Short Title:

Statistical Analysis Plan
EXB107-P001 / NCT02776670

Full Title:

Statistical Analysis Plan
EXB107-P001

Protocol Title:	Clinical evaluation following use of SYSTANE® BALANCE in subjects with lipid-deficient dry eye
Project Number:	EXB107-P001
Protocol TDOC Number:	TDOC-0051783
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Job Notes:	

This is the second amended Statistical Analysis Plan (Version 3.0) for this study. This version of the Statistical Analysis Plan is based on the following: Version 4.0 of the study protocol and Version 1.0 of the UK country specific study protocol.

Executive Summary:

Key Objectives:

This study is designed to evaluate the efficacy and safety of SYSTANE® BALANCE in subjects with lipid-deficient dry eye after 35 days of 4 times daily (QID) treatment.

Decision Criteria for Study Success:

Evidence of efficacy will be deemed established if the lower limit of the 95% 2-sided confidence interval (CI) (equivalent to the 1-sided 97.5% CI) of the adjusted estimate of the difference (SYSTANE BALANCE - REFRESH OPTIVE® Advanced/ OPTIVE® PLUS [UK]) in mean change from baseline in tear film break-up time (TFBUT) (seconds) between SYSTANE BALANCE and REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) at Day 35 (Visit 3) in the analysis eye is above the non-inferiority margin of -1.0 second.

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List of Abbreviations

AE	Adverse Event
AR(1)	Autoregressive
[redacted]	[redacted]
BCVA	Best-Corrected Visual Acuity
CI	Confidence Interval
CS	Compound Symmetry
CSR	Clinical Study Report
DBL	Database Lock
DEP	Deviations and Evaluability Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
GTT	Drop
ICF	Informed Consent Form
[redacted]	[redacted]
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LLT	Lipid Layer Thickness
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MAR	Missing at Random
MCAR	Missing Completely at Random
MMRM	Mixed Model Repeated Measures
OD	Right eye
OS	Left eye
OU	Both eyes
PD	Protocol Deviation
PK	Pharmacokinetics
PLS	Product Lifecycle Services
PPS	Per-Protocol Set
Q1	Lower Quartile
Q3	Upper Quartile
QID	Four times a day
RS	Randomized Set
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCR	Screened Set
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent AE
TFBUT	Tear Film Break-Up Time

Toep	Toeplitz
UN	Unstructured
VAS	Visual Analog Scale
VC	Variance Components
WHO	World Health Organization

1 Study Objectives and Design

This statistical analysis plan (SAP) describes the statistical analysis planned in Section 11 of the study protocol (Clinical Trial Protocol Version 4.0) and the UK country specific study protocol (UK Clinical Trial Protocol Version 1.0) along with any additional analyses, specifications or deviations from the protocol planned before unmasking of the data.

Determination of the sample size is specified in Section 0.

This document is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report (CSR) after the analysis has taken place.

The data will be analyzed by Novartis Product Lifecycle Services (PLS). Any data analysis carried out independently by the investigator should be submitted to Alcon before publication or presentation.

1.1 Study Objectives

The primary objective of the study is:

- To demonstrate that SYSTANE BALANCE is non-inferior to REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) using tear film break-up time (TFBUT) after 35 days of four times a day (QID) dosing in subjects with lipid-deficient dry eye.

The secondary objectives are:

- To demonstrate that SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) using TFBUT after 35 days of QID dosing in subjects with lipid-deficient dry eye.
- To evaluate changes in Global Ocular Discomfort using a visual analog scale (VAS) following use of SYSTANE BALANCE versus REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) after 35 days of QID dosing in subjects with lipid-deficient dry eye.

[redacted]

