Title Page

Protocol Title: A Multicenter, Single-masked, Randomized Study to Compare the Efficacy and Safety of a New Artificial Tear Formulation (011516X) with Systane® Ultra Multidose for 90 Days in Participants with Dry Eye Disease

Protocol Number: 2007-301-005

Amendment Number: 2

Interventions: 011516X

Brief Protocol Title: Efficacy and safety of a new artificial tear formulation compared with Systane Ultra multidose in participants with dry eye disease

Study Phase: 3

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Refer to the final page of this protocol for electronic signature and date of approval.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	June 2020
Amendment 1	February 2020
Original Protocol	July 2019

Amendment 2 (June 2020)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The rationale for changes implemented in Protocol Amendment 2 is to clarify inclusion and exclusion criteria such that there are no corneal staining scores that could potentially conflict, and to remove an error related to OSDI scores.

Section Number and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria, Inclusion Criterion 2.01	Added need not be the same eye at Screening and Baseline	Clarification
Section 5.1 Inclusion Criteria, Inclusion Criterion 2.02	Added need not be the same eye at Screening and Baseline or the same eye that meets Inclusion Criterion 2.01	Clarification
Section 5.2 Exclusion Criteria, Exclusion Criterion 1.02	Removed the lower bound of < 5 for the total cornea staining score, and changed application of the criterion from one or both eyes to either eye	Clarification to prevent potential corneal staining scores from conflicting with inclusion criterion 2.01
Section 8.1.3.5 Ocular Surface Disease Index Questionnaire	Removed sentence that reiterated entry criteria related to the OSDI score and contained an error (> 65)	Clarification to avoid unnecessarily repeating entry criteria language

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multicenter, Single-masked, Randomized Study to Compare the Efficacy and Safety of a New Artificial Tear Formulation (011516X) with Systane® Ultra Multidose for 90 Days in Participants with Dry Eye Disease

Protocol Number: 2007-301-005

Brief Title: Efficacy and safety of a new artificial tear formulation compared with Systane Ultra multidose in participants with dry eye disease

Study Phase: 3

Study Rationale: The purpose of this study is to evaluate the efficacy and safety of a new artificial tear formulation (NATF; 011516X) compared with Systane® Ultra multidose (MD) in participants with dry eye disease (DED). This study will provide final guidance towards selection of the formulation for commercialization and will support Allergan quality standards and product requirements.

Objectives and Endpoints:

Objectives	Measures
Primary	
• To evaluate the efficacy and safety of 011516X in participants with signs and symptoms of DED compared with Systane Ultra MD	*Primary Efficacy Measure* • Total staining (sum of corneal and conjunctival staining) *Secondary Efficacy Measure* • Current Symptom Survey *Other Efficacy Measures* • Corneal staining (modified National Eye Institute [NEI] grading scheme, with fluorescein) • Conjunctival staining (modified NEI grading scheme, with lissamine green) • Tear break-up time (TBUT, with fluorescein) • Schirmer test (with anesthesia) • Ocular Surface Disease Index© (OSDI) • Study Eye Drop Experience and Tolerability Questionnaire • Functional Vision Questionnaire • 5-Minute Blurry Vision and Ocular Discomfort Questionnaire *Safety Measures* • Adverse events (AEs) • Slit-lamp biomicroscopy • Currently corrected distance visual acuity • Best-corrected distance visual acuity (BCDVA) • Intraocular pressure (IOP) (participants with glaucoma or ocular hypertension [OHT] only)

Overall Study Design:

This study is designed as a multicenter, single-masked, randomized, 2-arm, parallel-group study comparing the efficacy and safety of a NATF (011516X) with Systane Ultra MD (see Figure 1-1). All qualified study participants will receive REFRESH PLUS® for approximately 7 days during a run-in period prior to the Day 1 (Baseline) visit. If still qualified at the Day 1 (Baseline) visit, participants will then be randomized in a 1:1 ratio to use 011516X or Systane Ultra MD, with central stratification by Day 1 (Baseline) total ocular staining score of the study eye (mild/moderate = score of 6 to 25 versus [vs] severe = score of 26 to 43). The primary efficacy measure is total ocular staining and the primary analysis timepoint is at Day 90.

Number of Participants:

Approximately 400 participants (200 participants in each arm) will be randomized in order to have 340 participants (170 participants in each arm) complete the study through Day 90, assuming an approximate 15% dropout rate. Participants who prematurely discontinue from the study will not be replaced.

Number of Sites:

The study will be conducted at approximately 28 sites in the United States (US).

