a Novartis company

Short Title

Clinical outcomes Following Treatment with SYSTANE® BALANCE

Long Title

Clinical Evaluation Following Use of SYSTANE® BALANCE in Subjects with Lipid-Deficient Dry Eye

Protocol Number:	EXB107-P001 / NCT02776670
Study Phase:	Phase 4
Sponsor Name and Address:	Alcon Research Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	SYSTANE® BALANCE Lubricant Eye Drops
Indication Studied:	Dry Eye
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described study in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Sponsor.

Principal Investigator:

Signature Date

Name:

Address:

1 SYNOPSIS

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	**Protocol Number: EXB107-P001**
Test Product:	SYSTANE® BALANCE Lubricant Eye Drops, FID 114657	**Study Phase:** ☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ N/A

Active Ingredient: Propylene glycol (PG), 0.6%

Protocol Title: Clinical evaluation following use of SYSTANE® BALANCE in subjects with lipid-deficient dry eye

Investigator(s)/ No. of Sites: Multicenter, approximately 10 sites

Center Location(s)/ United States and Asia Pacific region

No. of Subjects Approximately 242 subjects screened, 220 subjects randomized, 200 subjects evaluable

Duration of Treatment: 7-14 day Saline run-in period, followed by a 35 day active treatment period

Study Population: Adult subjects (≥ 18 years) with dry eye symptoms

Objectives:

Primary Objective

- To demonstrate that SYSTANE BALANCE is noninferior to REFRESH OPTIVE® Advanced using tear film break-up time (TFBUT) after 35 days of 4 times daily (QID) dosing in subjects with lipid-deficient dry eye.

Secondary Objectives

- To demonstrate that SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced using TFBUT after 35 days of QID dosing in subjects with lipid-deficient dry eye.
- To evaluate changes in lipid layer thickness (LLT) AUC_{120} following the use of SYSTANE BALANCE versus REFRESH OPTIVE Advanced 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 after 35 days of QID dosing in subjects with lipid-deficient dry eye.

[redacted]

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[redacted]

Methodology: This is a multicenter, prospective, double-masked, randomized, parallel-group study assessing 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 treatment period. Subjects will be randomized 1:1 into 1 of 2 treatment arms post run-in period.

Treatments:

Run-in Product:	Preservative-free Saline
Route of Administration:	Topical ocular
Duration of Treatment:	7-14 days
Dosage:	1 drop QID in each eye
Test Product:	SYSTANE BALANCE Lubricant Eye Drops
Route of Administration:	Topical ocular
Duration of Treatment:	35 days
Dosage:	1 drop QID in each eye
Control Product:	REFRESH OPTIVE Advanced Lubricant Eye Drops
Route of Administration:	Topical ocular
Duration of Treatment:	35 days
Dosage:	1 drop QID in each eye

Subject Selection: **Inclusion Criteria:**

1. Must be willing and able to attend all study visits
2. Must be 18 years of age or older at the time of informed

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consent [patients in Singapore must be 21 years of age or older and patients in Taiwan must be 20 years of age or older due to local regulations].

3. Must have both of the following in at least one eye at the Screening Visit and Visit 1 (Day 0):
    - The sum of 3 measures of TFBUT ≤ 15 seconds, and
    - Unanesthetized Schirmer I test of ≥ 3 mm to ≤ 12 mm
4. Must have best-corrected visual acuity (BCVA) of 55 letters or better in each eye as assessed using an early treatment diabetic retinopathy study (ETDRS) or Tumbling E chart
5. Must be willing to take the study products as directed for the entire study

Exclusion Criteria:

1. Use of any topical ocular medication preserved with benzalkonium chloride (BAK) or other products known to be toxic to the tear film lipid layer within 3 months prior to the Screening Visit
2. Lid hygiene therapy initiated ≤ 4 weeks prior to the Screening Visit.

    Note: Subjects who have been on a consistent lid hygiene therapy (ie, no change to the type of lid hygiene therapy being used or to the frequency of use) for more than 4 weeks prior to the Screening Visit are not excluded. However, they cannot stop or change this regimen for the duration of the study. In addition, subjects who do not currently use lid hygiene therapy cannot start for the duration of the study.
3. Women of childbearing potential (those who are not surgically sterilized or postmenopausal for at least 2 years) **are excluded** from participating in the study if they meet **any** of the following conditions:
    a. They are currently pregnant, or plan to become pregnant while participating in the study, or
    b. They have a positive result on a pregnancy test at the Screening Visit, or
    c. They are breast feeding
    d. Are not in agreement to use adequate birth control methods throughout the study

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4. Hypersensitivity to the use of any of the study products or allergy to any ingredient in the study products
5. Ocular abnormalities that could adversely affect the safety or efficacy outcome such as:
    - Eyelid anomalies that affect proper lid closure or proper blink function (eg, ectropion or entropion)
    - Corneal disorders or abnormality such as active corneal ulcer, current corneal abrasion, keratoconus or corneal dystrophies which are actively changing or affect vision
    - Metaplasia of the ocular surface
    - History of corneal erosion syndrome or recurrent corneal erosion syndrome
    - Clinically significant corneal epithelial anterior membrane dystrophy (subjects with minor/insignificant primary peripheral corneal epithelial dystrophy (not central dystrophy) without a history of corneal erosion syndrome can be included)
    - Current filamentous keratitis
    - Evidence of corneal neovascularization
    - Any history of herpes simplex or herpes zoster keratitis
6. Uncontrolled active systemic diseases. These conditions may include but are not limited to unstable diabetes, thyroid diseases, autoimmune diseases, and/or poorly controlled hypertension.
7. Active ocular infection (bacterial, viral, or fungal) or active inflammation not associated with dry eye such as uveitis, iritis, active blepharitis, active allergic conjunctivitis, etc.
8. Clinically significant congestive heart failure, renal failure, hepatic dysfunction, previous cardiovascular accident (CVA) with a significant residual motor or sensory defect, progressive neurologic disorders (eg, Parkinsonism, dementias, Multiple Sclerosis, unstable acquired seizure disorders, etc.)
9. Current or past participation in any clinical study within 30 days prior to the Screening Visit
10. Punctal plug insertion or diathermy procedure initiated within 30 days prior to the Screening Visit
11. Significant illnesses that could, in the opinion of the Investigator, interfere with the study parameters

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12. Use of any systemic medication known to cause dry eye (eg, anti-histamines, anti-depressants, anti-psychotics, etc.) for less than 1 month. The dosing regimen should not change during the study.
13. Contact lens use within 30 days prior to Screening Visit, or unwilling to avoid contact lens use during the course of the study
14. Unwilling to avoid the use of additional artificial tear products (other than the assigned study product) throughout the course of the study period
15. History of ocular or intraocular surgery, eyelid surgery, keratorefractive procedure, corneal transplant or serious ocular trauma, within 6 months prior to the Screening Visit
16. Initiation of any topical ocular (over-the-counter or prescribed) medication (with the exception of artificial tears/gels/ lubricants) ≤ 2 weeks prior to the Screening Visit

Assessments:

Screening:

The following assessments will be performed exclusively at the Screening Visit:

- Schirmer I test without anesthesia
- Intraocular pressure (IOP)
- Fundus examination (undilated)

Efficacy:

- Primary endpoint assessment: TFBUT
- Secondary endpoint assessments:
  - TFBUT
  - LLT (LLT AUC_{120} at Day 35)
  - Global Ocular Discomfort questionnaire

[redacted]

Safety:

- Adverse events (AEs)
- BCVA
- Slit-lamp examination

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Note: For eligible study subjects, all study assessments during each visit must be conducted at the same time of day within ± 1 hour of the start time of Visit 1 (Baseline).

Statistical Methods:

Variables

Primary Endpoint

- Change from baseline in TFBUT at Day 35 (assessment for noninferiority)

Secondary Endpoints

- Change from baseline in TFBUT at Day 35 (assessment for superiority)
- LLT AUC_{120} at Day 35
- Change from baseline in Global Ocular Discomfort VAS score at Day 35

[redacted]

Safety Variables

- AEs
- BCVA
- Slit-lamp examination

Planned Analyses

Three analysis sets will be defined for this study. The Full Analysis Set (FAS) will include all randomized subjects who have at least one post-baseline primary endpoint assessment. The Per Protocol Set (PPS) will consist of FAS subjects who have no major protocol deviations. The Safety Analysis Set will include all subjects exposed to post-randomization study product. In the event of a randomization or dispensing error, subjects in the Safety Analysis Set will be analyzed according to the study product they received; however, subjects in the FAS will be analyzed as randomized (regardless of the study product they received).