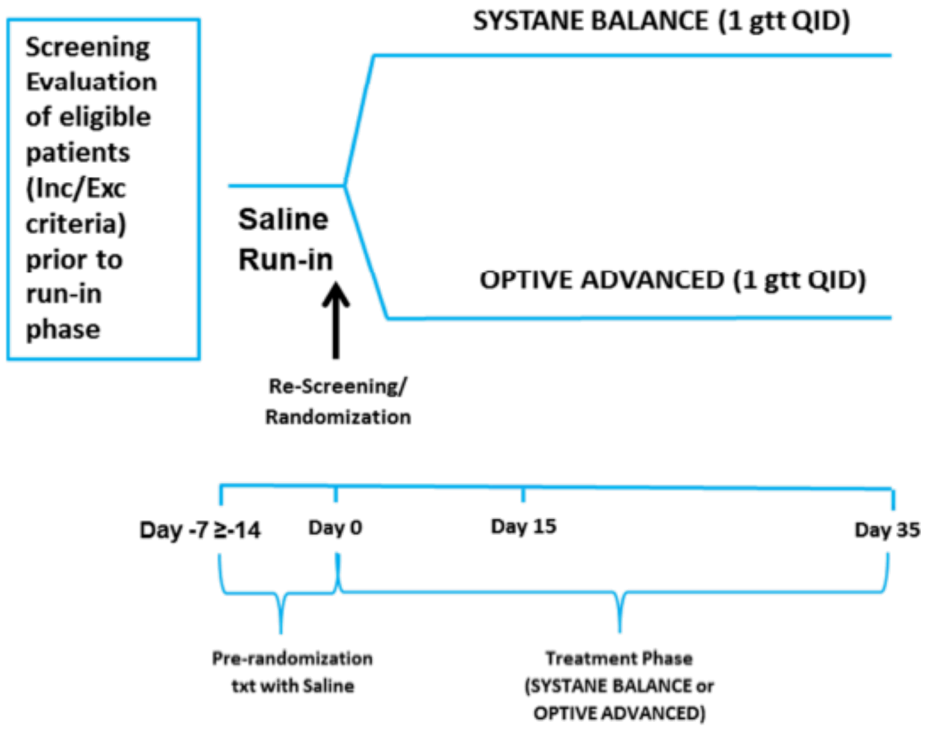
1.2 Study Description

This is a phase IV, multicenter, prospective, double-masked, randomized, parallel-group study. The study will enroll subjects with lipid-deficient dry eye who meet the protocol eligibility criteria. The expected duration of subject participation in the study is approximately 7 weeks (49 days) with 4 planned study visits (including Screening Visit). The main objective is to assess the efficacy and safety of SYSTANE BALANCE in subjects with lipid-deficient dry eye.

The study involves a Saline run-in period (ranging from 7 to 14 days prior to the Baseline Visit/ Visit 1) followed by a 35-day study treatment period (see Figure 1-1). The visits are as follows:

- Screening Visit (Day -14 to Day -7)
- Visit 1 (Day 0/ Baseline)
- Visit 2 (Day 15 ± 3)
- Visit 3 (Day 35/ End of Treatment ± 3)

Figure 1-1 Study design



1.3 Randomization

The randomization scheme will be generated and maintained by the Sponsor's (or designee) unmasked personnel who are not involved in the conduct or analysis of the study. Randomization will be implemented in an Interactive Response Technology (IRT) system. The randomization will be stratified by study site to ensure a balance of study treatment allocations within each investigational site. Randomization will be in a 1:1 ratio.

1.4 Masking

This study has an open-label run-in phase and a double-masked study treatment phase. The investigators, subjects and all Alcon/ Novartis personnel involved with the planning, execution and analysis of the study will be masked with regard to study treatment assignment while the study is in progress. However, there will be at least 1 designated person from each clinical site who will be unmasked. This person will be responsible for dispensing, reclaiming, conducting inventory, and will be available to address any study product irregularities.

Masking will be maintained by providing all study medications in identical packaging and labeling.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Data Analysis General Information

All analyses will be performed using SAS® statistical software (Version 9.4 or a more recent version), unless otherwise noted.

Assessments documented in the database that occur as "bilateral" (i.e. both eyes [OU]) will be summarized and listed for each eye separately. To facilitate derivations and analysis based on eye, database records for bilateral will be split into two records containing identical information as the original record with the exception of the laterality which shall be recoded to "Right" (i.e. right eye [OD]) and "Left" (i.e. left eye [OS]), respectively. It should be noted that dependent on the assessment and at the discretion of the medical team, the assessment may only be counted once.

Data will be summarized with respect to demographic and baseline characteristics, primary, secondary, and [redacted], along with safety observations.

Descriptive statistics (the number of non-missing observations, mean, median, standard deviation [SD], lower quartile [Q1], upper quartile [Q3], minimum and maximum values) will be presented for continuous variables. The following number of decimal places will be used: mean, median, Q1 and Q3 values to 1 more decimal place than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data.

For categorical variables, the number and percentage of each category within a variable will be calculated for non-missing data. If a count of zero is obtained for categorical data, the zero count and percentage will still be displayed. If no treatment satisfies a category, then the category will still be displayed, with the exception of the protocol deviations (PDs) summary. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present for any of the treatment groups. In addition, the corresponding percentage for this row will be displayed.

Change from baseline will only be summarized for subjects with both baseline and post-baseline data for the relevant visit and will be calculated as:

Change from baseline = Post-baseline value – baseline value

Unless otherwise specified, all statistical tests will be two-sided and performed using a 5% significance level, leading to 95% (two-sided) confidence intervals (CIs). If a CI is presented for the proportion of a categorical variable, then the exact Clopper-Pearson method will be used to calculate the 2-sided 95% CI.

All data will be listed by subject and eye, unless stated otherwise.

2.1 General definitions

All analyses will be based on assessments according to the investigator, with the exception of the subject reported outcomes (VAS, [redacted] questionnaire). This study will consist of the following epochs:

- a screening period
- a study treatment period

Study treatment refers to:

- SYSTANE BALANCE
- REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK)

For efficacy analyses, the study eye will be the worst eye at baseline for each parameter. If the baseline values are equivalent, the right eye will be selected. For safety analyses, the study eye will be selected as the eye with the worst change from baseline to any visit (scheduled or unscheduled). If both eyes have the same level of worsening, the right eye will be selected. A subject may have a different study eye for each parameter of interest, henceforth this eye will be referred to as the analysis eye.

2.2 Definition of baseline date

Baseline is referred to as Visit 1 (Day 0) of the study. It is defined as:

- the date of the first administration of study treatment, for treated subjects
- the date of randomization, for subjects who are randomized but not exposed to any study treatment

2.3 Baseline and post-baseline definitions

The baseline value for efficacy and safety variables is the last available, non-missing, scheduled or unscheduled value collected prior to exposure to study treatment. If a subject is

randomized but not treated then the baseline value for a variable is the last available non-missing value collected prior to randomization.

