicle BID

In Part 2, following a 2-week run-in phase with vehicle, subjects will be assigned at Visit 2 to one of the following two masked treatment arms/groups in a ratio of 3:1.

- ECF843 (concentration and dosing frequency to be determined from Part 1)
- ECF843 vehicle (dosing frequency to be determined from Part 1)

6.1.4 Treatment duration

The planned duration of double-masked treatment during Part 1 is 56 days. In Part 2, a 14-day open label vehicle run-in will be followed by 84 days of masked treatment. Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator, Sponsor, or the subject. Refer to Section 9.1 on discontinuation from the study for additional details.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All prescription and over-the-counter medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate electronic Case Report Forms (eCRFs). Concomitant topical ocular medications for reduction of intraocular pressure are permitted.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

[redacted]

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after Screening (Visit 1).

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Ocular, nasal, inhaled, or systemic corticosteroids	During the course of the study	Do not discontinue study treatment but document use of the product in the eCRF
Any topical ocular medications (prescription or over-the-counter; excluding IOP-lowering medication)	During the course of the study	Do not discontinue study treatment but document use of the product in the eCRF If the addition of a medication is needed for treatment of an adverse event, the decision to discontinue study treatment will be made by the Investigator and Sponsor based on the relevance and duration of the prohibited treatment
Intravitreal injections of any kind	During the course of the study	Do not discontinue study treatment, but document use of the product in the eCRF If the addition of a medication is needed for treatment of an adverse event, the decision to discontinue study treatment will be made by the Investigator and Sponsor based on the relevance and duration of the prohibited treatment
Medical device treatments such as those used to treat Meibomian gland dysfunction (eg, LipiFlow, pulse light therapy, etc)	During the course of the study	Discontinue study treatment
Punctal plugs or punctal cauterization	Placement of new occlusion during the course of the study	Discontinue study treatment

Subjects should be discouraged from using artificial tears, gels, lubricants during the study. However, if a subject is in need of occasional rescue and must use these products, the subject can remain in the study but the use of the products must be documented in the eCRF. If a subject is unable to refrain from use of these products and is unable to continue with the requirements of the study, the subject should be discontinued.

Topical ocular prescription medications should be administered at least 10 minutes before dosing with the study medication.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a subject Number (subject No.), that is assigned when the subject is enrolled for screening and is retained for the subject throughout his/her participation in the trial. A new subject No. will be assigned at every subsequent enrollment if

[redacted]

the subject is re-screened. The subject No. consists of the Site Number (Site No.) (as assigned by Novartis/Sponsor to the investigative site) with a sequential subject number suffixed to it, so that each subject's participation is numbered uniquely across the entire database. Upon signing the ICF, the subject is assigned to the next sequential subject No. available

6.3.2 Treatment assignment, randomization

Separate randomization lists will be generated for the two parts of the study.

For Part 1, all eligible subjects will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The same process applies to the subjects eligible to participate in Part 2.

Randomization in both Part 1 and Part 2 will be stratified by subjects with a documented diagnosis of Sjogren's Syndrome. Stratification of subjects with Sjogren's Syndrome is intended to ensure these subjects are evenly distributed across the treatment arms.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments, and Clinical Trial Team (CTT) will remain masked to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone involved in the study. (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Unmasking of the CTT members/site staff will occur at the end of Part 1 and again at the end of Part 2.

[redacted]

Table 6-3 Blinding levels

Role	Time and Event		
	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**
Subjects/Patients	B	B	B
Site staff	B	B	B
Drug Supply and Randomization Office	UI	UI	UI
Bioanalytical Team	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	B
All other sponsor staff not identified above	B	B	B
B Remains blinded UI Allowed to be unblinded on individual patient level			

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.5.1 Dose modifications

Dose interruptions and/or reductions are not allowed.

6.5.2 Follow-up for toxicities

Not applicable

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The Investigator must promote compliance by instructing the subject to dose the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the Investigator if he/she is unable for any reason to dose the study treatment as prescribed.

Compliance will be assessed by the Investigator and/or study personnel at each visit by questioning the subject and verifying drug accountability including the number of used and unused BFS containers. This information should be captured in the source document at each visit.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs). Due to the expected lack of systemic exposure of the drug, the nature of ECF843 as an endogenous protein, and the fact that to date there have been no significant adverse events (ocular or non-ocular), an abundance of caution is not warranted at this time point.

[redacted]

If the subject were to experience significant discomfort upon instillation of the investigational product, the eye should be flushed with sterile saline (or equivalent). Should the subject experience blurred vision for a time just after instillation of the investigational product, he/she should not drive or use machines until the effect has worn off. The Investigator must treat the subject as needed and appropriate for their condition.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Blinding codes may also be broken after a subject discontinues treatment due to disease progression if deemed essential to allow the investigator to select the subject's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis/sponsor monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- subject name (if available)
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Subjects will be discontinued from the study once the treatment code has been broken.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

For both Part 1 and Part 2, Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication secondary packaging has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

As per Section 4.6 during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a subject's home may be permitted (if allowed by Local or Regional

[redacted]

Health Authorities and IRBs/IECs as appropriate) in the event the Investigator has decided that an on-site visit by the subject is no longer appropriate or possible, and that it is in the interest of the subject's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the subject's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 2 week supply. In this case, regular phone calls or virtual contacts (e.g., every 2 weeks or more frequently if needed) will occur between the site and the subject for instructional purposes, safety monitoring, investigation of any adverse events, ensuring subjects continue to benefit from treatment, and discussion of the subject's health status until the subjects can resume visits at the study site.