The primary and secondary efficacy analyses will be performed on both the FAS and PPS with the PPS providing primary inference for the noninferiority hypothesis and FAS providing primary inference for

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the superiority hypotheses.

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.

The analysis of the primary efficacy parameter, change from baseline in TFBUT at Day 35 in the study eye, will be based on a mixed model. The mixed model will include terms for baseline TFBUT, treatment, visit (Day 15, Day 35), and treatment-by-visit interaction. Estimates of the difference (SYSTANE BALANCE - REFRESH OPTIVE Advanced) in mean change from baseline in TFBUT between SYSTANE BALANCE and REFRESH OPTIVE Advanced and associated 95% confidence interval (CI) will be presented. Evidence of noninferiority will be deemed established if the lower limit of the 95% CI for the difference is above -1.0.

The analysis of the secondary efficacy parameter LLT AUC_{120} at Day 35, change from baseline in Global Ocular Discomfort VAS score at Day 35, and change from baseline in TFBUT at Day 35 will be based on a mixed model. The mixed model will include terms for baseline parameter value, treatment, visit (Day 15, Day 35), and treatment-by-visit interaction. Estimates of the difference in mean change from baseline between SYSTANE BALANCE and REFRESH OPTIVE Advanced and associated 95% CI will be presented. The primary endpoint (ie, change from baseline in TFBUT at Day 35) and both secondary endpoints will be evaluated for superiority of SYSTANE BALANCE over REFRESH OPTIVE Advanced.

[redacted] The mixed model will include terms for baseline parameter value and treatment. Estimates of the difference in mean change from baseline between SYSTANE BALANCE and REFRESH OPTIVE Advanced and associated 95% CI will be presented.

[redacted]

To ensure overall control of the type I error rate, the secondary efficacy hypotheses will be relevant only if the primary efficacy null hypothesis is first rejected at the 5% level of significance (2-sided). Following the rejection of the primary efficacy null hypothesis, the secondary hypotheses will be tested following the Hochberg testing

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procedure.

Safety:

The safety analyses will consist of summaries of the AEs and measured safety parameter data. This will include summaries of BCVA and slit-lamp in addition to AEs. The statistics presented for each endpoint will be relevant to the measure of the value, ie, whether the data are categorical or numeric. Continuous measurements will be presented using number, mean, standard deviation, minimum and maximum at each visit. Categorical measurements will be tabulated with the number and percent of subjects in each category at each visit. No inferential testing will be performed for the safety analyses.

Sample size justification:

This study will randomize approximately 220 subjects to achieve 200 evaluable subjects in a 1:1 ratio between SYSTANE BALANCE and REFRESH OPTIVE Advanced. A total of 200 subjects provides approximately 80% power to reject the null hypothesis of inferiority of mean change from baseline in TFBUT at the 0.025 level of significance (1-sided), assuming a treatment difference of 0.0, a standard deviation of 2.5, and a noninferiority margin of 1.0.

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

1.1 Amendments

Amendment 3

Purpose of Amendment: The purpose of this amendment is to widen the range of Unanesthetized Schirmer I Test scores which are eligible for inclusion into the study, to revise the recruitment targets outlined in Section 8, to revise language in Section 10.2.1.1 to allow for patients to be rescreened, to allow for Tumbling E charts to be used to assess BCVA in the Synopsis, Section 10.2.1.1 (Screening Visit), Section 10.2.21 (Randomization Visit), Section 10.2.2.2 (Visit 2), Section 10.2.2.3 (Visit 4/Final Visit), and Section 10.3 (Unscheduled Visits), to clarify the definition of the Safety Analysis Set in both the synopsis (under Planned Analyses) Section 11.2 (Analysis Data Sets), and to correct an error in Section 11.3 (Demographic and Baseline Characteristics) which describes the race categories collected as baseline variables.

Rationale: The current range of Unanesthetized Schirmer I Test scores (5 – 10 mm, inclusive) have caused a high rate of screen-failures for participating sites in the study, who have limited methods to improve their pre-screening. The new range of 3 – 12 mm, inclusive, still requires patients to have some lacrimal function, and is within the clinically accepted range seen in dry eye patients. Sites are experiencing varying levels of difficulty in recruiting the target patients for this study, so site-specific recruitment targets have been made more flexible to achieve the target randomization numbers for the entire study within a limited recruitment period. In non-English speaking countries, Tumbling E charts have been provided to assess BCVA instead of ETDRS charts. Language in Section 10.2.1.1 has been revised to allow patients to be re-screened if they have a Schirmer score which re-qualifies them based on the revised inclusion criterion. The Safety Analysis Set should only capture patients that have been exposed to one of the two investigational products in the treatment phase, and should not include patients who have taken run-in saline only. The list of Race categories in Section 11.3 previously included a comma which changed the meaning of "African American" as a race category, and further omitted the category of "Other," although this is captured in the eCRF.

Current Study Status:

Case Report Form Revision Required:	☐ Yes	☒ No
Informed Consent Modifications Required:	☐ Yes	☒ No
Applicable Investigators:	☒ All	☐ Selected (list below)

Itemized Changes: Inclusion criteria #3 has been updated to read:

"Must have both of the following in at least one eye at the Screening Visit and Visit 1 (Day 0):

- The sum of 3 measures of TFBUT ≤ 15 seconds, and
- Unanesthetized Schirmer I test of ≥ 3 mm to ≤ 12 mm"

Section 8 [SUBJECT POPULATION] will be revised to: "The study population includes approximately 220 subjects to be randomized (200 evaluable subjects required) at approximately 10 sites. Up to 55 subjects may be recruited per site, and site recruitment targets may vary based on site capabilities, available patient population, and length of recruitment period."

The following sentence has been deleted from Section 10.2.1.1 [Screening Visit (Day -14 to Day -7)]: "No subjects may be re-screened if they fail entry criteria for any reason other than the required stabilization timeframes in the exclusion criteria." The following sentence has been added: "Also, a patient can be re-screened if they screen-failed due to the original Schirmer I assessment entry criteria and the patient's original Schirmer score is now within the new Schirmer I assessment entry criteria window."

Section 10.2.1.1 [Screening Visit (Day -14 to Day -7)], Point 6., sub-bullet #1, Section 10.2.2.1 [Randomization Visit (Day 0/Baseline)], Point 4., sub-bullet #1, Section 10.2.2.2 [Visit 2 (Day 15 ± 3 days)], Point 4., sub-bullet #1, Section 10.2.2.3 [Visit 3/Final Visit (Day 35 ± 3 days)], Point 4., sub-bullet #1, and Section 10.3 [Unscheduled Visits] Point 2., sub-bullet #1 have all been revised to read: "BCVA must be measured using an ETDRS or Tumbling E chart at a distance of 3 or 4 meters using the letters read method."

Synopsis [Planned Analyses] and Section 11.2 [Analysis Data Sets]: The Safety Analysis Set definition has been revised to: "The Safety Analysis Set will include all subjects exposed to post-randomization study product."

Section11.3 [Demographic and Baseline Characteristics] contains an update to the bullet point which lists Race categories. This bullet point has been updated to read:

- "Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other)"

Amendment 2

Purpose of Amendment: To modify the minimum age for patients in Singapore (21) and Taiwan (20) in response to feedback from local authorities. To replace incorrect "Day 1" reference with correct "Day 0" reference in statistical analysis section.

Rationale: The IRBs in Taiwan and Singapore provided feedback that per local regulations, the minimum age of adult patients in these countries are 20 and 21, respectively. The global protocol will be amended to address this minimum age per country by modifying inclusion criteria #2. In a previous version of the protocol, a typo was identified in the Statistical Analysis section that erroneously referred to the Day 0 time point as "Day 1." This is being corrected in this amendment, as well.

Current Study Status: Six sites in United States are open and recruiting patients. One site in Australia is open but has not yet recruited patients. Ethics Committee and Health Authority approvals are in the final stages in Taiwan and Singapore.