Some baseline assessments may be recorded on the day of the baseline visit (Visit 1). Since the time of the first study treatment at this visit is not recorded in the electronic case report form (eCRF), it is not possible to determine which baseline assessments at the baseline visit (Visit 1) were undertaken before and which after the first study treatment. Hence, only the assessments which, according to the protocol, should have been conducted pre-dose will be assumed to have been done before the first study treatment when deriving baseline values recorded on the day of the baseline visit (Visit 1).

All data collected after Visit 1 (Day 0) are defined as post-baseline.

2.4 Visit windowing

2.4.1 Early exit visits

Visit windowing will be performed for the early exit visit. The study day for this visit will be derived based on the following definition:

Study day = (Date of visit) - (Date of baseline visit) + 1

The study day for the early exit visit will be allocated to the nearest planned visit (see Table 2-1).

Table 2-1 Visit windows

Visit timepoint	Scheduled visit study day	Visit window (study days)
Screening Visit	< -7	-14 to -7
Visit 1 (Day 0/ Baseline)	0	0
Visit 2 (Day 15 ± 3)	15	2 to 24
Visit 3 (Day 35/ End of Treatment ± 3)	35	>=25

If data for the nearest planned visit already exist then the early exit visit will be assigned to the next visit.

2.4.2 Unscheduled visits

All data collected at unscheduled visits will be listed.

Adverse event (AE) and exposure to study treatment data collected at unscheduled visits will be used.

3 Analysis Sets

The **Screened Set (SCR)** will consist of all subjects who signed the informed consent form (ICF).

The **Randomized Set (RS)** will consist of all subjects who were randomized to one of the study treatment arms.

The **Full Analysis Set (FAS)** is used to describe the analysis set which is as complete as possible and as close as possible to the intent-to-treat (ITT) principle of including all randomized subjects. The FAS will include all randomized subjects who have at least 1 post-baseline primary endpoint (TFBUT) assessment.

The **Per Protocol Set (PPS)** will consist of FAS subjects who satisfy all inclusion/ exclusion criteria and who have no major PDs, which will be specified in the Deviations and Evaluability Plan (DEP).

The **Safety Analysis Set** will include all subjects exposed to post-randomization study product.

Evaluability for all subjects will be determined prior to breaking the code for masked study treatment assignment.

The primary and secondary efficacy analyses will be performed on both the FAS and PPS with the PPS providing the primary inference for the non-inferiority hypothesis and the FAS providing the primary inference for the superiority hypotheses.

Supportive analyses of the primary hypothesis will be conducted using the FAS. Similarly, supportive analyses of the secondary hypotheses will be conducted using the PPS.

The number of subjects excluded from the FAS and PPS and a listing of excluded subjects with reason for exclusion will be presented. Any inconsistencies in key study results between the FAS and PPS will be examined and discussed in the CSR.

All efficacy analyses will be according to randomized assignment (regardless of the study treatment they received).

Safety analyses will be conducted using the Safety Analysis Set on a treatment-emergent basis. The main safety analyses will focus on the investigational products (SYSTANE BALANCE, REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK]). For treatment-emergent safety analyses, subjects will be categorized under the actual study treatment received.

Subjects exposed to an incorrect study treatment for the entire study treatment period will be included in the group corresponding to the study treatment received. Subjects exposed to an incorrect study treatment for a portion of the study treatment period will be accounted for under the actual study treatment the subject was first exposed to in the study.

4 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, demographics and baseline characteristics tables (including age, sex, race and ethnicity), prior medications table, medical history table, listing of study treatment assignment by investigator and listing of subjects excluded from key analysis sets. Descriptive summary statistics will be presented by study treatment and overall.

No tests for differences in subject characteristics between study treatment groups will be performed.

4.1 Subject disposition

The number and percentage of subjects (based on the number of randomized subjects) who complete the study will be displayed by study treatment and overall. The primary reason for premature study discontinuation and premature study treatment discontinuation will be displayed by study treatment and overall.

The total number of subjects screened and the number of subjects screened but not randomized will be shown. The reasons for screening failure will be summarized.

The number of subjects within each of the analysis sets used in the study will be given. The reasons for exclusion from each set will be listed.

4.2 Background and demographic characteristics

Demographics, baseline characteristics and key efficacy variables at baseline will be summarized for the RS, FAS, PPS and Safety Analysis Set by study treatment and overall. These tables will also be repeated for the RS for the following subgroups: age, sex and region (see Section 5.3.2 for details on the subgroup categories).

The number and percentage of subjects will be presented for the following categorical variables:

- age (years) (<65, ≥65)
- sex (Female, Male, Unknown, Undifferentiated)

- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- region (Asia, United Kingdom, United States)
- baseline TFBUT (seconds) (<2, 2-4, >4) (for analysis eye only)
- baseline slit-lamp examination parameters (for analysis eye only)
    - Aqueous flare (None, Faint, Moderate, Marked, Intense)
    - Aqueous cells (< 1, 1-5, 6-15, 16-25, 26-50, >50)
    - Lens (Phakic, Pseudophakic, Aphakic)
    - Status of Lens (No Opacity, Any Opacity, Worsening of Opacity, Not Evaluable)
- baseline horizontal length (Grade 0, Grade 1, Grade 2, Grade 3) (for analysis eye only)
- baseline sagittal height (Grade 0, Grade 1, Grade 2, Grade 3) (for analysis eye only)
- [redacted]

Descriptive statistics will be presented for the following continuous variables:

- age (years)
- baseline TFBUT (seconds) (for analysis eye only)
- baseline Global Ocular Discomfort VAS score
- [redacted]
- [redacted]
- baseline BCVA (for analysis eye only)

All demographic and baseline data will be listed by treatment, center, subject and eye (where applicable) for the RS.