Intervention Groups and Study Duration:

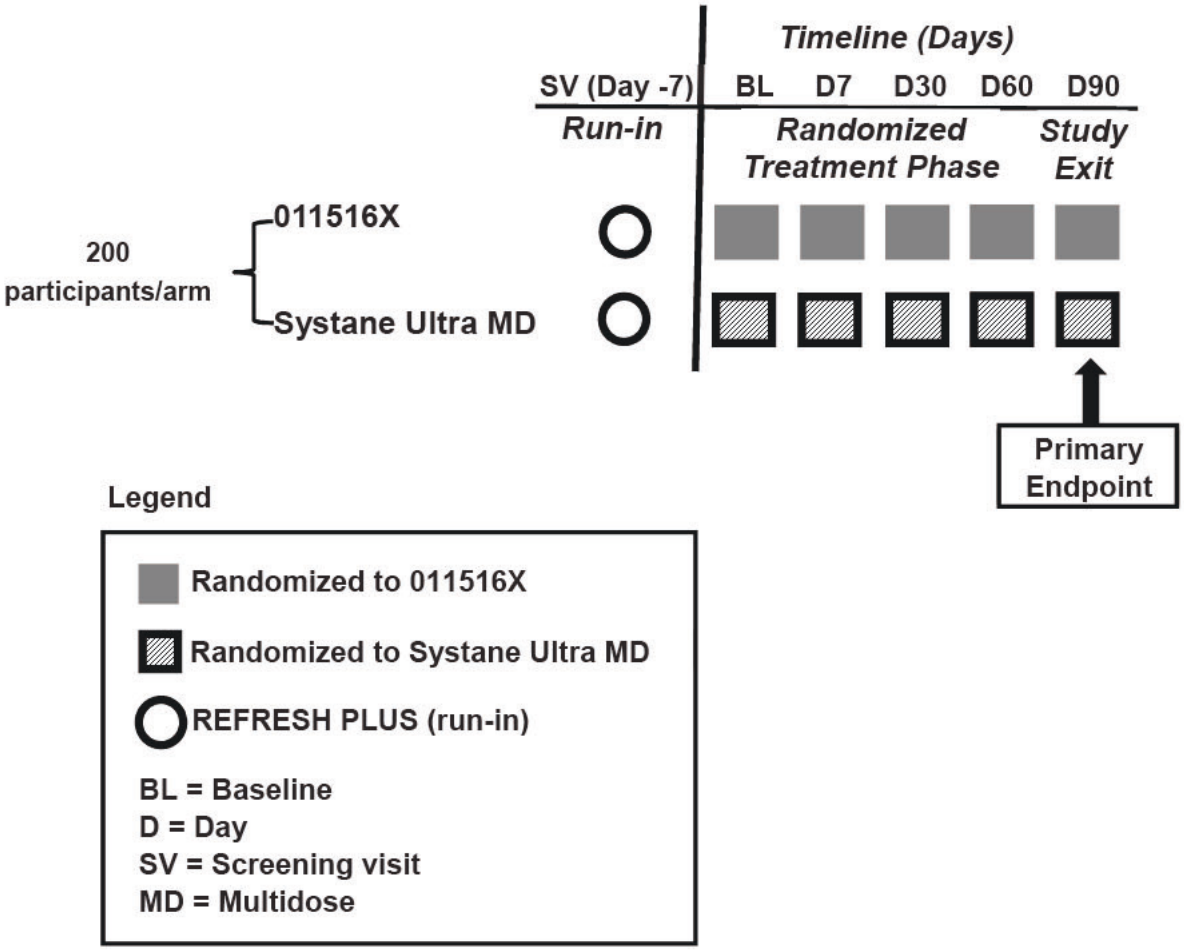
All qualified study participants will receive REFRESH PLUS for approximately 7 days during a run-in period prior to the Day 1 (Baseline) visit. Participants will be instructed to instill 1 to 2 drops of the run-in medication in each eye, 3 times per day for 7 days. If still qualified at the Day 1 (Baseline) visit, participants will then be randomized in a 1:1 ratio to use 011516X or Systane Ultra MD, with central stratification by Day 1 (Baseline) total ocular staining score of the study eye (mild/moderate = score of 6 to 25 vs severe = score of 26 to 43). Participants will be instructed to instill 1 to 2 drops of their assigned study intervention (investigational eye drops) in each eye, 3 times per day for approximately 90 days.

Data Monitoring Committee: There will be no Data Monitoring Committee for this study.

1.2. Schema

The study design is presented in Figure 1-1.

Figure 1-1 **Study Schema**



1.3. Schedule of Activities (SoA)

Study procedures are recommended to be done in sequence as listed in the schedule below.