6.7.1 Handling of study treatment and additional treatment

6.7.2 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all used and unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.3 Handling of additional treatment

Not applicable

6.7.4 Instruction for prescribing and taking study treatment

Table 6-4 Dose and treatment schedule

Investigational / Control Drug	Dose	Frequency and/or Regimen
ECF843 0.15 mg/mL	one drop in each eye	BID
ECF843 0.15 mg/mL	one drop in each eye	TID
ECF843 0.45 mg/mL	one drop in each eye	TID
Vehicle	one drop in each eye	BID or TID as per study design

[redacted]

Part 1

Each single use BFS container contains enough drug for instillation of one drop per eye at each dosing time point. There will be additional drug remaining in the container after dosing. However, subjects must NOT continue dosing beyond the single time point with any container.

Drug must be stored as indicated on the container label.

Subjects will dose according to their randomized dosing frequency (BID or TID). If dosing BID, subjects will dose in the morning upon wakening and in the evening prior to bed time. If dosing TID, subjects will dose morning upon wakening, mid-day, and evening prior to bed time. Subjects should avoid touching the tip of the container to any surface, including the eye or surrounding skin, to avoid contamination.

Part 2

ECF843 and Vehicle will be handled as described above; the dose frequency will be derived from the Part 1 results.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation) Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written ICF.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). For this study, the subject must sign informed consent prior to participation in Part 1, and again confirm and sign the informed consent prior to participation in Part 2 (the main informed consent form for a single subject contains both signatures). In the case of subjects who are enrolled only in Part 2, only 1 signature is required. The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or

an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

The following informed consents are included in this study:

- Main study informed consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - As applicable, Pregnancy Outcomes Reporting Consent for female subjects or the female partners of any male subjects who took study treatment
- [redacted]

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements.

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedules (Table 8-1 and Table 8-2) list when all of the assessments are to be performed. All data obtained from these assessments must be supported in the subject's source documentation.

Only subjects assigned exclusively to vehicle treatment in Part 1 may be eligible to participate in Part 2 of the study. A list of subjects eligible for screening in Part 2 of the study will be discussed between the Investigator and the Sponsor prior to initiating screening visits. In the event a study site was initiated close to the end of enrollment and did not have sufficient time to begin recruiting subjects in Part 1, the site may enroll subjects into Part 2 of the study if approved by the Sponsor.

Subjects are encouraged to stick to the scheduled visits as much as possible. If a subject is unable to return to the site as per the visit schedule, no visits should be missed, and efforts should be made to resupply the subject with sufficient drug (as needed). Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1 and Table 8-2) as close as possible to the target visit day and as close to the same time of day for each visit as possible. If a subject returns to the site for a visit earlier or later than planned, the next sequential visit should take place. The remaining subsequent visits should then be scheduled in a way that

[redacted]

brings the subject back to their original target dates for each visit as determined at Screening/Baseline.

Subjects must not have dosed with study medication within 4 hours of the visit assessments being conducted. [redacted]

Missed or rescheduled visits should not lead to automatic discontinuation.

Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product must be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

[redacted]

Table 8-1 Assessment Schedule, Part 1

Period	**Screening**	**Treatment**				
Visit Name	**Visit 1-Screening**	**Visit 1-Randomization**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5/EOS**
Days	**1**	**1**	**14**	**28**	**42**	**56**
Informed consent	X					
[redacted]						
Inclusion / Exclusion criteria	X					
Demography	X					
Medical history/current medical conditions	X					
Concomitant medications	X		X	X	X	X
Pregnancy Test (urine)	X					X
In office SANDE score	X					
[redacted]						
Corrected visual acuity	X		X	X	X	X
Slit lamp biomicroscopy	X		X	X	X	X
Ocular hyperemia	X		X	X	X	X
[redacted]						
Tear break-up time (TBUT)	X		X	X	X	X
Corneal fluorescein staining[2]	X		X	X	X	X
Conjunctival lissamine staining	X		X	X	X	X
Schirmer Tear Test	X					
Intraocular Pressure (IOP)	X		X	X	X	X
Fundus Exam	X					X
Contact IRT[3]			X	X	X	X
Randomization		X				
Dispense study medication		X	X	X	X	
In-office study drug administration		X				

[redacted]

Period	Screening	Treatment				
Visit Name	**Visit 1-Screening**	**Visit 1-Randomization**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5/EOS**
Days	**1**	**1**	**14**	**28**	**42**	**56**
Adverse Events	X	X	X	X	X	X
At home SANDE questionnaire (eDiary)[4]	X		X	X	X	
[redacted]						
Study completion information						X

X Assessment to be recorded in the clinical database or received electronically from a vendor

[redacted]

3 Sites will enter average SANDE score (obtained from the electronic diary) and the corneal fluorescein staining score from the eye with the highest composite score (sum of the 5 regions)
4 Subjects will complete an electronic diary once daily (in the evening before bed time and prior to the evening dose of study medication) from Visit 1-Screening through to the end of the study (at home SANDE questionnaire)

[redacted]

