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

Statistical Analysis Plan (SAP)

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Table of contents

List of abbreviations

AE	Adverse event
[redacted]	[redacted]
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BID	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DED	Dry Eye Disease
FAS	Full Analysis Set
Ecrf	Electronic Case Report Form
IE	Intercurrent event
IVR	Interactive Voice Response
IWR	Interactive Web Response
J2R	Jump to Reference
MAR	Missing at Random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model Repeated Measurement
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RDO	Retrieved drop-out
SAP	Statistical Analysis Plan
SANDE	Symptom Assessment in Dry Eye
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TID	ter in die/three times a day
WHO	World Health Organization

1 Introduction

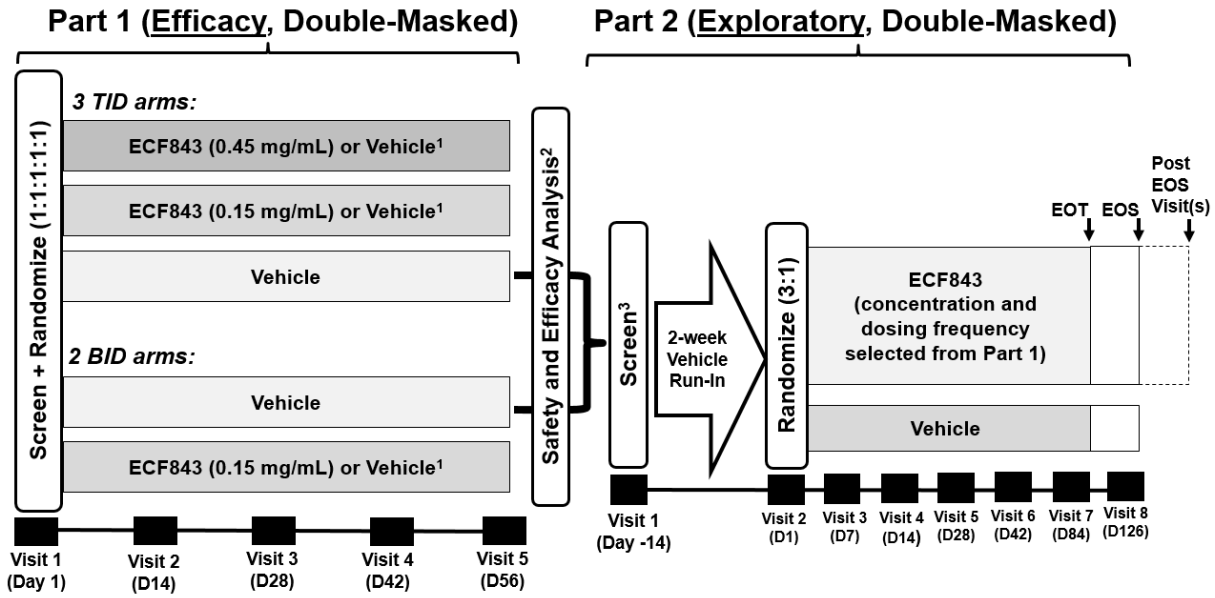
The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of statistical analysis planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study CECF843A2201.

Data will be analyzed according to the data analysis plan described in this document that will be incorporated into Section 9.7 and Appendix 16.1.9 of the CSR.

1.1 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 (Figure 1-1).

Figure 1-1 Study design in protocol



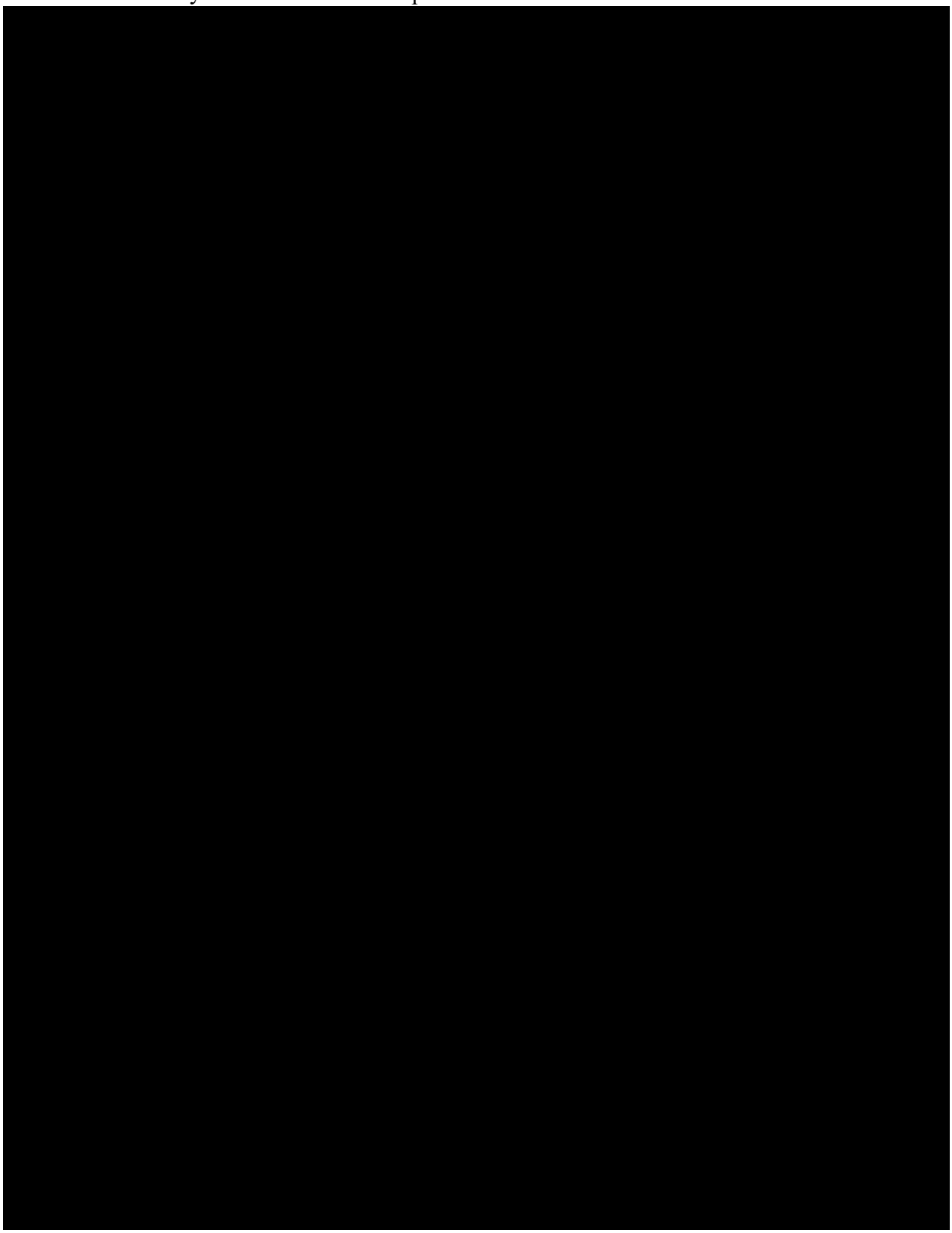
[1] Treatment sequence of ECF843 (up to 28 days) or Vehicle is random.
[2] Decision to start Part 2 based on safety and efficacy analysis from Part 1.
[3] Only subjects assigned exclusively to Vehicle in Part 1 may be eligible for participation in Part 2.