Study Day	Screening (Day -7)	Day 1 (Baseline)	Day 7	Day 30	Day 60	Day 90/ Early Exit	Notes
Visit Window	(-3 days)		(±3 days)	(±7 days)	(±7 days)	(±7 days)	Each follow-up visit should be consistently scheduled within ±90 minutes of the time of the Day 1 (Baseline) visit.
Written informed consent and written documentation in accordance with the relevant country and local privacy requirements (HIPAA for US sites)	X						
Inclusion/exclusion criteria assessment	X	X					
Demography	X						
Self-assessed surveys/questionnaires:							Not performed if a participant reports use of a prohibited intervention. Does not apply to Screening visit.
Study Eye Drop Usage Questionnaire		X	X	X	X	X	
Current Symptom Survey	X	X	X	X	X	X	
OSDI Questionnaire	X	X	X	X	X	X	
Study Eye Drop Experience and Tolerability Questionnaire			X	X	X	X	
Functional Vision Questionnaire		X	X	X	X	X	
Medical and ophthalmic histories	X	X					
Prestudy or concomitant medication assessment	X	X	X	X	X	X	
Urine pregnancy test (for females of childbearing potential only)	X					X	
Currently corrected distance visual acuity	X	X	X	X	X	X	
Best-corrected distance visual acuity	X					X	

Study Day	Screening (Day -7)	Day 1 (Baseline)	Day 7	Day 30	Day 60	Day 90/ Early Exit	Notes
Visit Window	(-3 days)		(±3 days)	(±7 days)	(±7 days)	(±7 days)	Each follow-up visit should be consistently scheduled within ±90 minutes of the time of the Day 1 (Baseline) visit.
Biomicroscopy	X	X	X	X	X	X	
Tear break-up time (with fluorescein)	X	X	X	X	X	X	Not performed if a participant reports use of a prohibited intervention.
Corneal staining (modified NEI grading scheme, with fluorescein)	X	X	X	X	X	X	Not performed if a participant reports use of a prohibited intervention.
Conjunctival staining (modified NEI grading scheme, with lissamine green)	X	X	X	X	X	X	Not performed if a participant reports use of a prohibited intervention.
Schirmer test (with anesthesia)	X	X	X	X	X	X	Not performed if a participant reports use of a prohibited intervention.
Intraocular Pressure (Goldmann applanation tonometer)	X	X	X	X	X	X	After the Screening visit, this needs to be completed only for participants who are treated for glaucoma or ocular hypertension.
Adverse event assessment	X	X	X	X	X	X	
Access IxRS	X	X		X	X	X	
Randomization		X					
Run-in medication dispensed	X						
Run-in medication returned		X					
Study intervention dispensed		X		X	X		
Predose and postdose 5-Minute Blurry Vision and Ocular Discomfort Questionnaire		X				X	Must be performed at least 20 minutes after anesthesia application. Not performed if a participant reports use of a prohibited intervention.
Used and unused study intervention returned				X	X	X	

HIPAA = Health Insurance Portability and Accountability Act; IxRS = interactive response system; NEI = National Eye Institute; OSDI = ocular surface disease index; US = United States

2. Introduction

2.1. Study Rationale

The purpose of this study is to evaluate the efficacy and safety of a new artificial tear formulation (NATF; 011516X) compared with Systane® Ultra multidose (MD) in participants with dry eye disease (DED). This study will provide final guidance towards selection of the formulation for commercialization and will support Allergan quality standards and product requirements.

2.2. Background

Dry eye disease is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Craig 2017). An estimated 25 million Americans are reported to have DED, making DED one of the most common reasons patients seek care with their eye care professional (Behrens 2006, Stapleton 2017).

Mechanistically, DED is recognized as a disturbance of the lacrimal functional unit, an integrated system comprised of the ocular surface (cornea, conjunctiva, accessory lacrimal glands, and Meibomian glands), the main lacrimal glands, and the sensory and interconnecting innervation (Stern 1998). The diagnosis and classification (ie, mild/moderate/severe) of DED is achieved by assessing both clinical signs (ocular surface epithelial damage [corneal and conjunctival staining]), tear volume (Schirmer score), tear film stability (tear break-up time [TBUT]), and patient-reported symptoms (questionnaires such as the Ocular Surface Disease Index© [OSDI] and Eye Dryness Score - Visual Analog Scale [EDS-VAS]) (Wolffsohn 2017).