Case Report Form Revision Required:	☐ Yes	☒ No
Informed Consent Modifications Required:	☐ Yes	☒ No
Applicable Investigators:	☒ All	☐ Selected (list below)

Itemized Changes: Inclusion Criteria #2 will be updated to read: "2. Must be 18 years of age or older at the time of informed consent [patients in Singapore must be 21 years of age or older and patients in Taiwan must be 20 years of age or older due to local regulations]."

"Day 1" will be replaced with "Day 0" in the following sections:

- Section 1: Synopsis, Assessments [redacted]
- Section 1: Synopsis, Statistical Methods, Variables
- Section 1: Synopsis, Statistical Methods, Planned Analyses
- [redacted]
- Section 11.4.3.2: ANALYSIS METHODS

Amendment 1

Purpose of Amendment: To remove reference to "0.9%" concentration of saline solution used during run-in phase.

Rationale: A search of saline products available globally determined that there were no suitable 0.9% saline solution products indicated for ophthalmic use in all four participating countries. As a result, saline supplies of different concentration, which has an ophthalmic use indication, had to be procured for use in this study. The saline remains preservative free, therefore, only the reference to "0.9%" has been removed.

Current Study Status: Recruitment has begun at two sites in the US. Ethics Committee and Health Authority submissions are in the early stages in Australia, Singapore, Taiwan.

Itemized Changes: Reference to "0.9%" has been removed from references to the saline solution in the following sections: 1 SYNOPSIS, Table 2-1, Section 9, Section 9.1, Section 9.2, Section 9.3, Section 9.4, Section 10.1, and Section 10.2.1.1.

2 OVERVIEW OF STUDY PLAN

Table 2–1 Schedule of Assessments

Procedure/ Assessment[1]	Screening	Visit 1 (Baseline)	Visit 2	Visit 3 (Exit)	Early Exit	Unscheduled
	Day -14 to -7	Day 0	Day 15 ± 3 days	Day 35 ± 3 days		
Informed consent	X					
Demographics	X					
Medical history	X					
Changes to medical conditions		X	X	X	X	X
Concomitant medications	X					
Changes to concomitant medications		X	X	X	X	X
Urine pregnancy test[2]	X			X	X	
Inclusion/exclusion criteria	X					
Undilated fundus examination	X					
Unanesthetized Schirmer I test	X					
Intraocular pressure	X					
Start run-in phase Saline	X[3]					
Dispense run-in phase Saline	X					
Stop run-in phase Saline		X				
Collect run-phase Saline empty and unused bottles		X				
Randomization		X				
Dispense treatment phase study products (SYSTANE BALANCE or REFRESH OPTIVE Advanced)		X	X			X[4]
Collect treatment phase study products (SYSTANE BALANCE or REFRESH OPTIVE Advanced)			X	X	X	X[4]
[redacted]						
Ocular Discomfort assessment		X	X	X	X[5]	
BCVA	X	X	X	X	X	X
Slit-lamp examination	X	X	X	X	X	X
Tear film break-up time	X	X	X	X	X[5]	
Lipid layer thickness		X	X	X	X[5]	
[redacted]						
Adverse events (both volunteered and elicited)	X	X	X	X	X	X
Electronic data capture	X	X	X	X	X	X
Complete exit form				X	X	

1. For eligible study subjects, all study assessments during each visit must be conducted at the same time of day within ± 1 hour of the start time of Visit 1 (Baseline).
2. For women who are of child bearing potential.
3. Preservative-free saline will be administered for 7 to 14 days prior to baseline i.e. from Day -14/Day -7 to Day -1.
4. If necessary.
5. These assessments should only be done if study subject exits the study early prior to Day 35 but has been on masked treatment for at least 14 days.

[redacted]

3 ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device/drug effect
ADR	Adverse drug reaction
AE	Adverse event
AEF	Adverse event form
BAK	Benzalkonium chloride
AUC_{120}	Area under the epidermal concentration-time profile
BCVA	Best-corrected visual acuity
CJD	Creutzfeldt-Jacob Disease
CRF	Case report form
DED	Dry eye disease
DMPG-Na	Dimyristoyl phosphatidylglycerol
EDC	Electronic data capture
EDTA	Ethylene diamine tetra acetic acid
ETDRS	Early treatment diabetic retinopathy study
EXC	Exclusion
FAS	Full analysis set
FDA	US Food and Drug Administration
FID	Formulation identification
GCP	Good clinical practice
GTT	Drop
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
[redacted]	[redacted]
IEC	Independent Ethics Committee
INC	Inclusion
IRB	Institutional Review Board
IRT	Interactive response technology
LLT	Lipid layer thickness
[redacted]	[redacted]
MMRM	Mixed model repeated measures analysis
MOP	Manual of procedures
OD	Right eye
OS	Left eye
OU	Both eyes
PG	Propylene glycol
PPS	Per Protocol Set
QID	Four times a day
SAE	Serious adverse event
SD	Standard deviation
TFBUT	Tear film break-up time
VAS	Visual analog scale

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5 INTRODUCTION

5.1 Study Rationale and Background

The purpose of this study is to evaluate the clinical effectiveness of SYSTANE BALANCE compared to REFRESH OPTIVE Advanced in patients with dry eye associated with lipid deficiency.

Dry eye disease (DED), also called keratoconjunctivitis sicca or dry eye syndrome, is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface (Lemp 2007). Dry eye may affect individuals with differing severity, from mild cases experiencing burning and other symptoms of ocular discomfort, to severe cases with substantially impaired vision. The global prevalence of DED reported in several large studies ranges from 5% to 35% (Smith 2007); meibomian gland dysfunction (obstruction or gland drop out) has been reported in up to 70% of dry eye cases (Schaumberg 2011).

SYSTANE BALANCE is a lipid-based artificial tear drop and has been formulated with a patented Lipitech™ system (consisting of phospholipids and mineral oil) to help address dry eye signs and symptoms caused by a deficiency in the lipid layer of the tear film. Potential benefits of SYSTANE BALANCE include improvement in clinical measures related to lipid-deficient tear film such as increased tear film break-up time (TFBUT) and lipid layer thickness (LLT), reduced ocular surface staining, reduction in the need for higher dosing or expensive alternative dry eye therapies, improvement in patient's quality of life and treatment satisfaction. A key ingredient in the Lipitech system, phospholipids (which contain both polar and non-polar groups) is a natural component of the lipid layer of the tear film which helps to provide stability at the interface between the lipid layer and the aqueous layer.

A new addition to the lipid-based subgroup of artificial tear products (REFRESH OPTIVE Advanced) contains castor oil and is launching across the globe in key growth markets. While there are no data comparing the effectiveness of both products, supplementing the lipid layer of patients with lipid-deficient dry eye with a key natural component may be a better alternative in improving or prolonging the integrity of the lipid layer.

This study is designed to show that the clinical benefits of SYSTANE BALANCE will be at least noninferior to REFRESH OPTIVE Advanced.

5.2 Systane Balance

Alcon has developed SYSTANE BALANCE Lubricant Eye Drops as an artificial tear supplement. The formulation is an oil-in-water emulsion containing propylene glycol as the

active demulcent, polyquad (polyquaternium-1) as the preservative, HP-Guar/borate gelling technology, an anionic phospholipid (dimyristoyl phosphatidylglycerol, DMPG-Na) and ethylene diamine tetra acetic acid (EDTA) as a chelating agent. SYSTANE BALANCE Lubricant Eye Drop was first marketed in the United States in 2008 and has sold over 8 million units worldwide since its introduction to the market. To date, Alcon has registered SYSTANE BALANCE Lubricant Eye Drops worldwide in multiple countries.

5.3 Known and Potential Risks

During the clinical development of SYSTANE BALANCE, a single non-serious adverse drug reaction (ADR) of mild blurred vision was reported. No systemic ADR was reported in any subject administered SYSTANE BALANCE in the clinical studies performed to date. Since the initial approval of the SYSTANE family of products, local ocular side effects have been the most common types of spontaneous reports observed through post marketing surveillance. Other most frequent AEs reported were: eye irritation, blurred vision, ocular hyperemia, and eye pain. No spontaneous report has been observed at a frequency that would indicate a safety concern for continued subject use of SYSTANE BALANCE.