1.1.1 Part 1

Part 1 uses a double-masked design where subjects will be randomized to receive twice a day (BID) or three times a day (TID) treatment with either ECF843 or vehicle for 56 days. For subjects randomized to active ECF843, the maximum drug exposure will be up to 28 days. Approximately 800 subjects will be enrolled into the Part 1 of the study.

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 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.



No interim analyses will be performed in Part 1.

1.1.2 Part 2

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 2 will be initiated only if safety and efficacy of at least one concentration and dosing frequency of ECF843 during Part 1 is demonstrated. Only subjects assigned to vehicle treatment in Part 1 may be eligible to participate in Part 2 of the study.

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.

Subjects will again be asked to sign the informed consent form 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.

Screening: Subjects will be screened for eligibility at Part 2 Visit 1.

Run-in period: Screened subjects will enter a 14-day vehicle run-in period after screening.

Randomization: At Part 2 Visit 2 (baseline), subjects must screen for eligibility criteria at Visit 2 again. Only eligible subjects will be randomized into the study treatment. The randomization will be stratified by subjects with a documented diagnosis of Sjogren's syndrome (yes/no). Subjects will be equally randomized to study treatment.

Treatment period: The randomized subjects will begin 12 weeks study treatment after randomization. They will attend the following study visits after baseline for treatment: at Day 7, Day 14, Day 28, Day 42 and Day 84. Day 84 is the time point for primary analysis.

[redacted]

Part 2 is double-masked and exploratory. No interim analyses will be performed in Part 2.

1.2 Study objectives and endpoints

Table 1-2 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]

2 Statistical methods

2.1 Data analysis general information

The analysis will be performed by the Biostatistics and statistical programming groups of Novartis, using SAS 9.4 or above.

For categorical variables, frequencies and percentages will be computed. For continuous variables, descriptive statistics, including number of non-missing observations, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented. Where appropriate, point estimates and two-sided 95% confidence intervals of treatment group differences will be provided.

These summary statistics will be presented by treatment group unless otherwise specified.

2.1.1 General definitions

The general definitions list below apply to both Part 1 and Part 2 unless otherwise specified.

2.1.1.1 Study treatment

Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), and control(s), which includes:

Part 1:

- ECF843 0.45mg/ml, TID
- ECF843 0.15mg/ml, TID
- Vehicle, TID
- ECF843 0.15mg/ml, BID
- Vehicle, BID

Part 2:

- ECF843 (concentration and dosing posology to be determined from Part 1)
- Vehicle (the same selected posology as ECF843)

2.1.1.2 Date of the first administration of randomized study treatment

The date of the first administration of randomized study treatment refers to:

- In Part 1, it is the date subjects receive the first dose of actually randomized study treatment [redacted]
- In Part 2, it is the date subjects receive the first dose of of randomized treatment at Visit 2 (first exposure date from ‘study treatment’ eCRF).

[redacted]

2.1.1.3 Baseline and post-Baseline

The baseline value for efficacy and safety variables is the last available value collected prior to or on the first administration of randomized study treatment [redacted]. Missing baseline data will not be imputed.

All data collected after the first administration of randomized study treatment are defined as *post-baseline* assessments.

2.1.1.4 Study day

The study day for a baseline or post-baseline scheduled or unscheduled visit is defined as

Study day = (Date of visit) – (Date of the first administration of randomized study treatment) + 1.

The study day for a scheduled or unscheduled visit before baseline is defined as

Study day = (Date of visit) – (Date of the first administration of randomized study treatment).