Table 8-2 Assessment Schedule, Part 2

Period	Screening	Treatment						Post Treatment Follow-up	
Visit Name	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ EOT**	**Visit 8/ EOS[8]**	**Safety F/U EOS[8] +4. +8, +12 Weeks**
Days	**-14**	**1**	**7**	**14**	**28**	**42**	**84**	**126**	**154, 182, 210**
Informed consent	X								
Inclusion / Exclusion criteria	X	X							
Demography	X								
Medical history/current medical conditions	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Pregnancy Test (urine)	X						X		

[redacted]

Period	**Screening**	**Treatment**						**Post Treatment Follow-up**	
Visit Name	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ EOT**	**Visit 8/ EOS[8]**	**Safety F/U EOS[8] +4. +8, +12 Weeks**
Days	**-14**	**1**	**7**	**14**	**28**	**42**	**84**	**126**	**154, 182, 210**
In office SANDE score	X	X							
[redacted]									
Corrected visual acuity		X					X		
[redacted]									
Slit lamp biomicroscopy	X	X	X	X	X	X	X		
Ocular hyperemia		X	X	X	X	X	X		
[redacted]									
Tear break-up time (TBUT)	X	X			X		X		
Corneal fluorescein staining[3]	X	X	X	X	X	X	X		
[redacted]									
Conjunctival lissamine staining	X	X	X	X	X	X	X		
Schirmer Tear Test	X	X							
Intraocular Pressure (IOP)		X			X		X		

[redacted]

Period	**Screening**	**Treatment**						**Post Treatment Follow-up**	
Visit Name	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ EOT**	**Visit 8/ EOS[8]**	**Safety F/U EOS[8] +4. +8, +12 Weeks**
Days	**-14**	**1**	**7**	**14**	**28**	**42**	**84**	**126**	**154, 182, 210**
Fundus exam		X					X		
[redacted]									
Randomization		X							
Dispense study drug	X	X		X	X	X			
In-office study drug administration		X		X	X	X			
[redacted]									
Adverse Events[6]	X	X	X	X	X	X	X	X	X
At home SANDE questionnaire (eDiary)[7]	X	X	X	X	X	X			
Study completion information							X		

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[redacted]

[6] Adverse events will not be collected from the time the subject completes Part 1 until the subject confirms/signs consent for participation in Part 2

[redacted]

Period	**Screening**	**Treatment**						**Post Treatment Follow-up**	
Visit Name	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ EOT**	**Visit 8/ EOS[8]**	**Safety F/U EOS[8] +4. +8, +12 Weeks**
Days	**-14**	**1**	**7**	**14**	**28**	**42**	**84**	**126**	**154, 182, 210**

[7] Subjects will complete an electronic diary (at home SANDE questionnaire) once daily (in the evening before bed time and prior to the evening dose of study medication) from Visit 1 (Screening) through to the end of the treatment

[8] Post treatment follow up visits begin at Visit 8/EOS for ALL subjects. [redacted]

[redacted]

8.1 Screening

No subjects may be re-screened if they fail entry criteria for any reason other than required stabilization time frames for medications and/or medical history.

If a subject is enrolled and it is determined prior to the completion of Visit 1 that the subject did not meet criteria pertaining to:

- duration of DED diagnosis;
- time frame required for stabilization of chronic medications or therapies, time frames related to medical history or use of contact lenses

the subject will be screen failed and brought back at a later date to re-attempt the screening process once the proper time frames have been achieved.

In the case of re-screening, the subject will receive a new subject number and all screening assessments required at Visit 1 must be completed on the day of randomization, regardless if the assessments were conducted at the previous screening visit.

Re-screening is only allowed one time for a particular subject and per part of the study. Re-screening must not be used as a method to force subject eligibility into the study.

For subjects requiring washout of prior medications or contact lenses, informed consent must be obtained prior to washout. Subject will be enrolled into the study and brought back for screening assessments (Visit 1) after the washout is completed.

8.1.1 Information to be collected on screening failures

Subjects who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see Section 10.1.3 for SAE reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail and that the subject was not randomized.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

The following information will be collected/documented at screening visit for each subject:

- Date of birth, age
- Gender
- Race/Ethnicity
- Concomitant medications

[redacted]

- Past relevant medical history and current medical conditions
- Completed clinical assessments
- Ocular assessment

8.3 Efficacy

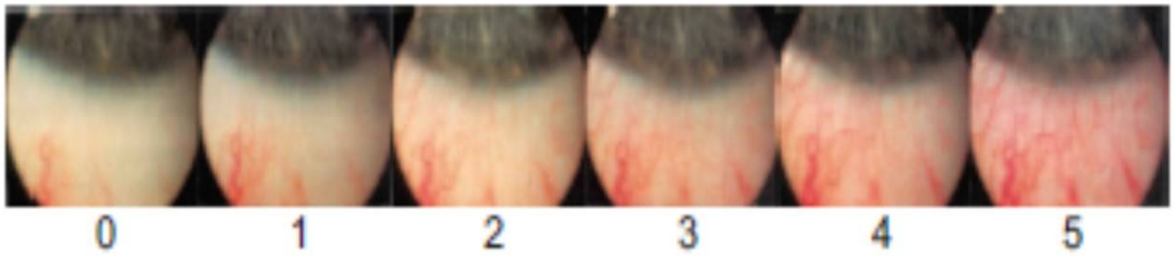
The following assessments are included to evaluate the efficacy of ECF843:

- Ocular hyperemia
- Tear break-up time (TBUT)
- Corneal fluorescein staining
- Conjunctival lissamine staining

8.3.1 Ocular Hyperemia

The investigator will grade conjunctival bulbar redness. Both nasal and temporal inter-palpebral bulbar conjunctival regions will be graded according to the McMonnies redness photographic scale.