4.3 Medical history

Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by system organ class (SOC) and preferred term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 19.0 or a more recent version) for the

RS. The SOCs will be presented in alphabetical order. PTs will be ordered for each study treatment in decreasing proportion in the SYSTANE BALANCE study treatment group of interest (study treatment group 1).

Separate tables will be provided by study treatment for subjects with ocular and non-ocular histories and conditions. Presentation of subjects with ocular histories will be overall, i.e. event occurring in one eye or both eyes will be counted once. The presentation of the data in the tables will be based on subject rather than event counts.

Furthermore, medical history data will be listed by treatment, center, subject and eye (where applicable) for the RS.

4.4 Prior and concomitant medications

The number and percentage of subjects taking concomitant medications will be summarized for subjects in the Safety Analysis Set.

Summaries will be presented separately for prior and/ or concomitant medications.

- Prior medications will be defined as drugs taken and stopped prior to baseline.
- Any medication given at least once between baseline and the last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the study treatment period.

Prior or concomitant medication will be identified based on recorded or imputed start dates of medication taking. The rules for imputing incomplete start dates are described in Section 12.2.2.

Medications will be identified by PT according to the World Health Organization (WHO) Drug Reference List dictionary (201603 or a more recent version).

Separate tables will be provided by study treatment for subjects with ocular and non-ocular prior and concomitant medications. Presentation of subjects with ocular prior and concomitant medications will be overall, i.e. medication administered in one eye or both eyes will be counted once. The presentation of the data in the tables will be based on subject rather than event counts. Tables will show the overall number and percentage of subjects within each study treatment group receiving at least one dose of the therapy.

Furthermore, prior and concomitant data will be listed by treatment, center, subject and eye (where applicable) for the RS.

5 Efficacy Analysis Strategy

5.1 Efficacy Endpoints

Primary Endpoint

- Change from baseline in TFBUT (seconds) at Day 35 (Visit 3) (non-inferiority)
    - TFBUT is the mean of the available measurements (maximum of 3 readings, minimum of 1 reading) for the analysis eye

Secondary Endpoints

- Change from baseline in TFBUT (seconds) at Day 35 (Visit 3) (superiority)
- Change from baseline in Global Ocular Discomfort VAS score at Day 35 (Visit 3) (superiority)
    - The overall score is a composite of the 2 scores (frequency and severity of ocular discomfort) using the following equation:

$$VAS\ Global\ Discomfort\ Scale = \sqrt{VAS\ Frequency\ Score\ \times VAS\ Severity\ Score}$$

5.2 Efficacy Hypotheses

The primary efficacy hypothesis to be tested is that SYSTANE BALANCE is non-inferior to REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) with respect to the change from baseline in TFBUT at Day 35 (Visit 3). The null and alternative hypotheses are:

H_0: $\mu_{SB} - \mu_{OA} \leq -1$

H_1: $\mu_{SB} - \mu_{OA} > -1$

where μ_{SB} and μ_{OA} denote the mean change from baseline in TFBUT at Day 35 (Visit 3) in the analysis eye for SYSTANE BALANCE and REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK), respectively.

The secondary efficacy hypotheses to be tested are that:

- SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) with respect to the change from baseline in TFBUT at Day 35 (Visit 3)
    - The null and alternative hypotheses are:

      H_0: $\mu_{SB} - \mu_{OA} \leq 0$

      H_1: $\mu_{SB} - \mu_{OA} > 0$

      where μ_{SB} and μ_{OA} denote the mean change from baseline in TFBUT at Day 35 (Visit 3) in the analysis eye for SYSTANE BALANCE and REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK), respectively.

- SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) with respect to the change from baseline in Global Ocular Discomfort VAS score at Day 35 (Visit 3)
    - The null and alternative hypotheses are:

      H_0: $\mu_{SB} - \mu_{OA} \leq 0$

      H_1: $\mu_{SB} - \mu_{OA} > 0$

      where μ_{SB} and μ_{OA} denote the mean change from baseline in Global Ocular Discomfort VAS score at Day 35 (Visit 3) in the analysis eye for SYSTANE BALANCE and REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK), respectively.

5.3 Statistical Methods for Efficacy Analyses

The analysis of the primary efficacy parameter, change from baseline in TFBUT at Day 35 (Visit 3) in the analysis eye will be based on a mixed model repeated measures (MMRM) analysis. MMRM is robust to data that are missing completely at random (MCAR) or missing at random (MAR).

The mixed model will include terms for baseline TFBUT (continuous), study treatment (SYSTANE BALANCE, REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK]), visit (Day 15 [Visit 2], Day 35 [Visit 3]), and study treatment-by-visit interaction. For each subject, the error terms from all the visits represent the within-subject variability, and are assumed to follow a multivariate normal distribution with an unstructured covariance matrix. If the model first fails to converge using an unstructured (co)variance structure, then a hierarchical approach will be applied until a (co)variance structure is obtained where the model converges. Therefore the following (co)variance structures will be tested according to the pre-specified order: (1) unstructured (UN), (2) toeplitz (Toep), (3) autoregressive [AR(1)], (4) variance components (VC), (5) compound symmetry (CS). As soon as one model converges this will be the final model used, therefore no further testing of subsequent (co)variance structures will be required.