2.1.1.5 End of study/end of randomized treatment

The end of study date (from 'Study disposition' CRF) is the date when a subject completes or discontinues the study.

[redacted]

In Part 2, the end of treatment date (from 'Treatment disposition' CRF) is the date of the last study treatment prior to/on the end of study date. This value must be compared to the "last exposure date"("Study treatment" eCRF). In case of different dates, the earlier will be used as treatment end date.

For reporting data by visit in outputs, visit window rules will be applied based on study day to allocate assessments to the actual (reported) visit number (Section 2.1.1.7).

2.1.1.6 Unscheduled visits

Unscheduled visit measurements will be included in the following:

1. derivations of measurements at scheduled visits per specified visit windowing rules below.
2. derivations of baseline/last on-treatment measurements.
3. derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses.
4. subject data listings where appropriate.

2.1.1.7 Visit Windows

Visit windows will be applied for all measurements except SANDE scores. Only one SANDE per day within a programmed window (5:00pm -11:59pm) can be entered into eDiary. If the subject does not complete the assessment within this window, the SANDE score will be missing for that day.

Table 2-1 Part 1: Allocation of assessments to analysis visit window

Scheduled main visit name	Target study day	Analysis visit window in study days	Visit Label
Visit 1(D1)	[redacted]		
Visit 2(D14)			
Visit 3(D28)			
Visit 4(D42)			
Visit 5(D56)			

[redacted]

Table 2-2 Part 2: Allocation of assessments to analysis visit window

Scheduled main visit name	Target study day	Analysis visit window in study days	Visit Label
Visit 1(D-14)	-14	≤ -1	Screening
Visit 2(D1)	1	1	Baseline
Visit 3(D7)	7	2 − 11	Day 7
Visit 4(D14)	14	12 − 21	Day 14
Visit 5(D28)	28	22 − 35	Day 28
Visit 6(D42)	42	36 − 63	Day 42
Visit 7(D84)	84	≥ 63	Day 84

For both Part 1 and Part 2:

- If no measurement is available within a visit window, the assessment will be considered missing for the visit.
- If there is more than one measurement available within the same visit window, use the following rules:
  1. The record closest to the target day will be used.
  2. If there are multiple records with the same distance to the target day, the latest record will be used.
  3. If there are multiple records with the same distance on the same day, the average will be used.

2.1.1.8 Change from baseline for continuous parameters

Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

For summary statistics the raw values (and not imputed values) will be used.

2.1.1.9 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 other eye will be fellow eye. All the efficacy endpoints will be based on the study eye if laterality applies. The safety analysis will be presented for both eyes.

2.2 Analysis sets

Part 1

- The All Enrolled Set 1 (ENS1) includes all subjects who signed informed consent for Part 1. This analysis set will be used to summarize patient disposition.
- The Full Analysis Set 1 (FAS1) comprises all subjects [redacted]

  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.

  FAS1 will be used for all efficacy analyses, unless otherwise stated.
- The Safety Set 1(SAF1) includes [redacted] who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the actual 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.

[redacted]

Part 2

- The All Enrolled Set 2 (ENS2) includes all subjects who signed informed consent for Part 2. This analysis set will be used to summarize patient disposition.
- The Full Analysis Set 2 (FAS2) 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 (SAF2) 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.

Rules of exclusion criteria of analysis sets with protocol deviations and subject classification are specified in Appendix 5.3. Rule of exclusion of subjects for analysis are specified in Appendix 5.4.

2.2.1 Subgroup of interest

The subgroups of interest are specified below:

- Baseline age group: < 65 years, and >=65 years
- Sex: male, female
- Documented diagnosis of Sjogren's syndrome: yes, no
- Race: asian, non-asian

2.3 Subject disposition, demographics and other baseline characteristics

Subject characteristics and study conduct summaries include tables and listings such as subject disposition table, demographics and baseline characteristics tables, summary of screen failures by reason and listing of subjects excluded from analysis sets.

2.3.1 Subject disposition

Subject disposition table will be reported for ENS1 and ENS2. [redacted]

In addition, the number and percentage of subjects who completed the study, discontinued from the randomized treatment/study by the reason of discontinuation, will be summarized by treatment and total. Percentages will be based on the number of subjects in FAS1 and FAS2.

Subjects who prematurely discontinue the randomized study treatment (treatment period) will be listed along with the reason for discontinuation.

In addition, protocol deviations (PDs) will be summarized through presenting the number and percentage of subjects with each deviation for FAS1 and FAS2.

2.3.2 Demographics and baseline characteristics

Demographic table will include age, sex, race, ethnicity, ancestry, eye color, Sjögren's Syndrome status.

Baseline characteristics table will include:

- SANDE score

- conjunctival lissamine staining score
- corneal fluorescein staining score
- intraocular pressure (IOP)
- tear break-up time (TBUT) average score
- schirmer score
- conjunctival redness

Demographic and baseline characteristics will be summarized for FAS1 and FAS2 populations by treatment group for study eye.

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, preferred term and treatment group separately for ocular and non-ocular histories/conditions.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SAF 1 and SAF 2 will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

2.4.1 Study treatment / compliance

The duration of exposure in days to randomized study treatment will be summarized by means of descriptive statistics by treatment group. The duration of exposure is defined as: date of the last administration of randomized study treatment (end of treatment date) – date of first administration of randomized study treatment +1 (Section 2.1.1.1).