The normal tear film is a relatively stable, thin film composed of a superficial lipid layer and an aqueous layer intermixed with a mucus gel layer, which is partially adherent to the corneal and conjunctival surface epithelium. The tear film is important for lubrication, protection, and nourishment of the ocular surface and serves as the primary refractive surface of the eyes visual system. DED is a complex disease characterized by a dysfunction of 1 or more components of the tear film, leading to the loss of tear film stability, a hyperosmolar shift in the tear film osmotic balance, and/or an inadequate amount of fluid on the ocular surface. This is characterized by rapid break-up of the tear film and numerous symptoms, including burning/stinging, foreign body sensation, blurred vision and photophobia.

DED is often brought about or exacerbated by a variety of adverse environmental conditions, including prolonged computer use (visual display terminal syndrome), excessive wind or air conditioning, and overheated or dry air. The majority of patients with DED are initially managed with artificial tears. Environmental modifications, lid compresses and scrubs, and the addition of essential fatty acids to the diet are often recommended as well. With advancing severity of DED, treatment options, if needed, can include topical cyclosporine or other anti-inflammatory

medications, as well as surgical options ranging from insertion of punctal plugs to tarsorraphy of the eyelids (Jones 2017).

The NATF (011516X) under investigation in this study is a sterile, buffered, preservative-free artificial tear solution that is designed to provide protection to the ocular surface and improve symptoms of DED. The NATF 011516X is specifically formulated to relieve DED symptoms such as burning, irritation, and eye dryness and to protect against further irritation. The NATF contains carboxymethylcellulose and glycerin as active ingredients that lubricate and moisturize the ocular surface. The solution also contains other inactive compatible solutes such as carnitine, erythritol, and trehalose. The NATF 011516X conforms to the US Food and Drug Administration (FDA) monograph on ophthalmic demulcents.

The comparator product is Systane Ultra MD from Alcon, which is currently one of the leading marketed artificial tear products in the US. Key ingredients in Systane Ultra MD include polyethylene glycol 400 (0.4%), propylene glycol (0.3%), and hydroxypropyl guar.

The purpose of this study is to evaluate the efficacy and safety of the NATF 011516X compared with Systane Ultra MD.

2.3. Benefit/Risk Assessment

To date, management and treatment of DED remains a large unmet medical need. Current mainstays include use of artificial tears and in more severe cases, tear retention (temporarily or permanently plugging the tear ducts) and anti-inflammatory therapies. Each approach has its own risk-benefit ratio. Artificial tears have been used in DED for decades and have proven to be safe and effective for lubricating and protecting the ocular surface from further irritation and relieving DED symptoms. Very few adverse events (AEs) are generally reported with artificial tears, such as blurred vision, eye redness, discomfort or other irritation not present before use of artificial tears, increased light sensitivity, matting or stickiness of eyelashes, swelling of eyelids, and watering of eyes. Because the risk-benefit ratio with artificial tears is low, they have been recognized as the first-line DED management option in both historical and contemporary practice ahead of the alternatives mentioned above.

Patients with DED generally present with ocular surface epithelial damage attributed to either or both inadequate tear production and tear film instability. These pathophysiological changes are generally accompanied by patient-reported symptoms of ocular surface discomfort, often described as dryness, burning, pain, blurred vision and grittiness.

For many people with DED symptoms, the regular use of artificial tears represents a suitable and affordable option. Artificial tears are used to lubricate the eyes and relieve burning, irritation, and eye dryness attributed to DED as well as protect against further irritation. The benefit of the new generation of artificial tears developed by Allergan is their ability to improve DED symptoms and provide lubrication and protection against further irritation, thus providing a valuable option for patients with DED.

The use of artificial tears is safe and well-tolerated and there are no unexpected safety concerns, although common side effects may include the following: mild eye burning or irritation, itching

or redness of eyes, watery eyes, blurred vision, unpleasant taste in mouth, and/or allergy to the product or its ingredients.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of 011516X may be found in the investigator's brochure (IB).

3. Objectives and Endpoints

Objectives	Measures
Primary • To evaluate the efficacy and safety of 011516X in participants with signs and symptoms of DED compared with Systane Ultra MD	*Primary Efficacy Measure* • Total staining (sum of corneal and conjunctival staining) *Secondary Efficacy Measure* • Current Symptom Survey *Other Efficacy Measures* • Corneal staining (modified National Eye Institute [NEI] grading scheme, with fluorescein) • Conjunctival staining (modified NEI grading scheme, with lissamine green) • Tear break-up time (TBUT, with fluorescein) • Schirmer test (with anesthesia) • OSDI • Study Eye Drop Experience and Tolerability Questionnaire • Functional Vision Questionnaire • 5-Minute Blurry Vision and Ocular Discomfort Questionnaire *Safety Measures* • AEs • Slit-lamp biomicroscopy • Currently corrected distance visual acuity • Best-corrected distance visual acuity (BCDVA) • Intraocular pressure (IOP) (participants with glaucoma or ocular hypertension [OHT] only)