Overall, the occurrence of nonserious local ocular side effects with the use of a topical ocular lubricant like SYSTANE BALANCE is not unexpected especially in subjects with a predisposing risk factor (eg, dry eye subjects) and do not represent a safety concern for the use of SYSTANE BALANCE.

5.4 Potential Benefits

SYSTANE BALANCE Lubricant Eye Drops is a multidose, artificial tear product that has been shown to improve the signs and symptoms of dry eye in multiple clinical studies. The product has been shown to lubricate the ocular surface, supplement and stabilize the lipid layer of the tear film, and reduce excessive tear evaporation, thereby providing long lasting relief from dry eye symptoms such as burning and irritation.

6 ETHICS

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline and other regulations as applicable. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

Before clinical study initiation, this protocol, the informed consent form, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB). The Investigator must provide documentation of the IEC/IRB approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, all applicable recruiting materials, written information for subject, and subject compensation programs. The IEC/IRB must be provided with a copy of the product monograph or equivalent, any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB. At the end of the study, the Investigator will notify the IEC/IRB about the study's completion. The IEC/IRB also will be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB.

Voluntary informed consent will be obtained from every subject prior to the initiation of any screening or other study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and will provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the study products, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject will also be told that his/her records may be accessed by appropriate

authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each subject.

7 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IEC/IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study may be required by the IRB/IEC to sign the approved, revised informed consent form.

8 SUBJECT POPULATION

The study population includes approximately 220 subjects to be randomized (200 evaluable subjects required) at approximately 10 sites. Up to 55 subjects may be recruited per site, and site recruitment targets may vary based on site capabilities, available patient population, and length of recruitment period. To participate in the study, subjects must be at least 18 years of age and exhibit dry eye symptoms. The expected duration of subject participation in the study is approximately 7 weeks (49 days); up to 2 weeks (14 days) during the run-in phase and 5 weeks (35 days) in the treatment phase. The complete inclusion and exclusion criteria are presented in Section 1.

9 TREATMENTS ADMINISTERED

Subjects who meet the eligibility criteria will first be dispensed Preservative-Free Saline to be used during the run-in period between the Screening Visit and Visit 1 (Baseline/ Day 0).

At Visit 1, subjects who meet the eligibility criteria (as determined by the re-evaluation of the TFBUT assessment prior to randomization) will be randomized in a 1:1 manner to receive treatment with SYSTANE BALANCE Lubricant Eye Drops or REFRESH OPTIVE Advanced Lubricant Eye Drops. Throughout the study, the Investigator will be responsible for the accounting of all study materials and will ensure that the study products are not used in an unauthorized manner.

This study is double-masked. Designated unmasked individual(s) at each site must be assigned to dispense and reclaim the masked study product. Unmasked individuals should not be involved in conducting any subject assessments. Extreme caution should be used to avoid potential unmasking of the individuals conducting subject assessments.

9.1 Identity of Study Products

Run-in Product: Preservative-Free Saline Solution

Test Product: SYSTANE BALANCE

Control Product: REFRESH OPTIVE Advanced (multidose preserved formulation)

Preservative-Free Saline will be provided for the run-in phase in the commercially available carton as an open-label product. Masked study products will be supplied in commercially approved bottles in identical cartons covered with approved clinical labeling. The carton labels will contain, at a minimum, the protocol number and kit identification number.

SYSTANE BALANCE and REFRESH OPTIVE Advanced should be stored in accordance with the approved clinical labeling. Products are to be shaken gently before use, and to avoid contamination, the tip of the container should never be touched to any surface.

A site temperature log will be maintained to document storage conditions of the study products and will be made available for the study monitor to inspect.

9.2 Usage

Open-label Preservative-Free Saline eye drops will be provided to each subject in sufficient quantity to accommodate QID dosing throughout the Run-in phase. One kit of masked study product will be provided to each subject at the time of randomization (Visit 1/ Day 0) and a second kit will be provided at Visit 2/Day 15. Extra kits of study product may be supplied as needed.

Run-in Phase:	During the run-in phase (between the Screening Visit and Visit 1), subjects will be given Preservative-Free Saline eye drops and instructed to dose each eye with 1 drop, QID.
Treatment Phase: Day 0 to Day 35	At Visit 1 (Day 0), subjects will be randomized and will receive either SYSTANE BALANCE or REFRESH OPTIVE Advanced. Subjects will be instructed to dose each eye with 1 drop, QID (with the last dose at bedtime, ie, no later than midnight) from Visit 1 to Visit 3 (Day 0 – Day 35).

The first dose of Preservative-Free Saline eye drops will be self-administered by the subject at the study site and observed by site staff to confirm the subject is using the correct administration technique.

9.3 Accountability Procedures

Upon receipt of the run-in Preservative-Free Saline, the test product (SYSTANE BALANCE) and the control product (REFRESH OPTIVE Advanced), the Investigator or designee will conduct an inventory. Designated study staff will dispense the run-in Preservative-Free Saline to all subjects who qualify for the study. On Visit 1 (Day 0/Baseline), subjects will return used and unused containers of run-in Preservative-Free Saline and sites will maintain an accurate inventory of the vials of run-in Preservative-Free Saline returned by the subjects.

If the subject qualifies for the study, the site will randomize the subject using an electronic data capture (EDC) system at Visit 1/Baseline. The site personnel will provide the masked study product to the subject in accordance with the interactive response technology (IRT) treatment kit numbers assigned at Visit 1 and at Visit 2.

During the study, the Investigator must maintain records of study products receipt, dispensation and collection for each subject. Subjects will be instructed to bring used and unused vials of Preservative-Free Saline to the Baseline Visit and the masked study product to all post-baseline visits. At Visit 3/ Day 35 (Final Visit) or at Early Exit, all used and unused study products should be returned. Sites will maintain an accurate inventory of the bottles/vials returned by the subjects. This record must be made available to the study monitor for the purposes of verifying the accounting of clinical supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation.

At the conclusion of the study, the Investigator will be responsible for returning all used and unused study products unless otherwise instructed by the Sponsor.

9.4 Subject Confidentiality and Methods Used to Minimize Bias

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. At the end of the clinical study, the Sponsor will collect a copy of the enrollment log without any identifying subject information. All documents submitted to the Sponsor will identify the subjects exclusively by number and demographic information. No other personally identifying information should be transmitted to the Sponsor.

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of

subjects, their subsequent care, the assessment of end points, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the study products by the Investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

The Run-in Phase is open-label and all subjects will use Preservative-Free Saline eye drops for at least 7 days. The Treatment Phase is double-masked, with subjects randomized to receive either SYSTANE BALANCE or REFRESH OPTIVE Advanced for the duration of the 5 week treatment period. The Investigator, clinical site staff (except designated unmasked site personnel), Sponsor, and monitors involved in reporting, obtaining, and/or reviewing the clinical evaluations will not be aware of the specific masked study product being administered. This level of masking will be maintained throughout the conduct of the study. 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. Subjects will be assigned randomly to treatment groups via IRT with stratification by site. The sponsor study specific personnel will be masked throughout the course of the study. Once all study data have been validated and the database locked, individual subjects will be unmasked. In the event of a medical emergency where the knowledge of subject treatment is required, an individual Investigator will have the ability to unmask the treatment assignment for a specific subject.

Although this is a double-masked study, at least 1 designated person from each clinical site will be unmasked. This person will be responsible for dispensing, reclaiming, conducting inventory, and will be available to address any study product irregularities. This individual will also perform the instillation of masked study product at Visit 1 (Baseline), Visit 2 and Visit 3. Sites should make every effort to have the same unmasked observer throughout the study.