Compliance will be presented by summarizing the total number of days with missing dose or dose interrupted within the randomized treatment period by treatment group. Reason of premature discontinuation from the randomized study treatment will also be summarized.

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as drugs taken and stopped prior to the first administration of randomized study treatment (Section 2.1.1.2). Any medication given at least once between the day of the first administration of the study treatment and the EORT Visit will be a concomitant medication, including those that were started pre-baseline visit and continued into the treatment period. Post therapies are defined as drugs taken after EORT Visit, including those taken prior to EORT Visit and continued until the end of study. Prior, concomitant medication and post therapies will be identified based on recorded or imputed start and end dates of taking the medication.

Prior, concomitant medication or post therapies will be summarized by treatment group (separately for ocular and non-ocular medications/therapies), presented in alphabetical order by ATC classification codes and preferred term. The tables will be presented with overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular preferred term. Medications will be coded according to the WHO Drug Reference List dictionary.

In addition, all information will be listed including the reported name, laterality, and treatment start/end date, etc.

2.4.2.1 Rescue medication

The number and percentage of subjects who received artificial tears/gels/lubricants for occasional rescue use during treatment period will also be summarized by treatment group.

2.4.2.2 Prohibited medication

Moreover, concomitant medications that are prohibited as per protocol (Table 2-3) during the conduct of the study will be summarized specifically. The number and percentage of subjects who used prohibited medications during treatment period will be summarized by treatment group.

Table 2-3 Prohibited medication

Medication	Prohibition period	Action taken
Ocular, nasal, inhaled, or systemic corticosteroids	During 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 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

Medication	Prohibition period	Action taken
Medical device treatments such as those used to treat Meibomian gland dysfunction (e.g., LipiFlow, pulse light therapy, etc.)	During the study	Discontinue study treatment
Punctal plugs or punctal cauterization	Placement of new occlusion during the course of the study	Discontinue study treatment

2.5 Analysis of the primary objective

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 symptoms measure of SANDE questionnaire is completed through an electronic diary every evening before bedtime during the study. The signs measure of corneal fluorescein staining will be conducted by the Investigator during site visits based on the Corneal Fluorescein Modified NEI Scale.

For the purpose of the statistical analyses presented in this document, the following terminology is used:

- Jump to Reference (J2R) – the multiple imputation model will be build based on the available vehicle data (including partial information from patients that discontinued prematurely). The imputation model will include important background characteristics and observed data.
- Missing at Random (MAR) – the multiple imputation model will be build based on similar patients (i.e. with the same covariates and observed measurement history) in the same treatment arm.
- Retrieved drop-out (RDO) patients - Patients who discontinue study treatment and decide to remain in the study by following an abbreviated schedule of assessments.
- Intercurrent events (IE) - Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation (e.g., rescue medications, discontinuation of treatment, switching treatment, terminal events such as death, etc.)

2.5.1 Primary endpoints

The primary clinical question of interest is: What is the effect of ECF843 versus its corresponding vehicle on change from baseline in signs and symptoms after treatment in subjects with moderate to severe DED, had they not taken occasional rescue use of artificial tears/gels/lubricants, prohibited medications and behaved like other subject who did not take them, had they not dicontinued treatment and behaved like other subjects who did not discontinue treatment?

The justification for the primary estimands is that they will capture the effect of the study drug when administered without confounding effects from prohibited medications， occasional

rescue use of artificial tears/gels/lubricants, and adjusting for unfavorable outcome treatment discontinuation

The analysis of the primary estimands will be based on FAS 1.

The primary estimand is defined as follows for signs and symptoms:

- The target **population** is subjects with moderate to severe DED who meet the inclusion and exclusion criteria [redacted].
- The primary **endpoints** are the change from baseline in SANDE score and change from baseline in composite corneal fluorescein staining score [redacted]
- The **treatment of interest** is ECF843 versus vehicle had they not needed occasional rescue use of artificial tears/gels/lubricants, prohibited medications and behaved like other subjects who did not take them, and had they not dicontinued treatment and behaved like other subjects who did not discontinue treatment.

Table 2-4 The handling of intercurrent events strategy for primary estimands

Intercurrent Events	Strategy
Artificial tears/gels/lubricants for occasional rescue use	• The data on the days will be excluded and treated as missing. • Missing data will be under MAR assumption in MMRM
Prohibited medications that could confound the primary endpoint (See Table 2-3) • Ocular, nasal, inhaled, or systemic corticosteroids • Intravitreal injections of any kind	• The data on the day(s) + 3 days following the last day of these prohibited medications will be excluded and treated as missing. • Missing data will be under MAR assumption in MMRM
• 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 days of prohibited medications will be excluded and treated as missing. • Missing data will be under MAR assumption in MMRM
Discontinuation of study treatment	• The data after study treatment discontinuation will be treated as missing. • Missing data after study treatment discontinuation will be based on the MAR assumption in MMRM

- The **summary measure** is the treatment difference of the variable means between ECF843 and vehicle within each dose regimen (BID or TID) respectively.
  - ECF843 0.45mg/ml, TID vs ECF843 vehicle, TID
  - ECF843 0.15mg/ml, TID vs ECF843 vehicle, TID

- ECF843 0.15mg/ml, BID vs ECF843 vehicle, BID

2.5.2 Statistical hypothesis, model, 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 $\alpha = 0.05$ (2-sided).

$$H_1: u_T = u_v \text{ vs. } H_2: u_T \neq u_v$$

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

$$H_3: \theta_T = \theta_v \text{ vs. } H_4: \theta_T \neq \theta_v$$

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 ($\alpha = 0.05$) 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 scores [redacted] on randomized study 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 [redacted] on randomized study 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.