Figure 8-1 McMonnies Redness Photographic Scale



8.3.2 Tear Break-Up Time

For individual subjects, TBUT should be assessed by the same examiner at all time points, and must be measured immediately after instillation of the fluorescein dye if performed at that visit.

Fluorescein impregnated strips supplied by the sponsor will be used according to package instructions. One drop of sterile saline, or equivalent, will be applied to the tip of the strip. DO NOT use anesthetic drops to wet the strips. Immediately after application of the wetting drop to the strip, gently flick the excess drop off the end of the strip prior instilling the dye. A new strip should be used for each eye.

Immediately after instillation of the fluorescein, position the subject's head in the headrest of the slit-lamp instrument and instruct the subject not to wipe or dab their eyes, and to gently blink 3 times (avoid forceful blinks), then stare and NOT BLINK. The Investigator will monitor the integrity of the tear film and, using a stopwatch, measure the time from the last blink until the first black (dry) spot appears in the precorneal tear film (record values to 2 decimal points).

[redacted]

Repeat this procedure to obtain three consecutive TBUT measurements.

8.3.3 Corneal Fluorescein Staining

Corneal fluorescein staining will be conducted by the Investigator. For individual subjects, corneal fluorescein staining should be assessed by the same examiner at all visits using the same slit lamp and the same settings. The right eye should be completed first, followed by the left eye.

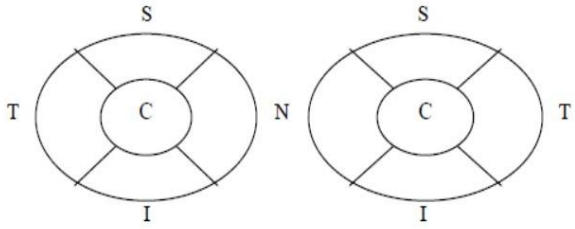
At visits where TBUT is also done, instillation of the sodium fluorescein dye will have already occurred. As long as the corneal staining assessment is done within the specified time frame, no additional instillation of fluorescein dye is required. At visits where TBUT is not done, follow the same procedure as described above for instillation of fluorescein dye to each eye.

Staining will be assessed a minimum of 2.5 minutes and preferably less than 5 minutes after instillation of the dye. Evaluation of the cornea will be done through a slit lamp with use of a cobalt blue filter.

The degree of staining is based on the Corneal Fluorescein Modified NEI Scale. Each of the five regions (as depicted in the diagram, and defined as central (C), superior (S), inferior (I), temporal (T), and nasal (N)) will be graded based on a scale of 0 to 4, with higher scores suggestive of higher degrees of corneal staining (Figure 8-2). The examiner will indicate the appropriate score for each region. If the assessment falls between grades, round up to the higher score. After entry of the scores per region, the total or composite (sum) score for each eye will be automatically calculated (maximum score = 20/eye).

A (+1) will be added to the sum score for any eye with the presence of filaments.

Figure 8-2 Corneal Fluorescein Modified NEI Scale



Grade 0	No staining
Grade 1	Superficial micropunctate staining covering < 25% of the corneal surface
Grade 2	Macropunctate staining AND/OR superficial micropunctate staining covering 25-50% of the corneal surface
Grade 3	Some coalesced macropunctate staining AND/OR superficial micropunctate staining covering 51-75% of the corneal surface
Grade 4	Numerous coalesced macropunctate areas and/or patches AND/OR superficial micropunctate staining covering > 75% of the corneal surface

[redacted]

[redacted]

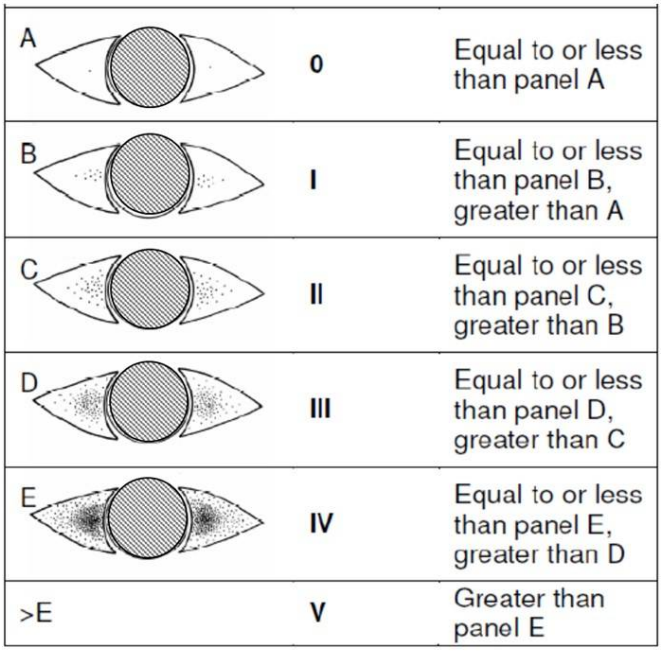
8.3.4 Conjunctival Lissamine Staining

Conjunctival lissamine staining will be conducted by the Investigator and assessed after corneal fluorescein staining. For individual subjects, lissamine staining should be assessed by the same examiner at all visits using the same slit lamp and the same settings. The right eye should be completed first, followed by the left eye.