Within-group estimates of the mean change from baseline and the associated 95% CI in the analysis eye will be presented. Within-study treatment and estimates of the difference (SYSTANE BALANCE - REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK]) in mean change from baseline in TFBUT between SYSTANE BALANCE and REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) and the associated 95% CI in the analysis eye will also be presented.

The assumptions of the above MMRM model will be evaluated using the Anderson-Darling Test and Normal-Probability plots. Homogeneity of variance between/ among study treatment groups will be evaluated visually. If the assumptions for MMRM are not met, further exploratory analyses will be performed, as necessary. If either assumption is clearly not met, then a non-parametric analysis will be performed for the analysis eye (e.g. an analysis of covariance [ANCOVA] model for change from baseline in TFBUT at Day 35 [Visit 3] with the terms baseline TFBUT and study treatment, but using ranked response and covariate variables).

Evidence of efficacy (non-inferiority) will be deemed established if the lower limit of the 95% CI (equivalent to the 1-sided 97.5% CI) for the adjusted estimate of the difference (SYSTANE BALANCE - REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK]) is above -1.0 second (non-inferiority margin). The non-inferiority margin was chosen as 1.0 second on the basis that an increase of at least 25% in the baseline TFBUT of a subject with lipid-deficient dry eye would be considered clinically meaningful since the subject would blink less often.

The analysis set for the primary efficacy assessment will be the PPS. As a sensitivity analysis, the analysis will be repeated for the FAS using the same model.

Observed values and change from baseline values for the analysis eye for the PPS and FAS will also be presented descriptively (N, mean, median, SD, standard error [SE], minimum, and maximum) at each study visit for each study treatment. A plot of mean change in TFBUT by study visit and study treatment with error bars representing +/ - 1 SE will be presented using the analysis eye. The x-axis will be study visit and the y-axis will be the change in TFBUT from baseline.

Observed values from all visits for the RS will also be listed along with the following variables: treatment, investigator, subject, age, sex, race, ethnicity, visit, eye, baseline value, and value at the visit.

The analysis of the secondary efficacy parameters will also be based on a MMRM model. The mixed model will include terms for the respective baseline parameter value (continuous), study treatment (SYSTANE BALANCE, REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK]), visit (Day 15 [Visit 2], Day 35 [Visit 3]), and study treatment-by-visit interaction. The same procedure as outlined for the primary efficacy analysis in selecting the best fitting covariance structure will be applied. Estimates of the difference in mean change from baseline between SYSTANE BALANCE and REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK) and the associated 95% CIs in the analysis eye will be presented.

Each secondary endpoint will be evaluated for superiority of SYSTANE BALANCE over REFRESH OPTIVE Advanced/ OPTIVE PLUS (UK).

The analysis set for the secondary efficacy assessments will be the FAS. As a sensitivity analysis, the analysis will be repeated for the PPS using the same model.

Descriptive statistics and listings of the secondary efficacy parameters will also be provided. The same approach as outlined for the primary efficacy parameter will be applied.

Table 5–1 Summary of analysis strategy for primary and secondary efficacy endpoints

Endpoint	Main vs. Sensitivity Approach[a]	Test	Statistical Method[b]	Analysis Set	Missing Data Approach
Primary					
Change from baseline in TFBUT at Day 35 (Visit 3)	M	Non-inferiority	Linear mixed model[c]	PPS	Likelihood-based
Change from baseline in TFBUT at Day 35 (Visit 3)	S	Non-inferiority	Linear mixed model[c]	FAS	Likelihood-based
Secondary					
Change from baseline in TFBUT at Day 35 (Visit 3)	M	Superiority	Linear mixed model[c]	FAS	Likelihood-based
Change from baseline in TFBUT at Day 35 (Visit 3)	S	Superiority	Linear mixed model[c]	PPS	Likelihood-based
Change from baseline in Global Ocular Discomfort VAS score at Day 35 (Visit 3)	M	Superiority	Linear mixed model[c]	FAS	Likelihood-based
Change from baseline in Global Ocular Discomfort VAS score at Day 35 (Visit 3)	S	Superiority	Linear mixed model[c]	PPS	Likelihood-based
[a]M=Main analysis approach; S=Sensitivity analysis approach					

Endpoint	Main vs. Sensitivity Approach[a]	Test	Statistical Method[b]	Analysis Set	Missing Data Approach
[b]Further details on statistical models are: [c]Linear mixed model with terms for baseline of the relevant endpoint, study treatment, visit and study treatment-by-visit interaction.					

[redacted] The mixed model will include terms for the respective baseline parameter value (continuous) and study treatment (SYSTANE BALANCE, REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK]). Estimates of the difference in mean change from baseline between SYSTANE BALANCE and REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK] and the associated 95% CIs in the analysis eye will be presented. [redacted]

[redacted]

The same approach as outlined for the primary and secondary efficacy parameters will be applied.

5.3.1 Multiplicity Strategy

To ensure overall control of the type I error rate, following the rejection of the primary efficacy null hypothesis (if the lower limit of the 95% CI [equivalent to the 1-sided 97.5% CI] for the difference of the primary efficacy endpoint is above -1.0 second), the secondary hypotheses will be tested using the Hochberg testing procedure.