10 STUDY PROCEDURES

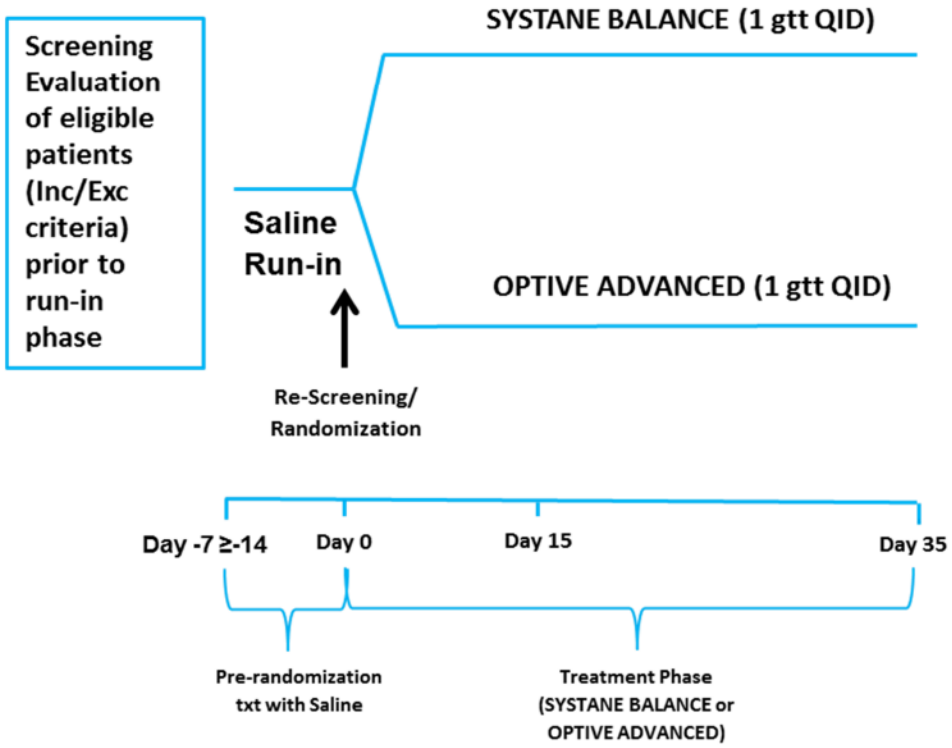
10.1 Outline of Study

This is a post-market, prospective, double-masked, randomized, multicenter, parallel-group study with 2 treatment arms:

1. SYSTANE BALANCE Lubricant Eye Drops
2. REFRESH OPTIVE Advanced Lubricant Eye Drops

Subjects must exhibit dry eye symptoms to be considered for inclusion in this study. The study consists of 4 required visits: Screening Visit (Day -14 to Day -7), Visit 1 (Day 0/Baseline), Visit 2 (Day 15) and Visit 3 (Day 35/End of Treatment).

Figure 10-1 Study Design



Subjects will be screened for eligibility at least 7 days prior to, but no more than 14 days (ie, Day -14 to Day -7) prior to Visit 1 (Baseline/Day 0) to simultaneously begin the Saline run-in phase. Subjects who meet eligibility criteria at Screening will be asked to discontinue all artificial tears/lubricants/gels/rewetting drops and will be given a supply of Preservative-Free Saline with instructions to administer 1 drop in each eye 4 times per day during the run-in period. Additionally, subjects must discontinue contact lens wear at least 30 days before Screening and agree not to wear contact lenses for the duration of the study.

Upon completion of the run-in period, eligible subjects will be randomized to either SYSTANE BALANCE or REFRESH OPTIVE Advanced at Visit 1 and other baseline evaluations will be conducted. An adequate supply of randomized test product (SYSTANE BALANCE) and control product (REFRESH OPTIVE Advanced) will be dispensed at Day 0 for the treatment period (Day 0 – Day 15). Subjects will be instructed to instill 1 drop of the assigned test or control product in each eye, 4 times per day. At the study visits during the treatment phase, the unmasked site personnel will instill the masked study product for each

subject. At Visit 2 (Day 15), a second kit will be dispensed for the remaining treatment period (Day 15 – Day 35).

10.2 Visits and Examinations

Subjects should come in for all regularly scheduled visits (even if a visit is "out of window"). Visit 3 (Day 35) is critical for evaluating the subject's response to therapy after completing the designated dosing period.

The schedule of study procedures/ assessments is presented in Table 2–1. For details of the procedures used and order of assessments in this protocol, refer to the manual of procedures (MOP). For eligible study subjects, all study assessments during each visit must be conducted at the same time of day within ± 1 hour of the start time of Visit 1 (Baseline). Adverse events (AEs) will be collected from the time of informed consent, until the subject exits the study. All AEs that are observed or reported should be recorded on an AE form as per Section 12.2 and reported to the IRB/IEC, as required.

10.2.1 Saline Run-in Phase (Day -14/-7 to Day 0)

The run-in phase includes the duration from the Screening Visit to the Baseline Visit (Day 0).

10.2.1.1 Screening Visit (Day -14 to Day -7)

Screening procedures must be completed at the Screening Visit. Informed consent must be obtained prior to conducting study-specific Screening assessments. Subjects who meet eligibility criteria at Screening will be given a supply of Preservative-Free Saline to be used during the 7 to 14 day run-in phase.

The Screening procedures include the following and must be completed in the order stated below:

1. Explain the purpose and nature of the study, and have the subject or legally authorized representative read, sign, and date the IRB/IEC-approved informed consent document. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the informed consent document. Provide a photocopy of the signed document to the subject and place the original signed document in the subject's chart.
2. If the subject consents, retrieve the 9-digit subject identification number from EDC.

3. Obtain demographic information and medical history, including information on all medications used within the past 30 days. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications.
4. Conduct urine pregnancy test on women of childbearing potential. If the test is positive, the subject is ineligible and must discontinue. Additionally, for women of childbearing potential, record method(s) of birth control in the subject's chart. For surgically sterile or post-menopausal women, record date of surgical sterilization (tubal ligation, hysterectomy or bilateral oophorectomy) or date of menopause (defined as 12 months since last menses).
5. Screen subjects for protocol inclusion and exclusion criteria.
6. The following assessments must be completed in both eyes (OU) (see the MOP for details regarding each assessment and the order of testing):
    - BCVA must be measured using an ETDRS or Tumbling E chart at a distance of 3 or 4 meters using the letters read method. The test may be performed using the subject's historical correction. Visual acuity testing should precede any examination requiring diagnostic drops (eg, dilating drops) or contact with the eye. BCVA must be ≥ 55 in both eyes for the subject to qualify for the study.
    - Slit-lamp examination
    - Undilated fundus examination
    - Unanesthetized Schirmer I test using the strips
    - TFBUT right eye (OD) × 3, left eye (OS) × 3
    - Intraocular pressure
7. If the inclusion/exclusion criteria are met, the site staff will dispense the appropriate number of containers of Preservative-Free Saline eye drops to provide QID treatment for the run-in phase.
8. The site staff will observe the subject instill the first dose of Preservative-Free Saline while at this visit.
9. Subjects will be instructed to dose with 1 drop of Saline in each eye, 4 times per day. The last dose should be at bedtime (ie, no later than midnight).

10. Subjects will be instructed to return used and unused containers of Preservative-Free Saline at the next visit (Visit 1).
11. Record any AEs that are observed or reported.
12. Schedule Visit 1 to take place 7 to 14 days after the Screening Visit.
13. Provide subjects with Run-in Phase Dosing Instructions card and Study Information card.
14. Enter the subject information and visit data into the EDC system.

If, at the Screening Visit, it is determined that a subject did not meet the timeframe required for stabilization of chronic medications or medical history, the subject may be brought back at a later date to re-attempt the Screening process once the timeframe(s) have been achieved. Also, a patient can be re-screened if they screen-failed due to the original Schirmer I assessment entry criteria and the patient's original Schirmer score is now within the new Schirmer I assessment entry criteria window.

10.2.2 Treatment Phase – Visit 1 to Visit 3 / Day 0 to Day 35

The duration of the Treatment Phase is 35 days ie, from Baseline Visit/Visit 1 (Day 0) to Visit 3 (Day 35). Randomization to a treatment group will be conducted at Visit 1. Sites will randomize each subject using the EDC system. The unmasked site personnel will dispense the appropriate masked study product kit.

Qualifying subjects will receive their first masked study product kit at Visit 1 (Day 0). The second kit will be dispensed at the Visit 2 (Day 15). However, subjects may return for additional kits if previous kits were lost or destroyed.