4. Study Design

4.1. Overall Design

This study is designed as a multicenter, single-masked, randomized, 2-arm, parallel-group study comparing the efficacy and safety of a NATF (011516X) with Systane Ultra MD (see Figure 1-1). All qualified study participants will receive REFRESH PLUS® for approximately 7 days during a run-in period prior to the Day 1 (Baseline) visit. Participants will be instructed to instill 1 to 2 drops of the run-in medication in each eye, 3 times per day for 7 days. If still qualified at the Day 1 (Baseline) visit, participants will then be randomized in a 1:1 ratio to use 011516X or Systane Ultra MD, with central stratification by Day 1 (Baseline) total ocular staining score of the study eye (mild/moderate = score of 6 to 25 vs severe = score of 26 to 43). Participants will be instructed to instill 1 to 2 drops of their assigned study intervention (investigational eye drops) in each eye, 3 times per day for approximately 90 days. The primary efficacy measure is total ocular staining and the primary analysis timepoint is at Day 90.

Approximately 400 participants (200 participants in each arm) will be enrolled at approximately 28 sites in the US in order to have 340 participants (170 participants in each arm) complete the study through Day 90, assuming an approximate 15% dropout rate. Participants who prematurely discontinue from the study will not be replaced.

4.2. Scientific Rationale for Study Design

This Phase 3 clinical study is designed to evaluate the efficacy and safety of the NATF 011516X versus a leading marketed artificial tear product, Systane Ultra MD, over a 90-day study intervention period in participants with DED.

The test formulation contains the same active ingredients (carboxymethylcellulose and glycerin) as the currently marketed REFRESH OPTIVE products. The solution also contains other inactive compatible solutes such as carnitine, erythritol, and trehalose.

The formulation of Systane Ultra MD incorporates hydroxypropyl-guar, and is currently the market leader.

The present study is designed to compare the relative relief of symptoms of DED between the formulations as well as to characterize the effect on ocular surface staining. In order to be able to show a reduction in DED symptoms and in ocular surface staining at Day 90, the inclusion criteria were selected to include a participant population with clinically significant ocular surface staining and symptoms of DED at the Screening (Day -7) and Day 1 (Baseline) visits. These participants are anticipated to have a clinically treatable condition with sufficient room for improvement.

4.3. Justification for Dose

The dosing regimen during the study will be to instill 1 to 2 drops in each eye, 3 times per day. Although use as needed is the typical dosing instruction in artificial tear product label, for this specific study, a controlled dose is necessary to ensure accurate comparison between the test and

control arms. Dosing 3 times per day is based on the average dosing frequency from prior Allergan artificial tear product clinical studies.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (Day 90).

5. Study Population

The study population will consist of adult male and female participants with objective and subjective evidence of DED. Approximately 400 participants will be randomized at approximately 28 US sites in order to have 340 participants (170 participants in each arm) complete the study, assuming an approximate 15% dropout rate.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be ≥ 18 years of age
2.	**Type of Participant and Disease Characteristics**
2.01	At the Screening (Day -7) and Baseline (Day 1) visits, at least 1 eye must qualify with both of the following ocular staining scores: • Corneal staining score of ≥ 0 to ≤ 4 in each of the 5 zones with a total of ≥ 5 to ≤ 19 based on the modified NEI grading scheme (score range = 0 to 5; graded in 5 zones of the cornea for a total score range of 0 to 25) • Conjunctival staining score of ≥ 0 to ≤ 4 in each of the 6 zones with a total of ≥ 1 based on the modified NEI grading scheme (score range = 0 to 5 per zone) (Need not be the same eye at Screening and Baseline)
2.02	At the Screening (Day -7) and Baseline (Day 1) visits, have 3 consecutive TBUT tests of ≤ 10 seconds in at least 1 eye (Need not be the same eye at Screening and Baseline or the same eye that meets Inclusion Criterion 2.01)
2.03	At the Screening (Day -7) and Baseline (Day 1) visits, have a Current Symptom Survey total mean score of ≥ 25
2.04	At the Screening (Day -7) visit, have an OSDI total score of ≥ 23; and at Baseline (Day 1) visit, have an OSDI total score of ≥ 18, with no more than 3 responses answered as not applicable (N/A)