For the secondary efficacy endpoints, let:

- H_{0i} refers to the corresponding null hypotheses
- p_i refers to the p-values for H_{0i} , which will be calculated without any multiplicity adjustment where i = 1, …, k such that [1], . . . , [k] refer to the order from $p_{[1]} \leq ... \leq p_{[k]}$.
- Hochberg's step-up method will proceed as follows:
    - Step 1: If $p_{[k]} < \alpha$ (where α is 0.025, 1-sided), reject all H_{0i} (where i = 1, …, k), and stop; otherwise go to Step 2.
    - Step 2: If $p_{[k-1]} < \alpha/2$ (where α is 0.025, 1-sided), reject $H_{0[i]}$, i = 1, …, k - 1, and stop; otherwise go to Step 3.

- …
- Step k: If $p_{[1]} < \alpha/k$ (where α is 0.025, 1-sided), reject $H_{0[i]}$, i = 1, and stop.

Both the adjusted and unadjusted p-values for the secondary efficacy endpoints will be presented.

[redacted]

5.3.2 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of the primary endpoint will be conducted to assess the consistency of study treatment effect across various subgroups in the analysis eye. The consistency of the study treatment effect on the primary endpoint will be assessed by replicating the primary efficacy analysis model for each category of the subgroup factor. The study treatment effects and nominal 95% CIs in the analysis eye by category of the following subgroups will be reported in tabular format:

- age category (<65, ≥65 years)
- region (Asia, United Kingdom, United States)
- sex (Male, Female)

In the event of sparsely populated subgroup categories, homogeneous categories may be pooled. The analysis set for the subgroup analyses of the primary endpoint will be the PPS.

5.3.3 Interim Analysis for Efficacy

Not applicable.

6 Safety Analysis Strategy

6.1 Safety Endpoints

The safety endpoints are:

- Extent of exposure
- AEs
- Best Corrected Visual acuity (BCVA)
- Biomicroscopy Findings/ Slit Lamp Examinations (cornea, lens, iris and anterior chamber)

- Quality Complaints

6.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of safety endpoints listed in Section 6.1.

6.3 Statistical Methods for Safety Analyses

Except otherwise stated, the analysis set for all safety analyses is the Safety Analysis Set as defined in Section 3. Baseline is defined in Section 2.3.

6.3.1 Extent of Exposure

Extent of exposure to study treatment is calculated as duration of exposure to study treatment. Duration of exposure to study treatment is defined as the last day of exposure to study treatment minus the first day of exposure to study treatment, plus 1. In the event that the last day of exposure is unknown, the date of last contact with subject will be used instead. Extent of exposure will be summarized as a continuous measure (N, mean, median, SD, minimum and maximum) and by counts and percentages of subjects in the following categories by study treatment: 1-11 days, 12-38 days, >38 days.

Extent of exposure will be presented overall and by demographic subgroups of interest (refer to Section 5.3.2 for details). The reporting level will be by subject (not eye).

6.3.2 Adverse Events

The applicable definition of an AE is in the study protocol. All AEs occurring from when a subject signs the ICF to when a subject exits the study will be accounted for in the reporting. Analysis and presentation of AEs occurring during the 2 week saline run-in period (the screening period) will be separated from those occurring during the investigational period where a comparative evaluation (descriptive only) of treatment-emergent AEs (TEAEs) is intended. A TEAE is an event not present prior to exposure to investigational product (SYSTANE BALANCE, REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK]) or any pre-existing event that worsens following exposure to investigational product. The period for TEAE analysis starts from exposure to the investigational product to 1 day following cessation of investigational product (it is not expected for the side effects of the investigational product to last more than 24 hours).

Descriptive summaries (subject counts and percentages, event counts) by study treatment for specific AEs will be presented by primary SOC and PT. The SOCs will be presented in

alphabetical order. PTs will be ordered for each study treatment in decreasing proportion in the SYSTANE BALANCE treatment group of interest (study treatment group 1). In addition to an overall presentation of all AEs, reports will be generated for special classes of AEs such as most frequent AEs, ocular AEs, non-ocular AEs, treatment-related AEs, serious AEs (SAEs), AEs by maximum severity (mild, moderate, severe), and AEs resulting in study treatment discontinuation. The overall presentation of all AEs will also be presented by demographic subgroups of interest (refer to Section 5.3.2 for details).

Both subject and event counts will be presented for AEs. Subject counts refer to the number of subjects with the respective AE of interest. Subjects who experience multiple AEs for a PT will be counted once, similarly for subjects with multiple AEs per SOC, for subject counts. Event counts refer to the number of occurrences of the respective AE of interest, regardless of whether a subject already had this event. However for ocular AEs, if an AE was classified as occurring in both eyes, dependent on the event and at the discretion of the medical team the event may only be counted once.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on TEAEs which are not SAEs with an incidence greater than 1% and on treatment emergent SAEs and SAE suspected to be related to study treatment will be provided by SOC and PT.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

These reports will be supported by individual subject's listings, as necessary.

Individual subject's listings will be provided for the Screened Set. This listing will contain: AEs that occur after signing the informed consent but prior to exposure to investigational product, TEAEs and post-treatment AEs (if available).

6.3.3 Best Corrected Visual Acuity (BCVA)

Visual acuity assessment will be conducted at the following visits: Day -14 to -7 (Screening), Day 0 (Visit 1), Day 15 (Visit 2), Day 35 (Visit 3) and Early Exit.

The analysis eye will be selected as the eye with the greatest decrease in the number of letters read from baseline to any visit (scheduled or unscheduled). If both eyes have the same level of decrease, the right eye will be selected. Analysis of BCVA will use the data from the analysis eye.