10.2.2.1 Randomization, Visit 1 (Day 0/ Baseline)

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. The site staff will perform accountability, record, and collect the number of used and unused containers of Saline.
3. Subjects should complete the following questionnaires:
    - [redacted]
    - Ocular Discomfort questionnaire
4. The following assessments must be completed OU (see the MOP for details regarding each assessment and the order of testing).

- BCVA must be measured using an ETDRS or Tumbling E chart at a distance of 3 or 4 meters using the letters read method. The test may be performed using the subject's historical correction. Visual acuity testing should precede any examination requiring diagnostic drops (eg. dilating drops) or contact with the eye. BCVA must be ≥ 55 in both eyes for the subject to qualify for the study.
- Slit-lamp examination
- LLT assessments
- TFBUT OD × 3, OS × 3
- [redacted]

5. Re-confirm subject eligibility. Eligible subjects must have a TFBUT (sum of 3 measures ≤ 15 seconds at Screening and baseline in the same eye(s)), and BCVA (≥ 55 letters in each eye at Screening and baseline). The qualifying eye with the shorter mean TFBUT at baseline would be the study eye. The same study eye must also have qualified at Screening.
6. If the subject does not qualify, the visit should stop and the subject should be exited from the study as a screen failure.
7. If the subject qualifies, randomize the subject and obtain the masked study product kit number(s) to be dispensed. The unmasked site staff will retrieve and dispense the assigned masked study product kit(s).
8. The unmasked site staff will instill a single drop of the masked test/control product that was dispensed to the subject in each eye. Masked site personnel must not be present while the bottle of masked test/control product is removed from the kit and administered.
9. Subjects will be instructed to dose 1 drop of the test/control product in each eye QID. The last dose should be at bedtime (ie, no later than midnight).
10. Subjects will be instructed to retain and return all used and unused kits at their next visit.
11. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.
12. Schedule Visit 2 to take place 15 ± 3 days after Visit 1.

13. Provide subject with Treatment Phase Dosing Instructions card. Provide Study Information card if original card is lost or unavailable.
14. Enter the subject information and visit data into the EDC system.

10.2.2.2 Visit 2 (Day 15 ± 3 days)

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. The unmasked site staff will perform drug accountability, record, and collect the kit(s) of masked study product.
3. Subjects should complete the following questionnaires:
    - [redacted]
    - Ocular Discomfort questionnaire
4. The following assessments must be completed in both eyes (OU) (see the MOP for details regarding each assessment and order of testing).
    - The BCVA must be measured using an ETDRS or Tumbling E chart at a distance of 3 or 4 meters using the letters read method. The test may be performed using the subject's historical correction. Visual acuity testing should precede any examination requiring diagnostic drops (eg. dilating drops) or contact with the eye.
    - Slit-lamp examination
5. The unmasked site staff will instill a single drop of the masked test/control product that was dispensed to the subject in each eye. Masked site personnel must not be present while the bottle of masked test/control product is removed from the kit and administered.
6. The following assessments must be completed in both eyes (OU) (see the MOP for details regarding each assessment and order of testing).
    - LLT assessment
    - TFBUT assessment
    - [redacted]
7. The unmasked site staff will dispense an additional masked study product kit.

8. Subjects will be instructed to continue to dose 1 drop of the test/control product in each eye QID. The last dose should be at bedtime (ie, no later than midnight).
9. Subjects will be instructed to retain and return all used and unused kits at their next visit.
10. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.
11. Schedule Visit 3 to take place 35 ± 3 days after Visit 1.
12. Provide subject with Treatment Phase Dosing Instructions card and provide Study Information card if original card is lost or unavailable.
13. Enter the subject information and visit data into the EDC system.

10.2.2.3 Visit 3/Final Visit (Day 35 ± 3 days)

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Conduct urine pregnancy test on women of childbearing potential.
3. Subjects should complete the following questionnaires:
    - [redacted]
    - Ocular Discomfort questionnaire
4. The following assessments must be completed in both eyes (OU) (see the MOP for details regarding each assessment and order of testing).
    - The BCVA must be measured using an ETDRS or Tumbling E chart at a distance of 3 or 4 meters using the letters read method. The test may be performed using the subject's historical correction. Visual acuity testing should precede any examination requiring diagnostic drops (eg. dilating drops) or contact with the eye.
    - Slit-lamp examination
5. The unmasked site staff will instill a single drop of the masked test/control product that was dispensed to the subject in each eye. Masked site personnel must not be present while the bottle of masked test/control product is removed from the kit and administered.
6. The following assessments must be completed OU (see the MOP for details regarding each assessment and order of testing).

- LLT assessments
- TFBUT assessment
- [redacted]

7. The unmasked site staff will perform drug accountability, record, and collect all kit(s) of study products.
8. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.
9. Exit the subject from the study.
10. Enter the subject information and visit data into the EDC system.

10.3 Unscheduled Visits

Any visit that occurs between the regularly scheduled visits must be documented in the Unscheduled Visit pages of the case report form (CRF). During all unscheduled visits, the following procedures must be conducted:

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. The following assessments must be completed OU (see the MOP for details regarding each assessment).
    - BCVA must be measured using an ETDRS or Tumbling E chart at a distance of 3 or 4 meters using the letters read method. The test may be performed using the subject's historical correction. Visual acuity testing should precede any examination requiring diagnostic drops (eg. dilating drops) or contact with the eye.
    - Slit-lamp examination.
3. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.
4. Unmasked site staff will collect and dispense masked study product kits as necessary.

Other assessments may be done at the discretion of the Investigator to appropriately treat the subject. If the subject is discontinuing at the unscheduled visit, the Early Exit CRFs should be completed rather than the CRFs for an Unscheduled Visit and the appropriate Exit procedure should be completed as described in the following sections.

10.4 Discontinued Subjects

Discontinued subjects are those who withdraw or are withdrawn from the study after the Screening Visit. Subjects may discontinue from the study at any time for any reason. Subjects may also be discontinued from the study at any time if, in the opinion of the Investigator, their continued participation poses a risk to their health. Discontinued subjects will not be replaced (ie, their subject numbers will not be re-assigned/re-used).

Should a subject exhibit any clinically relevant signs, symptoms, or other clinical observations that could be possibly associated with suspected sensitivity or intolerance to one of the study products, the Investigator must document those observations on an AE Form.

Any subject who exits early from the study (ie, prior to Day 35) must undergo all the procedures outlined at Early Exit in Section 0. Additionally, the Exit Form must be completed and one of the following reasons for discontinuation must be identified:

- Discontinued due to Screen Failure
- Discontinued due to AE
- Discontinued due to Death
- Discontinued due to Lost to Follow Up
- Discontinued due to Non-Compliance with Study Drug
- Discontinued due to Physician Decision
- Discontinued due to Pregnancy
- Discontinued due to Protocol Violation
- Discontinued due to Study Terminated by Sponsor
- Discontinued due to Technical Problems
- Discontinued study due to Withdrawal by Subject
- Discontinued due to Other Reason (specify)

Finally, to ensure the safety of all subjects who discontinue early, Investigators should assess each subject and, if necessary, advise them of any therapies and/or medical procedures that might be needed to maintain their health.

10.5 Clinical Study Termination

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities (if necessary) of the termination/ suspension and the reason(s) for the termination/suspension. The Investigator should promptly notify the IEC/IRB of the termination or suspension and of the reasons. The Sponsor reserves the right to close the study site or terminate the study in its entirety at any time, for reasonable cause. Reasons for the closure of a study site or termination of a study may include:

- Successful completion of the study
- The study's enrollment goals are met
- The Investigator fails to comply with the protocol or GCP guidelines
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the Investigator

The Investigator may also terminate the study at his/her site for reasonable cause. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator(s) by telephone and will subsequently provide written confirmation of and instructions for study termination.

11 ANALYSIS PLAN

11.1 Subject Evaluability

All subjects who satisfy the inclusion and exclusion criteria, and who sign the informed consent form, will be considered evaluable.

The final subject evaluability will be determined prior to breaking the code for masked treatment assignment and locking the database.

11.2 Analysis Data Sets

Three analysis sets will be defined for this study: the Safety Analysis Set, Full Analysis Set (FAS) and Per Protocol Set (PPS).

The FAS will include all randomized subjects who have at least 1 post-baseline primary endpoint assessment.