Lissamine impregnated strips supplied by the sponsor will be used according to package instructions. One drop of sterile saline, or equivalent, will be applied to the tip of the strip. DO NOT use anesthetic drops to wet the strips. Immediately after application of the wetting drop to the strip, gently flick the excess drop off the end of the strip prior instilling the dye. A new strip should be used for each eye.

The degree of staining is based on the Lissamine Conjunctival Oxford Staining Scale. The nasal and temporal conjunctival regions are assessed for interpalpebral lissamine conjunctival staining (the corneal region must not be assessed). Each of the two regions (as depicted in the diagram) will be graded on a scale of 0 to 5 (Figure 8-3). The examiner will indicate the appropriate score for each region. If the assessment falls between grades, round up to the higher score. After entry of the scores per region, the total or composite (sum) score for each eye will be automatically calculated (maximum score = 10/eye).

Figure 8-3 Lissamine Conjunctival Oxford Staining Scale



[redacted]

8.3.5 Appropriateness of efficacy assessments

The efficacy assessments included in this study for the evaluation of ocular signs and symptoms are commonly used in clinical research for DED and are accepted methods for evaluation of drugs for market authorization by the US FDA.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10 (Safety monitoring and reporting).

Table 8-3 Assessments & Specifications

Assessment	Specification
Corrected Visual Acuity	Qualified site personnel will conduct Snellen visual acuity testing in each eye separately per standard clinical practice and should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Subjects must use their standard prescribed correction or pin hole. No refraction will be conducted at the visit to determine best correction.
Slit Lamp Exam	The Investigator will perform a slit-lamp assessment of the anterior portion of the eye of both eyes before instillation of any diagnostic eye drops, including evaluation of the lids, cornea, conjunctiva, iris, anterior chamber, and lens.
Intraocular Pressure	Intraocular pressures will be measured in both eyes by a qualified technician and according to the study site's regular practice. The same method must be used throughout the study for both eyes in each subject.
Fundus Exam	The Investigator will perform an ophthalmoscopic examination of the posterior segment of both eyes including the vitreous, retina, macula, choroid and optic nerve. Dilation can be performed at the Investigator's discretion.

8.4.1 Laboratory evaluations

Not Applicable.

8.4.2 Pregnancy

A urine pregnancy test will be conducted for all women of childbearing potential to assess pregnancy as indicated in the Schedule of Assessments.

Additional pregnancy testing might be performed if requested by local requirements.

8.4.3 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

[redacted]

[redacted]

Subject questionnaires should be completed in the language most familiar to the subject, and given sufficient time to complete the questionnaires truthfully and accurately.

For questionnaires completed by the subject in the clinic, the site personnel should check PRO measures for completeness and ask the subject to complete any missing responses. The responses that are stored electronically in the database will be considered the source file.

Completed measures and any unsolicited comments written by the subject should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the subject to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10 (e.g. reference "Adverse Events" section) of the study protocol.

Site personnel should monitor a subject's compliance with completion of the daily diary. If the subject is not compliant with diary entries, the reason for the non-compliance should be determined and corrective efforts should be made. If the subject is repeatedly unable to comply with the daily diary requirements, the subject should be considered not appropriate for the study due to inability to follow protocol requirements, and should be discontinued.

8.5.2 Patient Reported Outcomes (PRO)

8.5.2.1.1 Symptom Assessment in Dry Eye (SANDE) Questionnaire

The SANDE questionnaire is completed through an electronic diary by the subject at the Screening Visit(s) of Part 1 and Part 2, and thereafter every evening before bedtime during the study. The SANDE uses a 100 mm visual analog sacle (VAS) and asks the subject to score frequency and severity of their ocular discomfort over the past 24 hours by putting a vertical mark on two separate horizontal scoring lines. The frequency scoring line utilizes the anchors of 'Rarely' to 'All the Time', while the severity scoring line utilizes the anchors of 'Very Mildly' to 'Very Severely' uncomfortable. The overall SANDE score is calculated by taking the square root of the product of the frequency and severity scores.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.5.5.2 Unanesthetized Schirmer Test

[redacted]

Qualified site personnel will conduct the test with the subject seated in the examining chair with the room lights dimmed and their head against a headrest for comfort. Both eyes will be assessed simultaneously.

- Prepare the strips while they are still in the package by folding the rounded end at the indentation.
- Position the strips into the inferior cul-de-sac at the lateral third of the eyelid.
- After inserting the strip into each eye, instruct the subject to gently close their eyes. The subject should avoid forceful lid closure.
- Leave the strips in place for 5 minutes.
- After 5 minutes, ask the subject to gently open their eyes. The study staff will remove the strip from the eye and immediately record the length of the strip that is wetted by the tears. The measurement should be made to the nearest whole number.

[redacted]

[redacted]

9 Study discontinuation and completion

The investigator should discontinue study treatment for a given subject and/or withdraw the subject from the study if he/she believes that continuation would be detrimental to the subject's well-being, or that the subject is unable or unwilling to comply with protocol requirements.