For composite corneal fluorescein staining score, an unstructured within subject correlation structure will be used for covariance matrix. If the unstructured covariance matrix results in a lack of convergence then other covariance structures will be investigated: Toeplitz, First-order autoregressive (AR1) and Compound symmetry will be applied, in the specified order, until the model converges.

For SANDE symptom score, Toeplitz within subject correlation structure will be used for covariance matrix. If the Toeplitz covariance matrix results in a lack of convergence then other covariance structures will be investigated: First-order autoregressive (AR1) and Compound symmetry will be applied, in the specified order, until the model converges.

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 values for the least square mean (LSM) difference between the ECF843 and corresponding vehicle group [redacted] will be reported for primary inference.Line plots (LSM ± 1 SE) will be presented by treatment groups and post-baseline day/visit. The x-axis will be study day/visit and the y-axis will be the change from baseline value.

2.5.3 Handling of missing values/censoring/discontinuations

For other missing values not related to intercurrent event, the primary MMRM model implicitly imputes missing data under a MAR assumption.

2.5.4 Supportive analyses

The subgroup analyses will be conducted to assess the consistency of treatment effect across various subgroups described in Section 2.2.1. Subgroup analyses will be conducted using the same model and analysis strategies described in the primary analyses but fitted by category of each of the subgroups. Subgroup variables that are used as fixed effects in the model will be removed from the model statement in the subgroup analysis if applicable. Subgroups will be presented graphically using forest plots. If a subgroup has limited number of subjects, the analyses on this subgroup may fail to converge and not be implemented. Instead, summary statistics for subgroup will be provided.

The summary statistics (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) for change from baseline in SANDE symptom score and composite corneal fluorescein staining will be provided by treatment group for each post-baseline visit [redacted].

Line plots with error bar (mean ± 1 SE) will be presented by treatment groups and all post-baseline visits [redacted]. Subgroup summary and plot will also be presented.

2.5.4.1 Supplementary estimand

The target population, the primary variable and the summary measure of this estimand are the same as for the primary estimand. The supplementary estimand is defined to estimate the treatment effect of ECF843, regardless of occasional rescue use of artificial tears/gels/lubricants , prohibited medications and treatment discontinuations.

The justification for the supplementary estimand is that they will capture the effect of the study drug when administered in the real world with intercurrent events considered as inherent in the treatment regimen.

Table 2-5 The handling of intercurrent events strategy for supplementary estimand

Intercurrent Events	Strategy
Artificial tears/gels/lubricants for occasional rescue use	• All observed data will be used for analysis • Missing data on the days of IEs, if any, will be multiple imputed under MAR assumption
Prohibited medications that could confound the primary endpoint (See Table 2-3) • Ocular, nasal, inhaled, or systemic corticosteroids	• All observed data will be used for analysis

Intercurrent Events	Strategy
• Intravitreal injections of any kind	• Missing data on the days of IEs + 3 days, if any, will be multiple imputed under MAR assumption
• 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	• All observed data will be used for analysis • Missing data on the days of IEs, if any, will be multiple imputed under MAR assumption
Discontinuation of study treatment	• RDO data collected after study treatment discontinuation will be used for analysis. • Missing data after the treatment discontinuation, if any, will be multiple imputed based on J2R assumption for the ECF843 arms and under MAR assumption for vehicle arms

2.5.4.2 Sensitivity Analysis

Not applicable.

2.6 Analysis of the key secondary objective

There is no key secondary objective in either Part 1 or Part 2 of the study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The second efficacy objective is to evaluate the improvement of ECF843 vs vehicle in corneal damage by quadrant. The analysis of the secondary endpoints will be based on FAS 1.

- Change from baseline in central corneal fluorescein staining [redacted]
- Change from baseline in inferior corneal fluorescein staining [redacted]
- Change from baseline in tear breakup time (TBUT) [redacted]
- Change from baseline in conjunctival lissamine staining score [redacted]

2.7.2 Statistical hypothesis, model, and method of analysis

No statistical hypothesis test will be performed. The summary statistics (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) for change from baseline in inferior and

central corneal fluorescein staining will be provided by treatment group for each post-baseline visit.

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

2.7.3 Handling of missing values/censoring/discontinuations

All observed data will be used for analysis and missing data will not be imputed.

2.8 Safety analyses

Safety analyses for Part 1 and Part 2 will be based on SAF1 and SAF2, respectively. All listings and tables will be presented by treatment group. [redacted]

Safety analyses [redacted] will be based on ESS1 and will be presented by dosing posology (TID and BID). The reporting will include all the data from [redacted] until the end of the study. The baseline value for all safety endpoints in ESS1 is the last available value collected prior to or on the first administration [redacted].

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.

Adeverse Events will be reported at subject level and other safety endpoints will be reported for each eye.

2.8.1 Adverse events (AEs)

In Part 1, AEs will be summarized for TEAE, pre-treatment AE and post-treatment AE separately.

1. Pre-treatment AEs are adverse events started between ICF signature and prior to the first administration of randomized study treatment.
2. Treatment emergent adverse events (TEAEs) are adverse events started after the first administration of randomized study treatment or events present prior to start of the randomized treatment but increased in severity based on preferred term.
3. Post-treatment AEs are adverse events started after the last administration of randomized study treatment to the end of the study.