2.05	Have used an artificial tear product for DED within 6 months of the Screening (Day -7) visit
2.06	Have ability/agreement to continue to wear existing current spectacle correction during the study period (if applicable)
2.07	Have corrected distance visual acuity of at least 20/32 Snellen equivalent in each eye using the 3-meter LogMar chart, with current correction (if necessary) at Screening (Day -7) visit
2.08	If using any form of topical ophthalmic cyclosporine (ie, RESTASIS®) or lifitegrast 5% ophthalmic solution (Xiidra®), participants must be using the drops for ≥ 90 days prior to the Screening (Day -7) visit and plan to continue without change for the duration of the study
3.	**Sex**
3.01	Male or female
4.	**Contraceptives**
4.01	A female participant is eligible to participate if she is not pregnant (ie, has a negative in-office urine pregnancy test at Screening [Day -7] and does not verbally report pregnancy at the Day 1 [Baseline] visit; see Appendix 6), is not breastfeeding, and at least 1 of the following conditions applies: a. A woman not of childbearing potential (WOCBP) as defined in Appendix 6 OR b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 for the duration of the study
5.	**Informed Consent**
5.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
5.02	Written informed consent from the participant has been obtained prior to any study-related procedures
5.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable

6.	Other
6.01	Able, as assessed by the investigator, to understand and willing to complete all study-related questionnaires/surveys, follow study instructions and likely to complete all required study visits

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	Medical Conditions
1.01	Have uncontrolled severe systemic disease that, in the assessment of the investigator, would put safety of the participant at risk through participation, or which would prevent or confound protocol-specified assessments (eg, hypertension and diabetes, Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, immunodeficiency disease, etc.)
1.02	At the Screening (Day -7) or Baseline (Day 1) visits, either eye has • Corneal staining score of 5 in any of the 5 zones or a total score of > 19 based on the modified NEI grading scheme (score range = 0 to 5; graded in 5 zones of the cornea for a total score range of 0 to 25) or • Conjunctival staining score of 5 in any of the 6 zones based on the modified NEI grading scheme (score range = 0 to 5 per zone)
1.03	Participant has worn contact lenses in the last 90 days prior to the Screening (Day -7) visit and/or participant anticipates contact lens wear during the study
1.04	Have any scheduled or planned systemic surgery or procedure during the study, which in the investigator's opinion, may impact the participant's study participation

1.05	Presence of 1 or more of the following ocular conditions: • Active ocular infection or non-keratoconjunctivitis sicca (KCS) ocular inflammation • Active ocular allergy • History of recurrent herpes keratitis or active disease within 6 months prior to the Screening (Day -7) visit • Corneal disorder or abnormality that affects corneal sensitivity or normal spreading of the tear film (except superficial punctate keratitis) • Severe blepharitis or obvious inflammation of the lid margin, which in the judgment of the investigator, may interfere with the interpretation of the study results • Keratoconjunctivitis sicca secondary to the destruction of conjunctival goblet cells, such as occurs with vitamin A deficiency or scarring such as that with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation • Substantial non-KCS keratitis with overlying corneal stain or other significant corneal findings not directly related to DED; in addition, participants with DED signs/symptoms (eg, filamentary keratitis) of a severity where topical monotherapy with an artificial tear would be inappropriate
2.	**Prior/Concomitant Therapy**
2.01	The start date of any systemic medication (including over-the-counter [OTC], herbal, prescription, or nutritional supplements) which may affect DED or vision is < 90 days prior to the Screening (Day -7) visit or a change in dosage is anticipated during the study. Systemic medications, which may affect DED or vision, include but are not limited to the following: flax seed oil, fish oil, omega-3 supplements, cyclosporine, antihistamines, cholinergic agents, anticholinergics, antimuscarinics, beta blocking agents, tricyclic antidepressants, phenothiazines, estrogen, progesterone, and other estrogen derivatives
2.02	Have occlusion of the lacrimal puncta for either eye, with punctal plugs or cauterization < 6 months prior to the Screening (Day -7) visit or anticipated use of such procedures during the study
2.03	Use of lid-heating therapy (ie, LipiFlow®, iLUX®, etc.), Meibomian gland probing, or therapeutic Meibomian gland expression in either eye < 6 months prior to the Screening visit (Day -7) or anticipated use during the study