A subject will be considered to have completed Part 1 of the study when the subject has completed the last visit planned for Part 1. The subject should NOT be discontinued from the study after Part 1 unless the subject withdraws informed consent, or is deemed not eligible for participation in Part 2 of the study. Subjects who discontinue the study in Part 1 will no longer be eligible for Part 2.

For subjects who discontinue treatment but do not discontinue the study during Part 1, or for subjects who experience a treatment related AE or SAE, eligibility for Part 2 will be dependent on the reasons for treatment discontinuation or nature of the AE/SAE. The decision for participation in Part 2 will be at the discretion of the Investigator, with guidance from the Sponsor as needed.

The investigator and/or referring physician will recommend the appropriate follow-up medical care, if needed, for all subjects who are prematurely withdrawn from the study.

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the subjector the investigator

Discontinuation from study treatment is required under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 6.2.2)
- Any situation in which continued study participation might result in a safety risk to the subject
- Inability or unwillingness of the subject to follow the protocol requirements
- Following emergency unblinding (see Section 6.6.3)
- Adverse events that indicate a safety risk to the subject
- Unsatisfactory therapeutic effect

[redacted]

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue from study treatment agree to **return for the end of treatment and follow-up visits indicated** in the Assessment Schedule (refer to Section 8).

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Discontinuation from study

Discontinuation from study is when the subjectpermanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the subject agrees, a final evaluation at the time of the subject's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw informed consent to participate in the study for any reason at any time. Withdrawal of informed consent/opposition to use data/biological samples occurs when a subject explicitly requests to stop use of their biological samples and/or data (opposition to use data and biological samples:

and

- No longer wishes to receive study treatment ,

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw their informed consent/opposition to use data/biological samples and record this information.

Where consent to the use of personal and coded data is not requiredin a certain country's legal framework, the subject therefore cannot withdraw informed consent. However, they still retain the right to object to the further collection or use of their personal data.

[redacted]

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. If the subject agrees, a final evaluation at the time of the subject's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis/Sponsor will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of informed consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons.

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a subject who discontinued from study treatment. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes the Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

Once a subject completes the study in its entirety, no further study treatment will be made available to the subject.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

[redacted]

[redacted]

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. Severity grade
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities
2. its relationship to the study treatment (i.e., blinded study medication [ECF843 vs Vehicle],as applicable). If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment (i.e., blinded study medication [ECF843 vs Vehicle], as applicable)
6. its outcome

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug withdrawn

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event collection will be performed through the End of Study (EOS) visit.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

[redacted]

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to an event in which the subject was at risk of death at the time of the event; it does not refer to a reaction that hypothetically might have caused death if it were more severe (ICH-E2D).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (ICH-E2D).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode

[redacted]

within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial subject becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial subject. The subject must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the ECF843 treatment to any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the

safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 10.

10.2 Additional Safety Monitoring

Not Applicable

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

[redacted]

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unmasked** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The study monitor will visit the site as detailed in the study-specific monitoring plan to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the study monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Trial Monitoring organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original ICF signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the

[redacted]

study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

All the efficacy endpoints will be based on the study eye. Study eye is defined as the eye with the highest composite corneal staining score at baseline. If both eyes have equal composite corneal staining scores, then the right eye will be selected as the study eye. The safety analysis will be presented for both eyes.

12.1 Analysis sets

The analysis sets will be defined for Part 1 and Part 2, respectively.

Part 1:

The Full Analysis Set (FAS) 1 comprises all subjects to whom study treatment has been assigned by randomization in Part 1. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

The Safety Set 1 includes all subjects who received at least one dose of study treatment in Part 1. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Part 2:

The Full Analysis Set (FAS) 2 comprises all subjects to whom study treatment has been assigned by re- randomization in Part 2. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

The Safety Set 2 includes all subjects who received at least one dose of study treatment in Part 2. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the re-randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the re-randomized treatment was never received.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for FAS 1 and FAS 2, respectively.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by study part and treatment group.

[redacted]

12.3 Treatments

The Safety set 1 and Safety Set 2 will be used for the analyses below, respectively. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to ECF843 and vehiclewill be summarized by means of descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis supporting primary objectives

The primary aim of the study is to demonstrate improvement in moderate to severe DED with ECF843. This will be evaluated by measuring signs and symptoms as primary estimands. The analysis of the primary estimands will be based on FAS 1.

12.4.1 Definition of primary endpoint(s)

The two primary endpoints are the change from baseline in SANDE symptom score and the change from baseline in composite corneal fluorescein staining score in Part 1.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary objective of Part 1 of the study is to show that at least one ECF843 arm will improve SANDE symptom score and/or composite corneal fluorescein staining score in comparison with its corresponding vehicle (BID or TID) by rejecting the null hypothesis below at a significance level α=0.05 (2-sided).

H1: $u_T=u_v$ vs. H2: $u_T\neq u_v$

where u_T and u_v are mean change from baseline of SANDE symptom score in ECF843 arm and the corresponding vehicle arm.

H3: $\theta_T=\theta_v$ vs. H4: $\theta_T\neq\theta_v$

where θ_T and θ_v are mean change from baseline of composite corneal fluorescein staining score in ECF843 arm and the corresponding vehicle arm.

Hochberg method will be used to adjust overall type I error (0.05) among the comparisons between each ECF843 arm and its corresponding vehicle for each primary endpoint.