For Part 1 and Part 2, the number (and percentage) of subjects with AEs will be summarized for ocular and non-ocular respectively, by treatment, in the following ways:

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

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

For ESS1, the number (and percentage) of subjects with AEs will be summarized for ocular and non-ocular respectively, by dosing posology (TID and BID) in the following ways:

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

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. All these analyses will be based on the most updated MedDRA version available prior to the database lock.

All adverse events reporting will be included in the subject listings respectively.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

All deaths that occurred during the study will be summarized by system organ class, preferred term and treatment group. A subject listing will be presented for all deaths including date and cause of death.

2.8.3 Laboratory data

Not applicable.

2.8.4 Other safety data

2.8.4.1 Corrected Visual Acuity

Snellen visual acuity (VA) testing in each eye will be conducted. The Snellen numerator and denominator will be entered in the eCRF. ETDRS will be derived from the Snellen visual acuity for summary.

Descriptive summaries (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) of change from baseline VA values will be presented at each study visit by treatment group in SAF1 and SAF2, by dosing posology (TID and BID) in ESS1.

2.8.4.2 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole number for summary.

Descriptive summaries (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) of change from baseline IOP values will be presented at each study visit by treatment group in SAF1 and SAF2, by dosing posology (TID and BID) in ESS1.

2.8.4.3 Slit Lamp Exam and Fundus Exam/Ophthalmoscopy

Slit lamp and Fundus exams will be performed, and results will be captured in the source document at each visit. The eCRF will record only if those assessments were indeed performed or not for compliance perspective.

A subject listing will be presented by visit.

2.9 Pharmacokinetic endpoints

Not Applicable.

2.10 PD and PK/PD analyses

Not Applicable.

2.11 Patient-reported outcomes

[redacted]

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.

All observed data will be used for analysis and missing data will not be imputed. And the analysis for Part 1 and Part 2 will be based on FAS 1 and FAS 2, respectively

[redacted]

2.13 Other Exploratory analyses

The analysis of exploratory endpoints for Part 1 and Part 2 will be based on FAS 1 and FAS 2, respectively. Only observed data will be used for analysis and no missing data will be imputed.

2.14 Interim analysis

Two interim analyses are planned for the study. The first interim analysis will be perfromed when after all subjects have completed their participation in Part 1. The data will be analyzed to determine the efficacy and safety of ECF843 vs vehicle and selection of the optimal concentration and posology.

Part 2 will be initiated only if safety and efficacy of ECF843 during Part 1 is demonstrated. The second interim 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. The final analysis will be performed at the end of Part 2.

3 Sample size calculation

3.1 Primary endpoints(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.

3.1.1 SANDE symptom scores

In one previous rhLubricin clinical study (LUB0114MD) there was an observed standard deviation of 20 mm in change from baseline of SANDE score (measured with a visual analog scale (VAS)100mm)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 Table 3-1 for power to detect a significant difference from vehicle under various assumed treatment effect of SANDE Symptom score and standard deviation.

Table 3-1 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%

3.1.2 Composite corneal fluorescein staining score

[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.

3.2 Secondary endpoint(s)

There are no power considerations for secondary endpoints.

4 Change to protocol specified analyses

The following analyses are updated and changed from protocol amendment version 1 dated 20 Apr 2021.

1. Section 2.5.2 Statistical hypothesis, model, and method of analysis: The initial within subject correlation structure used for SANDE symptom score in MMRM is updated from “Unstructured” to “Toeplitz”. This also applies to the supportive analysis for SANDE symptom score stated in 2.5.4 Supportive analyses.

5 Appendix

5.1 Imputation rules of missing dates

5.1.1 AE date imputation

5.1.1.1 Adverse event end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).

2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).

3. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.1.2 Adverse event start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant treatment end date imputation

1. If CM end day is missing and CM month/year are non-missing, then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end month are missing and CM year is non-missing, then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. Only include if ongoing records will have an imputed CM end date. If CM day/month/year is missing, then use the treatment end date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.2.2 Concomitant treatment start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing, or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.2 Statistical models

5.2.1 Primary analysis

The following MMRM model will be used for the primay estimand and supplementary estimand.

change from baseline in SANDE = intercept + baseline SANDE + treatment + day + Sjogren's Syndrome (yes/no) + treatment*day + baseline SANDE * day + error

change from baseline in corneal fluorescein staining score = intercept + baseline corneal fluorescein staining score + treatment + visit + Sjogren's Syndrome (yes/no) + treatment*visit + baseline corneal fluorescein staining score * visit + error

The SAS Proc MIXED will be used to perform the MMRM analyses. The data structure is one record per subject per analysis visit. SAS codes for all statistical methodology described in this section, including the imputation implementation, will be included as programming note in TFL Shells.

The following SAS code can be used to perform the primary analyses:

```
PROC MIXED DATA=<Dataset> order=Internal;
   CLASS USUBJID <Treatment> <Visit> < Sjogren's Syndrome>;
   MODEL <Chg> = <Treatment> <Visit> <Baseline> < Sjogren's Syndrome>
            <Visit>*<Treatment>
            <Visit>*<Baseline>/ DDFM=KENWARDROGER;
   REPEATED <Visit>/TYPE=UN SUBJECT=USUBJID;
   LSMEANS  <Visit>*<Treatment> /DIFF CL ALPHA = 0.05;
   ODS OUTPUT LSMEANS=outLsm DIFFS=Diffs;
RUN;
```

Where

`<Dataset>` = dataset to store SANDE score or corneal fluorescein staining score where the structure is one record per FAS subject per day/visit.