Observed values and change from baseline values for the analysis eye will be presented descriptively (N, mean, median, SD, SE, minimum, and maximum) at each study visit for each study treatment. A plot of mean change in BCVA by study visit and by study treatment with error bars representing +/ - 1 SE will be presented using the analysis eye. The x-axis will be study visit and the y-axis will be the change in BCVA from baseline.

Counts and percentages of subjects who experience pre-specified category of worst change from baseline across all post-baseline assessments and category of change from baseline to last on-treatment BCVA assessment will be presented according to the following categories: ≤4 letter decrease or improvement, 5-9 letter decrease, 10-14 letter decrease, ≥15 letter decrease. For change to any visit, a subject will be counted only in the category that represents their worst change from baseline across all post-baseline assessments.

A listing will be provided which presents all subjects with a ≥10 letter decrease in BCVA from baseline to any visit. The listing will include the following variables: treatment, investigator, subject, age, sex, race, ethnicity, visit, eye, baseline value, value at the visit and a change from baseline value.

All analyses will also be performed by age and by sex.

6.3.4 Biomicroscopy Findings/ Slit Lamp Examination

A slit-lamp examination will be performed at the following visits: Day -14 to -7 (Screening), Day 0 (Visit 1), Day 15 (Visit 2), Day 35 (Visit 3) and Early Exit to evaluate the cornea, lens, iris and anterior chamber. Assessments related to the conjunctiva (bulbar, palpebral and limbal conjunctiva), cornea, iris and lids/ lashes will only be entered in the EDC system if clinically significant abnormalities are noted in a subject's medical history or as an AE, if applicable. Ocular signs (aqueous flare, aqueous cells, lens and status of lens) will be captured according to the following grading criteria:

- aqueous flare (None, Faint, Moderate, Marked, Intense)
- aqueous cells (< 1, 1-5, 6-15, 16-25, 26-50, >50)
- lens (Phakic, Pseudophakic, Aphakic)
- status of Lens (No Opacity, Any Opacity, Worsening of Opacity, Not Evaluable)

The analysis eye will be selected as the eye showing the greatest increase in slit-lamp grade from baseline to any visit (scheduled or unscheduled). If both eyes have the same amount of increase, the right eye will be selected. Note that the worst eye will be chosen at the parameter level; therefore it is possible that a given subject may not have the same worst eye for all parameters. Analysis of ocular signs will use the data from the analysis eye.

For each parameter, a shift table showing slit-lamp grade at baseline relative to each post- baseline visit will be presented for the analysis eye by study treatment. For each slit-lamp parameter, counts and percentages of subjects (based on the analysis eye) who experience increase from baseline to any subsequent visit will be presented.

All analyses will also be performed by age and by sex.

A listing will be provided which presents all subjects with an increase in any slit-lamp parameter at any visit compared to the grade of the same eye at baseline. The listing will include all slit-lamp data from all visits with the following variables: treatment, investigator, subject, age, sex, race, ethnicity, visit, eye, parameter, baseline value, and value at the visit.

6.3.5 Quality Complaints

The applicable definition of a device deficiency is in the study protocol. A frequency table showing counts for each Device Deficiency category will be presented.

In addition, a listing of all device deficiencies, as recorded on the Device Deficiency Form will be provided.

6.4 Interim Analysis for Safety

Not applicable.

7 Pharmacokinetic Analysis Strategy

Not applicable.

8 Analysis Strategy for Other Endpoints

Observed lipid layer thickness (LLT) values from all visits will be listed for the RS.

9 Sample Size and Power Calculations

This study will include approximately 220 randomized subjects in a 1:1 ratio of SYSTANE BALANCE to REFRESH OPTIVE Advanced/ OPTIVE PLUS [UK] to achieve 200 evaluable subjects. A total of 200 subjects will provide approximately 80% power to reject the null hypothesis of inferiority of mean change from baseline in TFBUT in the analysis eye at the 0.025 level of significance (1-sided), assuming a study treatment difference of 0.0, a SD of 2.5, and a non-inferiority margin of 1.0 seconds (NQuery, version 7.0).

Table 9-1 Sample size required to achieve 80% and 90% power with different assumed values of SD

Power	Assumed SD	Sample size (total evaluable)
80%	2.5	200
	2.75	240
	3.0	286
90%	2.5	266
	2.75	320
	3.0	382

10 References

Not applicable.

11 Revision History

The reason for the first amended (Version 2.0) Statistical Analysis Plan was to reflect Version 4.0 of the study protocol and Version 1.0 of the UK country specific study protocol and to add clarity to some of the study endpoints.

The reason for the second amended (Version 3.0) Statistical Analysis Plan is to reflect the change to protocol specified analyses (outlined in Section 11.1).

The current version of the Statistical Analysis Plan is based on the following: Version 4.0 of the study protocol and Version 1.0 of the UK country specific study protocol.

11.1 Change to protocol specified analyses

LLT will only be listed in this study. In the protocol, it was originally planned to analyze LLT as part of the secondary [redacted] endpoints. However the device used to measure LLT was unable to provide a credible LLT value if the LLT value was greater than 100 nm.

Therefore as this impacted at least 25% of the LLT values, it was agreed by the clinical trial team with input from upper management to only list the LLT data.