2.04	Have history of ocular/ophthalmic surgery or trauma, which could affect corneal sensitivity and/or tear distribution (eg, cataract surgery, laser-assisted in situ keratomileusis [LASIK], photorefractive keratectomy, or any surgery involving a limbal or corneal incision) within 12 months prior to the Screening (Day -7) visit
2.05	Are currently using topical ocular medication (OTC, herbal or prescription) or TrueTear® (intranasal neurostimulator), or have used topical ocular medication (OTC, herbal or prescription) or TrueTear within 1 month of the Screening (Day -7) visit or plan use of such treatments during the study. Exception: participants who are using the following can be considered: • Marketed artificial tear product for the management of DED, which must be discontinued at the Screening (Day -7) visit • Monotherapy for glaucoma or OHT using a prostaglandin analog, beta blocker, alpha-2 agonist, or carbonic anhydrase inhibitor; any topical IOP-lowering medications must have a start date of ≥ 90 days prior to the Screening (Day -7) visit and dosage is not expected to change during the study • Cyclosporine topical ophthalmic preparation (eg, RESTASIS or other ophthalmic form) or lifitegrast 5% ophthalmic solution (Xiidra), with a start date of ≥ 90 days prior to the Screening (Day -7) visit and dosage is not expected to change during the study **NOTE:** ***Participants currently being treated with BOTH an IOP-lowering medication and topical ocular cyclosporine or lifitegrast cannot be enrolled.***
2.06	IOP > 21 mm Hg at the Screening (Day -7) visit in both eyes. Participants with primary open-angle glaucoma or OHT may be included provided they are on stable monotherapy bilaterally as mentioned in exclusion criterion 2.05, with both eyes IOP controlled (≤ 21 mm Hg). The type of medication will be recorded at the Screening (Day -7) visit along with other concomitant medications
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Are currently enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study at the Screening (Day -7) visit
4.	**Diagnostic Assessments**
4.01	Have a Schirmer test (with anesthesia) ≤ 2 mm in either eye at the Screening (Day -7) visit
4.02	Report an average daily artificial tear use of > 6 times per day within 6 months of the Screening (Day -7) visit
5.	**Other**

5.01	Females who are pregnant, nursing, or planning a pregnancy during the study ***or*** females who are of childbearing potential and not using a reliable method of contraception (see Appendix 6)
5.02	Have history of allergies or sensitivity to the study interventions or its components (including all REFRESH and Systane product lines) or diagnostics (eg, topical ocular anesthetic, sodium fluorescein, or lissamine green)
5.03	Have a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study
5.04	Are directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator or other study staff member; employee of Allergan or a first-degree family member, significant other or relative residing with one of the above persons involved directly or indirectly in the study; are enrolled in this study at another clinical site; or, are a student with a direct relationship with the investigator or investigational site staff

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened with sponsor pre-approval.

6. Study Intervention

Study intervention is defined as any investigational interventions intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

The study interventions to be administered are as follows:

Study Intervention Name	NATF (011516X)	Systane Ultra MD	REFRESH PLUS (8197X)
Dosage Formulation	Topical eye drop	Topical eye drop	Topical eye drop
Manufacturer	Allergan, Waco, TX	Alcon	Allergan, Waco, TX
Identity of Formulation and Strengths	Carboxymethyl-cellulose sodium 0.5% Glycerin 0.9% with trehalose	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Carboxymethyl-cellulose sodium 0.5%
Route of Administration	Topical eye drop	Topical eye drop	Topical eye drop
Dosing Instructions	Instill 1 to 2 drops in each eye, 3 times per day	Instill 1 to 2 drops in each eye, 3 times per day	Instill 1 to 2 drops in each eye, 3 times per day
Packaging and Labeling	Study intervention will be provided in unit-dose vials. Study intervention will be labeled as required.	Study intervention will be provided in MD bottles. Study intervention will be labeled as required.	Study intervention will be provided in unit-dose vials. Study intervention will be labeled as required.
Number and Timing of Interventions	Participants will administer 1 to 2 drops in each eye 3 times daily	Participants will administer 1 to 2 drops in each eye 3 times daily	Participants will administer 1 to 2 drops in each eye 3 times daily
Volume Per Intervention Vial or Bottle	0.4 mL vial	10 mL bottle	0.4 mL vial

As this is a single-masked study, 011516X and Systane Ultra MD will each be supplied in identical outer cartons (kit). Each kit label will include the study number, kit number, and a place for the site to write-in the participant's study ID once assigned by the interactive response system (IxRS) to a particular participant.

6.1.1. Run-in Medications and Administration

The REFRESH PLUS solution (8197X) contains the following: CMC sodium, sodium hydroxide, sodium chloride, sodium lactate, potassium chloride, calcium chloride, magnesium chloride, and water for injection/purified water. The solution is supplied in 0.4 mL unit-dose vials. The solution is sterile and isotonic.