`<Chg>` = change from baseline in SANDE score or corneal fluorescein staining score

`<Treatment>` = randomized treatment assignment

`< Sjogren's Syndrome>` = diagnosis of Sjogren's Syndrome at baseline

`<Visit>` = ordered day or visit

<Baseline> = baseline value for SANDE score or corneal fluorescein staining score

The terms in the brackets are to be adjusted according to the real data set and variable names. If an MMRM model (for corneal fluorescein staining score) with unstructured covariance matrix does not converge, choose the covariance structures in the following order until convergence is reached:

- Toeplitz: change to TYPE = TOEP in the 'Repeated' statement;
- First-order autoregressive: change to TYPE = AR(1) in the 'Repeated' statement;
- Compound symmetry: change to TYPE = CS in the 'Repeated' statement.

If an MMRM model (for SANDE score) with Toeplitz covariance matrix does not converge, choose the covariance structures in the following order until convergence is reached:

- First-order autoregressive: change to TYPE = AR(1) in the 'Repeated' statement;
- Compound symmetry: change to TYPE = CS in the 'Repeated' statement.

P-values from three comparisons requested in Section 2.5.1 will be extracted from <Diffs> and adjusted p-values will be calculated using following code:

```
PROC multtest inpvalues= <rawPvalues> hoc; Run;
```

5.2.2 Supplementary Analysis

The multiple imputation for the Supplementary estimand will be done using the "five macros", which fit a Bayesian Normal RM model and then impute post withdrawal data under a series of possible post-withdrawal profiles including J2R, CIR and CR as described by Carpenter et al (Carpenter et al. 2013).

In "five macro", all intermediate missing values will be imputed assuming MAR and the MNAR part of the model is restricted to patterns that are monotone. That means control-based imputations method is only applicable to monotone missing pattern, therefore we need prepare the data in several tweaks in order to use "five macro".

0. Prepare the data <in_data>: <in_data> stores SANDE score or corneal fluorescein staining score where the structure is one record per FAS subject per **day/visit**
    a. For subjects in treatment arms, if a subject experience IEs stated in Section 2.5.4.1, where J2R method is proposed for imputation. Define a new variable <Method_var> = "J2R" for the subject. Otherwise <Method_var> = "MAR".
    b. For subjects in vehicle arm, <Method_var> = "MAR"
1. Part1A declares the parameter estimation model and checks consistency with the dataset

```
%part1A(Jobname=ECF,Data=<in_data>,Subject=USUBJID,Response=<Chg>,Time=<
Visit>,Treat=<Treatment>,Covbytime=<Baseline>);
```

2. Part1B fits the parameter estimation model using the MCMC procedure and draws a pseudo-independent sample from the joint posterior distribution for the linear predictor parameters and the covariance parameters.

```
%part1B(Jobname=ECF,Ndraws=1000,thin=250,seed=20210301);
```

3. Part2A calculates the predicted mean under MAR, and under MNAR for each subject based on their withdrawal pattern once for each draw of the linear predictor parameter estimates. The choice of MNAR is controlled by the method used, which may vary from subject to subject.

```
%part2A(Jobname=ECF,methodV=<Method_var>,refV=<Ref_var>);
```

<Ref_var> is the variable indicating the reference group for all subjects in the study

4. Part2B imputes the intermediate missing values using MAR and the trailing missing values using MNAR, by deriving the conditional distribution for the missing values conditional on the observed values and covariates, using the appropriate sampled covariance parameter estimates.

```
%part2B(Jobname=ECF,seed=20210302);
```

5. Instead of running Part3 from 'five macros', we will carry out MMRM analysis as stated in Section 5.2.1 per imputation for <Dataset>. It then combines the least-squares means, their differences and p-values using the MIANALYZE procedure to provide final results.

```
PROC MIXED DATA=<Dataset> order=Internal;
   BY _imputation_;
   CLASS USUBJID <Treatment> <Visit> < Sjogren's Syndrome>;
   MODEL <Chg> = <Treatment> <Visit> <Baseline> < Sjogren's Syndrome>
         <Visit>*<Treatment>
         <Visit>*<Baseline>/ DDFM=KENWARDROGER;
   REPEATED <Visit>/TYPE=UN SUBJECT=USUBJID;
   LSMEANS  <Visit>*<Treatment> /DIFF;
   ODS OUTPUT LSMEANS=outLsm DIFFS=Diffs;
RUN;
```

P-values from three comparisons requested in Section 2.5.1 in PROC MIANALYZE will be extracted from <Diffs> and adjusted p-values will be calculated using following code:

```
PROC multtest inpvalues= <rawPvalues> hoc; Run;
```

5.3 Rule of exclusion criteria of analysis sets

The following table provides the definitions of the protocol deviations of the study, together with the exclusion rules.