At the time of the second amended Statistical Analysis Plan, subject follow-up is complete and all subjects have exited the study. The study database is not yet locked and masked treatment code has not been broken. Due to the fact that subject follow-up is complete and the current change to analysis strategy is an operational matter with no impact on study design or subject safety, the decision was taken only to amend the Statistical Analysis Plan and not undertake a corresponding amendment to the protocol.

12 Appendix

12.1 SAS code

12.1.1 Mixed model repeated measures

This SAS code will be used for the MMRM analysis for the primary and relevant secondary endpoints.

```
proc mixed data=<analysis dataset>;
class usubjid treatment visit;
model <endpoint of interest>=<baseline of endpoint of interest> treatment
visit treatment*visit/solution ddfm=kr;
repeated visit / subject=usubjid type=un;
lsmeans treatment*visit / pdiff=all cl alpha=0.05 slice=visit;
run;
```

12.2 Imputation rules

12.2.1 AE date imputation

12.2.1.1 AE end date

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (study 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 (study 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.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

12.2.1.2 AE start date

AEs with completely missing onset dates will be considered to be treatment emergent. AEs with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of first administration of study treatment.

Partial AE start dates are imputed with reference to the first administration of study treatment (TRTSTD) as outlined in the table below.

The date value is split into day, month and year sections and referenced in the imputation table as outlined below:

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Study Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	NC	NC	NC	NC
YYYY<TRTM	(D) = 01JULYYYY Before Study Treatment Start	(C) = 15MONYYYY Before Study Treatment Start	(C) = 15MONYYYY Before Study Treatment Start	(C) = 15MONYYYY Before Study Treatment Start
YYYY=TRTY	(B) = TRTSTD+1 Uncertain	(C) = 15MONYYYY Before Study Treatment Start	(A) = TRTSTD+1 Uncertain	(A) = 01MONYYYY After Study Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Study Treatment Start	(A) = 01MONYYYY After Study Treatment Start	(A) = 01MONYYYY After Study Treatment Start	(A) = 01MONYYYY After Study Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Study Treatment start	Partial date indicates AE start date prior to Study Treatment Start Date
After Study Treatment start	Partial date indicates AE start date after Study Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of AE start date to Study Treatment Start Date
Imputation calculation	
NC / Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B) Uncertain	TRTSTD+1
(C) Before Study Treatment Start	15MONYYYY
(D) Before Study Treatment Start	01JULYYYY
(E) After Study Treatment Start	01JANYYYY

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

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

To 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 study treatment start date year value, the AE started before study 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 study treatment start date year value, the AE started after study 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 study 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 study 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 study treatment start date month or greater than the study 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.

12.2.2 Concomitant medication date imputation

12.2.2.1 Concomitant medication end date

To impute concomitant end date:

1. If the concomitant end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the concomitant end year value is missing or ongoing, the imputed concomitant end date is set to NULL.
2. Else, if the concomitant end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow up period date, 31DECYYYY, date of death).
3. If the concomitant end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow up period date, last day of the month, date of death).

If the imputed concomitant end date is less than the existing concomitant start date, use the concomitant start date as the imputed concomitant end date.

12.2.2.2 Concomitant medication start date

Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the first administration of study treatment (TRTSTD) in accordance with the rules outlined below.

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Study Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY<TRTM	(D) = 01JULYYYY Before Study Treatment Start	(A) = 15MONYYYY Before Study Treatment Start	(A) = 15MONYYYY Before Study Treatment Start	(A) = 15MONYYYY Before Study Treatment Start
YYYY=TRTY	(C) Uncertain	(A) = 15MONYYYY Before Study Treatment Start	(C) Uncertain	(B) = 01MONYYYY After Study Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Study Treatment Start	(B) = 01MONYYYY After Study Treatment Start	(B) = 01MONYYYY After Study Treatment Start	(B) = 01MONYYYY After Study Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Study Treatment start	Partial date indicates CMD start date prior to Study Treatment Start Date
After Study Treatment start	Partial date indicates CMD start date after Study Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of CMD start date to Study Treatment Start Date
Imputation calculation	
NC / Blank Uncertain	No convention
(A) Before Study Treatment Start	15MONYYYY
(B) After Study Treatment Start	MAX(01MONYYYY, TRTSTD+1)
(C) Uncertain	IF CMDTYP1C IN (1, 3) THEN TRTSTD-1 ELSE IF CMDTYP1C IN (. 2) THEN TRTSTD+1
(D) Before Study Treatment Start	01JULYYYY
(E) After Study Treatment Start	01JANYYYY

To compute concomitant start date:

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

c. Else if the concomitant month is greater than the treatment start date month, the imputed concomitant start date is set to the month start point (01MONYYYY).

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

12.2.3 Other imputations

The age of subjects with a completely missing date of birth will be set to missing. If a subject's date of birth is partially missing then:

- If the year is missing then the age will be set to missing
- Else if the month is missing then the day will be set to 01 and the month will be set to July
- Else if the day is missing then the day will be set to 15.

If a subject has a partially missing date of birth and an imputed age of 17 years then this will be set at 18 years. However, if the imputed age were 16 years then the imputed age will remain at 16 years.

Missing baseline data of a primary/ key secondary variable may be imputed for use as a sensitivity analysis.

Other missing baseline data will not be imputed. This includes variables which are not allowed to be collected according to local regulations (e.g. race in France).

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
07/19/2018 12:55:29	[redacted]	[redacted]
07/19/2018 14:21:48	[redacted]	[redacted]