For SANDE symptom score, mixed model repeated measures (MMRM) will be used with change from baseline at all post-baseline score on treatment as response variable, and treatment, day, randomization strata and baseline score as covariates. Two interaction term (treatment*day and baseline*day) will also be included in the model.

For composite corneal fluorescein staining score, MMRM will be used with change from baseline at all post-baseline visits on treatment as response variable, and treatment, visit, randomization strata and baseline score as covariate. Two interaction term (treatment*visit and baseline*visit) will also be included in the model.

[redacted]

For both endpoints, an unstructured within subject correlation structure will be used for covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degree of freedom. Residual/restricted maximum likelihood (REML) method will be used to estimate parameters.

The two-sided p value for the least square mean (LSM) difference between the ECF843 and the vehicle group at each post-baseline day/visit will be reported for the difference.

12.4.3 Handling of intercurrent events of primary estimand

The primary estimands will be the treatment effect of ECF843 against its corresponding vehicle, had subjects not taken artificial tears/gels/lubricants or prohibited medications as described in Section 6.2.2, and had they stayed on study treatment for the whole study duration. The hypothetical strategy assumes the subjects with intercurrent events (IEs) will behave like other subjects who did not take rescue/prohibited medications and stayed on study treatment. The primary analysis will account for different IEs as following:

1. Use of artificial tears/gels/lubricants: For subjects who use artificial tears/gels/lubricants occasionally for rescue, the data on the day(s) will be excluded and treated as missing.
2. Use of prohibited medications:

- For subjects who took ocular, nasal, inhaled, or systemic corticosteroids, intravitreal injections of any kind, the data on the day(s) + 3 days following the last day of prohibited medications will be excluded and treated as missing.
- For subjects who took the following prohibited medications,
  - Any topical ocular medications (prescription or over the counter; excluding IOP-lowering medication)
  - Medical device treatments such as those used to treat Meibomian gland dysfunction (eg, LipiFlow, pulse light therapy, etc)
  - Punctal plugs or punctal cauterization
- The data on the day(s) of prohibited medications will be excluded and treated as missing.

3. Discontinuation of study treatment for any reason: For subjects who discontinue study treatment, the data collected following the discontinuation will be excluded and treated as missing.

Missing data will be implicitly imputed under Missing at Random (MAR) assumption for MMRM analysis, that is missing data are imputed based on the treatment-specific information for the repeated measurements at baseline and post-baseline days/visits.

12.4.4 Handling of missing values not related to intercurrent event

For all analyses, imputation of intermittent missing observations before discontinuation from study treatment will be carried out following a MAR mechanism for all treatment arms.

12.4.5 Sensitivity analyses for primary estimand

Not applicable.

[redacted]

12.4.6 Supplementary analysis

A supplementary clinical question of interest is: what is the effect of ECF843 versus vehicle on change from baseline in signs and symptoms after treatment in subjects with moderate to severe DED, regardless of discontinuation from study treatment for any reason,and regardless of use of artificial tears/gel/lubricants, or prohibited medications?

The supplementary estimands will be the difference between change from baseline in each primary endpoint for ECF843 vs corresponding vehicle, regardless of intercurrent events (treatment policy).

- Use of artificial tears/gels/lubricants: For subjects who use artificial tears/gels/lubricants occasionally for rescue, all observed data will be used for analysis. If not available, missing data on the days of the IEs will be multiple imputed under MAR assumption for both ECF843 and vehicle arms.
- Use of prohibited medications: For subjects who take ocular, nasal, inhaled, or systemic corticosteroids, intravitreal injections of any kind, all observed data will be used for analysis. Missing data on the day(s) + 3 days following the last day of prohibited medications, if any, will be multiple imputed under MAR assumption for both ECF843 arms and vehicle arms.
- For subjects who take the following prohibited medications,
- Any topical ocular medications (prescription or over the counter; excluding IOP-lowering medication)
- Medical device treatments such as those used to treat Meibomian gland dysfunction (eg, LipiFlow, pulse light therapy, etc)
- IVT injections, punctal plugs or punctal cauterization
- all observed data will be used for analysis. If not available, missing data on the days of the IEs will be multiple imputed under MAR assumption for both ECF843 arms and vehicle arms.
- Discontinuation of study treatment
- For subjects who discontinue treatment due to any reason, Retrieved drop-out (RDO) data collected after study treatment discontinuation will be used for analysis. If not available, missing data after treatment discontinuation will be multiple imputed based on J2R assumption for ECF843 arms and under MAR assumption for vehicle arms.
- The supplementary analysis will be performed using MMRM but includes all the observed data and imputed data if appropriate.

Subgroup analyses

Subgroup analyses of the primary endpoints will be outlined in the statistical analysis plan (SAP).

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

For secondary endpoints, change from baseline in inferior and central corneal fluorescein staining, summary statistics (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence

[redacted]

interval) by treatment arm will be provided. A 95% confidence interval will be provided for the difference between the ECF843 arm vs. its corresponding vehicle at each post-baseline visit.

12.5.2 Safety endpoints

Safety analysis for Part 1 and Part 2 will be performed separately, based on respective safety set. All listings and tables will be presented by treatment group.

The safety analysis will consist of descriptive summaries. Continuous variables will be presented with n, mean, standard deviation, median, minimum and maximum. Categorical data will be displayed with frequency and percentage.