The PPS will consist of FAS subjects who satisfy all inclusion/exclusion criteria and who have no major protocol deviations, 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.

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

In the event of a randomization or dispensing error, subjects in the Safety Analysis Set will be analyzed according to the study product they received; however, subjects in the FAS will be analyzed as randomized (regardless of the study product they received).

11.3 Demographic and Baseline Characteristics

Demographic characteristics will be summarized by treatment group. The following demographic characteristics will be summarized for all data sets:

1. Continuous baseline variables: age (years)
2. Categorical baseline variables:
    - Age (< 65, ≥ 65 years)
    - Gender (female, male)
    - Ethnicity (Hispanic, not Hispanic); and
    - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)

Summary statistics (sample size, mean, median, standard deviation (SD), minimum and maximum for continuous variables and sample size, counts and percentages for categorical variables) will be provided by treatment group. A listing of randomized treatment assignment for each subject, their evaluability status and demographic characteristics will be provided.

Visit 1 (Baseline/Day 0) summary statistics will be presented overall and by treatment group. Descriptive statistics (sample size, mean, SD, minimum and maximum) will be presented by treatment at Visit 1 for TFBUT, LLT AUC_{120}, Global Ocular Discomfort VAS score, [redacted] BCVA, and slit-lamp examination.

11.4 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.

11.4.1 Primary Efficacy

The primary objective of this study is to demonstrate noninferiority of SYSTANE BALANCE over RERESH OPTIVE ADVANCED using TFBUT after 35 days of QID dosing in subjects with lipid-deficient dry eye.

The primary endpoint is the change from baseline at Day 35 in TFBUT. The TFBUT will be assessed at Visit 1 (Day 0), Visit 2 (Day 15), and Visit 3 (Day 35).

11.4.1.1 Statistical Hypotheses

The primary efficacy hypothesis is that SYSTANE BALANCE is noninferior to REFRESH OPTIVE ADVANCED with respect to the change from baseline in TFBUT at Day 35 in subjects with lipid-deficient dry eye.

The null and alternative hypotheses are:

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

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

where $\mu_{SB}$and μ_{OA}denote the mean change from baseline in TFBUT at Day 35 for SYSTANE BALANCE and REFRESH OPTIVE ADVANCED, respectively.

The noninferiority margin was chosen as 1 second on the basis that an increase of at least 25% in the baseline TFBUT of a patient with lipid-deficient dry eye would be considered clinically meaningful since the patient would blink less often. Based on historical data, the mean TFBUT at baseline for a patient with lipid-deficient dry eye is approximately 4 seconds.

11.4.1.2 Analysis Methods

The primary efficacy analysis population will be the PPS.

The analysis of the primary efficacy parameter, change from baseline in TFBUT at Day 35 in the study eye, will be based on a mixed model repeated measures (MMRM) analysis. The mixed model will include terms for baseline TFBUT, treatment (SYSTANE BALANCE,

REFRESH OPTIVE Advanced), visit (Day 15, Day 35), and treatment-by-visit interaction. The response variable is the change from baseline in TFBUT for the study eye.

An unstructured variance-covariance matrix will be used to model the within-subject correlation. If the unstructured variance-covariance matrix results in a lack of convergence then other covariance structures will be investigated.

Within-treatment and estimates of the difference (SYSTANE BALANCE – REFRESH OPTIVE Advanced) in mean change from baseline in TFBUT between SYSTANE BALANCE and REFRESH OPTIVE Advanced and associated 95% CI will be presented. Evidence of noninferiority will be deemed established if the lower limit of the 95% CI for the difference is above -1.0.

11.4.2 Secondary Efficacy

The secondary efficacy objectives are:

- To demonstrate that SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced using TFBUT after 35 days of QID dosing in subjects with lipid-deficient dry eye.
- To evaluate changes in LLT AUC_{120} following the use of SYSTANE BALANCE versus REFRESH OPTIVE Advanced after 35 days of QID dosing in subjects with lipid-deficient dry eye.
- To evaluate changes in Global Ocular Discomfort using a VAS score following use of SYSTANE BALANCE versus REFRESH OPTIVE Advanced after 35 days of QID dosing in subjects with lipid-deficient dry eye.

The secondary efficacy endpoints are:

- Change from baseline in TFBUT at Day 35
- LLT AUC_{120} at Day 35
- Change from baseline in Global Ocular Discomfort VAS score at Day 35

11.4.2.1 Statistical Hypotheses

The hypotheses for the secondary analysis are:

- SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced with respect to change from baseline in TFBUT at Day 35
- SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced with respect to LLT AUC_{120} at Day 35

- SYSTANE BALANCE is superior to REFRESH OPTIVE Advanced with respect to change from baseline in Global Ocular Discomfort VAS score at Day 35

The null and alternative hypotheses for the first secondary endpoint are:

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

H_1: $\mu_{SB} - \mu_{OA} > 0$where $\mu_{SB}$and μ_{OA}denote the mean change from baseline in TFBUT at Day 35 for SYSTANE BALANCE and REFRESH OPTIVE Advanced, respectively.

The null and alternative hypotheses for the second secondary endpoint are:

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

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

where $\mu_{SB}$and μ_{OA}denote the mean LLT AUC_{120} at Day 35 for SYSTANE BALANCE and REFRESH OPTIVE Advanced, respectively.

The null and alternative hypotheses for the third secondary endpoint are:

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

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

where $\mu_{SB}$and μ_{OA}denote the mean change from baseline in VAS score at Day 35 for SYSTANE BALANCE and REFRESH OPTIVE Advanced, respectively.

11.4.2.2 Analysis Methods

The analysis of the secondary efficacy parameter LLT AUC_{120} at Day 35, and change from baseline in Global Ocular Discomfort VAS score at Day 35, and change from baseline of the TFBUT at Day 35 will be based on a MMRM. The mixed model will include terms for baseline parameter values, treatment, visit (Day 15, Day 35), and treatment-by-visit interaction. Estimates of the difference in mean change from baseline between SYSTANE BALANCE and REFRESH OPTIVE Advanced and associated 95% CIs will be presented.

Each endpoint will be evaluated for superiority of SYSTANE BALANCE over REFRESH OPTIVE Advanced. The p-value from the one-sided test less than 0.025 for a difference in favor of SYSTANE BALANCE will indicate superiority of SYSTANE BALANCE over REFRESH OPTIVE Advanced.

[redacted]

11.5 Handling of Missing Data

The mixed-effects repeated measures (MMRM) model approach will be used to analyze the continuous variables. The MMRM model is suitable for longitudinal data with missing values

under the missing at random (MAR) assumption. It is a likelihood-based analysis that can provide valid inference without the need for explicit modeling or imputation of missing data.

11.6 Multiplicity

To ensure overall control of the type I error rate, the secondary efficacy hypotheses will be relevant only if the primary efficacy null hypothesis is first rejected at the 5% level of significance (2-sided). Following the rejection of the primary efficacy null hypothesis, the secondary hypotheses will be tested following the Hochberg testing procedure.

[redacted]

11.7 Safety Analysis

The safety endpoints in this study are:

- AEs
- BCVA
- Slit-lamp examination (cornea, lens, iris and anterior chamber)

The safety analyses will consist of summaries of the AEs and measured safety parameter data. This will include summaries of BCVA and slit-lamp in addition to AEs. The statistics presented for each endpoint will be relevant to the measure of the value, ie, whether the data are categorical or numeric. Continuous measurements will be presented using number, mean, standard deviation, minimum and maximum at each visit. Categorical measurements will be tabulated with the number and percent of subjects in each category at each visit. No inferential testing will be performed for the safety analyses.

11.8 Health Economics

Not applicable.

11.9 Interim Analyses

Not applicable.

11.10 Sample Size Justification

In this study, approximately 220 subjects will be randomized to SYSTANE BALANCE or REFRESH OPTIVE Advanced in a 1:1 ratio in order to achieve 200 evaluable subjects. A total of 200 subjects provides approximately 80% power to reject the null hypothesis of

inferiority of mean change from baseline in TFBUT at the 0.025 level of significance (1-sided), assuming a treatment difference of 0.0, a standard deviation of 2.5, and a noninferiority margin of 1.0 second.