Table 5-1 Protocol deviations

PD ID	Deviation Text	Data exclusion
INCL01	written informed consent not obtained	Exclude from all analysis sets

PD ID	Deviation Text	Data exclusion
INCL02	Patient < 18 years of age at Screening	Include in all analysis sets
INCL03	patient not able or willing to follow protocol or assessments	Include in all analysis sets
INCL04	< 6 months dry eye diagnosis in both eyes	Include in all analysis sets
INCL05	not use or need AT, gels or lubricants	Include in all analysis sets
INCL06	Tear Break-up Time (TBUT) > 5 seconds in both eyes	Include in all analysis sets
INCL07	Composite corneal fluorescein staining score < 4 (modified NEI scale) in both eyes	Include in all analysis sets
INCL08	In office SANDE global ocular discomfort score < 60mm	Include in all analysis sets
INCL09	Eye Dryness Score < 40mm	Include in all analysis sets
INCL10	Schirmer score 0 or > 10 mm after 5 min both eyes	Include in all analysis sets
INCL11	Sjogrens Syndrome patient lacks confirmed diagnosis	Include in all analysis sets
EXCL01	Ocular infection (bacterial, viral, or fungal) in either eye within 30 days prior to Screening	Include in all analysis sets
EXCL02	Use of artificial tears, gels, lubricants within 4 hrs of conducting assessments at Screening	Include in all analysis sets
EXCL03	contact lens use in either eye within 14 days of Screening, and any use during study	Include in all analysis sets
EXCL04	uncontrolled ocular rosacea, posterior blepharitis, or MGD	Include in all analysis sets
EXCL05	Clinically significant conjunctivochalasis in either eye	Include in all analysis sets
EXCL06	Corneal conditions, dystrophies, scar, pterygia, keratoconus in either eye	Include in all analysis sets
EXCL07	history ocular HSV or infection, GvHD, Stephen's Johnson Syndrome, sarcoidosis	Include in all analysis sets
EXCL08	active or history of ocular allergies during time patient will be in study	Include in all analysis sets
EXCL09	hypersensitivity to ECF843, stains, Xiidra, or other	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
EXCL10	current punctal plugs or punctal cauterization or occlusion	Include in all analysis sets
EXCL11	unstable chronic meds 30 days prior to Screen	Include in all analysis sets
EXCL12	Use of Restasis, Cequa, or Xiidra within 30 days prior to Screening	Include in all analysis sets
EXCL13	Medical device use to treat MGD within 3 months prior to Screen	Include in all analysis sets
EXCL14	Use of ocular, nasal, inhaled, or systemic corticosteroids within 30 days of Screen or during the study	Include in all analysis sets
EXCL15	history of corneal refractive surgery	Include in all analysis sets
EXCL16	any intraocular surgery including cataract surgery within 6 months prior to Screening	Include in all analysis sets
EXCL17	Chronic systemic disease diagnosed within the last 30 days or not stable 30 days prior to Screen	Include in all analysis sets
EXCL18	Use of other investigational drugs within 5 half-lives of enrollment, 30 days, or return to baseline	Include in all analysis sets
EXCL19	History of malignancy of any organ system treated or untreated within 5 yrs	Include in all analysis sets
EXCL20	any systemic or ophthalmic condition that precludes study participation per Investigator opinion	Include in all analysis sets
EXCL21	Pregnant or nursing (lactating) women	Include in all analysis sets
EXCL22	women of child bearing potential unless using basic methods of contraception during study	Include in all analysis sets
WITH01	Subject withdrew consent but continued to receive study medication	Include in all analysis sets
TRT01	randomized subject administered incorrect treatment and/or dose	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
TRT02	Investigational or other study treatment dose adjustments and/or interruptions made	Include in all analysis sets
COMD01	Prohibited concomitant medication and/or procedure as per protocol	Include in all analysis sets
COMD02	Prohibited concomitant medication change as per protocol	Include in all analysis sets
OTH01	Any other protocol deviation with impact on patient rights or safety	Include in all analysis sets
OTH02	Any other protocol deviation with impact on trial's scientific value/data integrity	Include in all analysis sets
OTH03	Any other PD without impact on patient safety/rights or trials's scientific value/data integrity	Include in all analysis sets
OTH04	Subject missed a visit or assessment not allowed in the study	Include in all analysis sets
OTH05	Missed visit due to COVID-19	Include in all analysis sets
OTH06	Visit not done at study site due to COVID-19	Include in all analysis sets
OTH07	Assessment / procedure changed due to COVID-19	Include in all analysis sets
TRT03	Drug supply method changed due to COVID-19	Include in all analysis sets
TRT04	Treatment not given due to COVID-19	Include in all analysis sets
OTH08	Discontinuation due to COVID-19	Include in all analysis sets
OTH09	Unblinding for non-emergent situation	Include in all analysis sets
OTH10	staining strips moistened with anesthetic	Include in all analysis sets
TRT05	patient noncompliance with study drug	Include in all analysis sets
OTH11	SANDE compliance <50%	Include in all analysis sets

5.4 Exclusion of subjects with data issue of conjunctival lissamine staining from analysis

Site [redacted] used a conjunctival lissamine green grading scale different from the Oxford scale in the protocol. The reported scores could not be adjusted or correlated retrospectively.

The impacted subjects [redacted] will be flagged in listings but excluded in the summary for conjunctival lissamine staining.

5.5 Handling of subject with incorrect randomization stratum

If randomization stratum (Sjogren's status) collected from diagnosis in RAVE is different from that in Cenduit IRT, the actual stratum in RAVE will be used for all analyses.

6 Reference

1. Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat; 23(6):1352-71.
2. DIA missing data: https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data
3. Five marcos: https://lshtm.sharepoint.com/:u:/s/MissingDataPublicFiles/EZzccbzMWopLndHoj-gzBNoBzYx-GVYqQSvwDf-lUJhPsQ?e=elHD6Z