Adverse events

All information obtained on adverse events (ocular and non-ocular), will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of subjects with adverse events of special interest/related to identified and potential risks will be summarized by treatment.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

For Part 1, the primary analysis will be performed after all subjects in Part 1 have completed randomized treatment or discontinued prior to that. The analysis will be used to evaluate efficacy and safety of ECF843 vs. Vehicle. For Part 2, the primary analysis will be performed when all subjects in Part 2 have completed 12 weeks of treatment or discontinued treatment. The analysis will be used to explore efficacy and safety of ECF843 vs. vehicle after 12 weeks of treatment.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Part 1 of the study is powered on 2 primary endpoints, change from baseline in SANDE symptom score and composite corneal fluorescein staining score.

In one previous rhLubricin clinical study (LUB0114MD) there was an observed standard deviation of 20 mm in change from baseline of SANDE score at Day 28. A second rhLubricin clinical study (LUB0115MD) showed a standard deviation of 23 mm in change from baseline in SANDE symptom score at Day 14.

Assuming a true treatment difference in change from baseline in SANDE symptom score of 10 mm and a standard deviation of 23 mm, a sample size of 112 subjects per arm provides approximately 80% power that the primary analysis will be statistically significant at the two-sided 5% significance level adjusted by 3 comparisons.

See the table below for power to detect a significant difference from vehicle under various assumed treatment effect of SANDE Symptom score and standard deviation.

Table 12-1 Power to Detect a Significant Difference from Vehicle

	Treatment effect: difference from vehicle in change from baseline in SANDE Symptom Score				
Standard deviation of change from baseline in SANDE symptom score	10	11	12	13	14
23	80%	88%	93%	97%	98%
25	72%	81%	88%	93%	96%
27	64%	74%	82%	88%	93%

[redacted]

[redacted]

Assuming a true treatment difference in change from baseline in composite corneal fluorescein staining of 1 and a standard deviation of 1, a sample size of 112 subjects per arm provides more than 99% power that the primary analysis will be statistically significant at the two-sided 5% significance level adjusted by 3 comparisons.

nQuery Advisor 8.4 is used for the estimate.

12.8.2 Secondary endpoint(s)

There are no power considerations for secondary endpoints.

[redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

[redacted]

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written ICF, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study subjects. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction/prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to

Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study subjects.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request

Cheriyan T, Schmid TM, Spector M (2011) Presence and distribution of the lubricating protein, lubricin, in the meibomian gland in rabbits. Mol. Vis.; 17:3055-61.

Craig JP, Nelson JD, Azar DT, et al (2017a) TFOS DEWS II Report Executive Summary. Ocul Surf; 15:802-812.

Craig JP, Nichols KK, Akpek EK, et al (2017b) TFOS DEWS II Definition and Classification Report. Ocul Surf; 15:276-283.

Gleghorn JP, Jones AR, Flannery CR, et al (2009) Boundary mode lubrication of articular cartilage by recombinant human lubricin. J. Orthop. Res.; 27:771-7.

Hamm-Alvarez SF, Janga SR, Edman MC, et al (2014) Tear cathepsin S as a candidate biomarker for Sjögren's syndrome. Arthritis & Rheumatology; 66:1872-81.

ICH E2D (2004) Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. London, UK.

Jones AR, Flannery CR (2007) Bioregulation of lubricin expression by growth factors and cytokines. Eur Cell Mater; 13:40-5; discussion 45.

Keating GM (2017) Lifitegrast Ophthalmic Solution 5%: A Review in Dry Eye Disease. Drugs; 77:201-8.

Mandal A, Gote V, Pal D, et al (2019) Ocular Pharmacokinetics of a Topical Ophthalmic Nanomicellar Solution of Cyclosporine (Cequa®) for Dry Eye Disease. Pharm. Res.; 36:36.

McDonald M, Patel DA, Keith MS, et al (2016) Economic and Humanistic Burden of Dry Eye Disease in Europe, North America, and Asia: A Systematic Literature Review. Ocul Surf; 14:144-67.

O'Neil EC, Henderson M, Massaro-Giordano M, et al (2019) Advances in dry eye disease treatment. Curr Opin Ophthalmol; 30:166-78.

Regmi SC, Samsom ML, Heynen ML, et al (2017) Degradation of proteoglycan 4/lubricin by cathepsin S: Potential mechanism for diminished ocular surface lubrication in Sjögren's syndrome. Exp. Eye Res.; 161:1-9.

Rhee MK, Mah FS (2017) Clinical utility of cyclosporine (CsA) ophthalmic emulsion 0.05% for symptomatic relief in people with chronic dry eye: a review of the literature. Clin Ophthalmol; 11:1157-1166.

Samsom ML, Morrison S, Masala N, et al (2014) Characterization of full-length recombinant human Proteoglycan 4 as an ocular surface boundary lubricant. Exp. Eye Res.; 127:14-9.

Schmidt TA, Sullivan DA, Knop E, et al (2013) Transcription, translation, and function of lubricin, a boundary lubricant, at the ocular surface. JAMA Ophthalmol; 131:766-76.

Yu J, Asche CV, Fairchild CJ (2011) The economic burden of dry eye disease in the United States: a decision tree analysis. Cornea; 30:379-87.

[redacted]

16 Appendices

None

[redacted]