Table 11–1 shows the sample size required to achieve 80% and 90% power with different assumed values of standard deviation.

Table 11–1 Sample Size Calculation

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

12 COLLECTION OF COMPLAINTS

12.1 General Information

Adverse Event

An AE is any untoward medical occurrence in a subject who is administered a study product regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study product, whether or not related to the treatment. In clinical studies, an AE can include an untoward medical occurrence occurring at any time, including run-in or washout periods, even if no study product has been administered. The determination of clinical relevance is based upon the medical judgment of the Investigator.

Quality Complaints

Deficiency of a product includes inadequacy with respect to its identity, quality, durability, reliability, safety or performance. Note: This definition includes malfunctions, use errors, and inadequate labeling.

- Malfunction is defined as a failure of a product to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the product. The intended performance of the product refers to the intended use for which it is labeled or marketed.

Use error is defined as the act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user.

Adverse Drug/Device Effect (ADE)

An ADE is defined as an AE related to the use of study product. *Note: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the study product.*

Serious Adverse Event (SAE)

Adverse event that led to any of the following:

- Death
- A serious deterioration in health that either resulted in:
    a. A life-threatening illness or injury.

    Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.

    b. Any potentially sight-threatening event or permanent impairment to a body structure or a body function.

    c. In-patient hospitalization or prolonged hospitalization

    Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a SAE. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization

or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.

d. A medical intervention to prevent a) or b), or any surgical intervention.

e. Any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use.

- Fetal distress, fetal death, or a congenital abnormality or birth defect.

  Note: This includes quality complaints that might have led to a SAE if:

  a. suitable action had not been taken or

  b. intervention had not been made or

  c. circumstances had been less fortunate. These are handled under the SAE reporting system.

- Is an important medical event. An important medical event is an event that may not result in death, be life- threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in a subject's hospitalization, or the development of drug dependency or drug abuse.

Serious Public Health Threat

Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, eg, human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD).

Nonserious adverse event

Any AE that does not meet seriousness criteria described above.

Contributory cause (causality assessment)

In assessing the association of the device/product to the event, the following should be taken into account:

- The opinion, based on available evidence, of healthcare professionals
- The results of the preliminary assessment of the event
- Evidence of previous, similar events

This judgment may be difficult when there are multiple devices/products and drugs involved. In complex situations, it should be assumed that the device may have caused or contributed to the event and the MANUFACTURERS should err on the side of caution.

Reference Safety Information

For SAEs potentially qualifying expedited reporting, the following will serve as the reference safety information for the purposes of determining expectedness:

- Product Label for SYSTANE BALANCE

12.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions:

- "Have you had any health problems since the last study visit?"
- "Have there been any changes in the medicines you take since the last study visit?"

AEs should be reported for any clinically relevant change in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.

Changes in any protocol specific parameters and questionnaires (if applicable) evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol specific parameter or questionnaire response that is clinically relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

12.3 Procedures for Recording and Reporting

Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on an Adverse Event Form (AEF). A separate AEF must be filed out for each event. When possible, signs and symptoms

indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity, (ie, severity), any action with study product taken as a result of the event, and an assessment of the AE's relationship to the study product.

Reporting Serious Adverse Events

All available information on SAE(s) and any other associated AE, if applicable, must be forwarded to the study Sponsor immediately (ie, within 24 hours of the Investigator's or site's knowledge of the event) as follows: In studies utilizing EDC, all available information for the SAE and any associated AE(s) must be entered immediately into the EDC system.

NOTE: Should the EDC system become non-operational, the site must complete the appropriate paper Serious Adverse Event Form. The completed form is communicated to the study Sponsor either by fax at [redacted] *or by email at* [redacted] *within 24 hours of the Investigator's or site's awareness, however, the reported information must be entered into the EDC system once it becomes operational.*

Additional information for any applicable event is to be reported as soon as it becomes available. Any complaints from the subject on a past event previous to initiation of the study but that is resolved at the time of the first visit must be reported to Alcon following the usual pharmacovigilance circuit.

Reporting Quality Complaints

Any malfunction or quality complaint, which occurs during this study must be reported within 10 calendar days via data entry within the clinical study EDC system or by fax to the Sponsor in the event that electronic data entry is not possible. See the MOP for the list of Study Staff personnel to contact.

The Investigator will be asked to determine whether they believe the study product was associated with, or contributed to, the event. This information is to be documented via data entry within the clinical study EDC system.

The Sponsor's Medical Safety Department is responsible for archiving and submitting all reportable quality complaints and AEs to the appropriate regulatory authorities.

12.4 Intensity and Causality Assessments

For every AE, the Investigator must assess the seriousness, intensity (severity) and causality (relationship to study product). Specifically, events should be classified as mild, moderate, or severe. The assessment of causality will be based upon the categories of related and not related. An assessment of causality will also be performed by Sponsor physician utilizing the same definitions. These classifications should be based on the following definitions:

Intensity (Severity):

- Mild An event is mild if the subject is aware of, but can easily tolerate the sign or symptom.
- Moderate An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
- Severe An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

Causality:

- Related An AE considered related to the use of the study product.

Adverse events classified as related may be either definitely related or possibly related where a direct cause and effect relationship between the study product and the event has not been demonstrated but there is a reasonable possibility that the event was caused by the study product.

- Not Related An AE considered unrelated to the use of the study product. Adverse events classified as not related may either be definitely unrelated or simply unlikely to be related (ie, there are other more likely causes for the AE).

For a SAE reported by an Investigator as not related that upon review of the available data by the Sponsor physician is assessed (upgraded) to be related, the Investigator will receive a notification.

12.5 Unmasking of the Study Information

Masked information on the identity of the assigned study product should not be disclosed during the study. If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate Sponsor representative prior to unmasking the information if there is sufficient time. Depending upon the individual

circumstances (ie, medical emergency), the code may be broken prior to contact with the Sponsor. The Sponsor must be informed in all cases in which the code was broken and of the circumstances involved. Additionally, the Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

12.6 Follow-Up of Safety Information

The Investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study. Any additional data from these follow-up procedures must be documented and available to the Sponsor who will determine when the data need to be documented on the case report forms.

12.7 Pregnancy in the Clinical Study

Women who are pregnant or breast-feeding are excluded from participation in the study. Women of childbearing potential or women considered post-menopausal are not excluded from the study as long as adequate birth control methods are being utilized. All women of childbearing potential are required to use adequate birth control methods which are summarized in the protocol's exclusion criteria.

Prior to clinical study enrollment, female subjects of childbearing potential must be advised of the importance of avoiding pregnancy during the study and the potential risks associated with an unintentional pregnancy. During the study, female subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. Sponsor must be contacted immediately, treatment discontinued, and the subject exited from the study.

In addition, complications of pregnancy may be reportable and will be decided on a case by case basis. A Sponsor prepared form will be utilized to capture all pregnancy related information until the outcome of the pregnancy.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor. If electronic records are maintained, the method of verification must be determined in advance of starting the study.

At a minimum, source documents should include the following information for each subject:

- Subject identification (name, sex, race/ethnicity)
- Documentation of subject eligibility
- Date of informed consent
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- Study medication accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

Case report forms will be provided to the sites (electronic); only designated individuals may complete the CRFs. The CRFs will be submitted at regular intervals based upon the clinical study visit schedule. It is expected that all data reported will have corresponding entries in the source documents and that the Principal Investigator will review the reported data and certify that the CRFs are accurate and complete. No subject identifiers should be recorded on the CRFs beyond subject number, and demographic information.

13.2 Data Review and Clarifications

The CRF data will be reviewed against the subject's source data by the study monitors to ensure completeness and accuracy. After monitoring has occurred at the clinical sites and the CRFs have been submitted, additional data clarifications and/or additions may be needed. Data clarifications and/or additions are documented and are part of each subject's CRFs.

13.3 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Sponsor and the Investigator's files will be reviewed as part of the ongoing

study monitoring. Financial information is not subject to regulatory inspection and should be kept separately.

Additionally, the Investigator must keep study records and source documents until the Sponsor provides written approval for their destruction. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the **latest** marketing approval).

14 References

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Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
03/06/2017 08:20:01	[redacted]	[redacted]
03/06/2017 14:20:17	[redacted]	[redacted]
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