6.1.2. Study Supplies

The following supplies will be provided by Allergan:

- Urine pregnancy tests
- Distance logarithmic visual acuity chart for testing at 3 meters
- Stopwatch (for TBUT)
- 2% preservative-free liquid sodium fluorescein (for TBUT and corneal staining)
- Micropipettes and sterile disposable tips (for fluorescein administration)
- Yellow barrier filter (for TBUT and corneal staining with fluorescein)
- Lissamine green strips (for conjunctival staining)
- Saline (used to wet the lissamine green strips)
- Timer (for Schirmer test with anesthesia)
- Topical anesthetic (for IOP measure and Schirmer test)
- Schirmer strips (for Schirmer test with anesthesia)
- Visual analog scale ruler (for converting the participant's VAS responses to numerical values)

The following will be provided by the investigator:

- Slit-lamp biomicroscope
- Goldmann applanation tonometer
- Internet connection (high-speed connection for electronic case report form [eCRF] completion)
- Temperature monitoring device for study intervention storage

6.1.3. Instructions for Use and Administration

At Screening (Day -7), run-in medication (REFRESH PLUS) will be dispensed to each eligible participant. Each participant will be instructed to instill 1 to 2 drops in each eye, 3 times per day. The same vial can be used for both eyes, and should be used 1 time only. The used and unused vials should be collected and returned to the sites for accountability as instructed.

Assigned study intervention will be dispensed to each randomized participant at the Days 1, 30, and 60 by the impartial dispenser. Participants randomized to the NATF unit-dose formulation (011516X) will be instructed to instill 1 to 2 drops in each eye, 3 times per day. The same vial

can be used for both eyes, and should be used 1 time only. The used and unused vials should be collected and returned to the site for accountability as instructed. Participants randomized to Systane Ultra MD (10 mL bottles) are to use 1 bottle until the bottle is empty, and then use a new bottle. Both the used and unused bottles are to be returned to the site for accountability as instructed. If the participant is concurrently using an ocular cyclosporine product, lifitegrast 5% ophthalmic solution (Xiidra) or glaucoma therapy drops as allowed per inclusion/exclusion criteria during the study, the participant should be instructed to wait a minimum of 15 minutes between drop instillations (with study intervention being administered first). ***In addition, participants should be instructed to not use study intervention within 4 hours of each follow-up visit (ie, Days 7, 30, 60, and 90/Early Exit).***

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. Participants will be instructed on the proper storage of study intervention and to keep it out of the reach of children at all times.
4. Acceptance of the returned used and unused vials and used and unused bottles should be handled by the impartial dispenser. However, the investigator, institution, or the head of the medical institution (where applicable) is ultimately responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. At the end of the study, all used and unused study intervention will be reconciled and used and unused vials and bottles must be returned to Allergan.

6.3. Measures to Minimize Bias: Randomization and Masking

This study will use a 1:1 treatment allocation to 011516X:Systane Ultra MD, with a central stratification by Day 1 (Baseline) total ocular staining score in the study eye (mild/moderate = score of 6 to 25 vs severe = score of 26 to 43). The study eye is defined as the worst eye based on total ocular staining score at Day 1 (Baseline). If both eyes have the same total ocular staining score, the right eye will be designated as the study eye.

Prior to initiation of study intervention, each participant who provides informed consent will be assigned to a participant number through an automated IxRS that will serve as the participant's identification number on all study documents. Participant numbers will be assigned in ascending order across all sites and should not be omitted or reused.

At the end of the Screening (Day -7) visit, all eligible participants will receive a run-in medication kit (REFRESH PLUS) for use during the 7-day run-in period. Sites will dispense the run-in medication kit according to the IxRS instructions.

At the end of the Day 1 (Baseline) visit, all eligible participants will be stratified by their Day 1 (Baseline) study eye total ocular staining score and be randomly assigned to 1 of 2 treatment arms in a 1:1 ratio based on a randomization scheme prepared by Allergan Biostatistics. This will require the delegated site personnel to enter the participant's Screening Visit (Day -7) and Baseline (Day 1) total corneal and conjunctival staining scores of each eye directly into IxRS. IxRs will then determine which eye is the study eye and assign the participant to a stratification group and a treatment arm, thus providing the site with the specific study intervention kit assignment. Sites will dispense study intervention according to the IxRS instructions.

Sites will also need to access the IxRS at the Days 30 and 60 visits to obtain a study intervention kit (30-day supply) number to dispense to the participant. Sites will receive the IxRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

In addition, sites will need to access IxRS to "complete" the participant at Day 90 or to "discontinue" the participant if they exit the study early.

6.4. Study Intervention Compliance

When the participants are dispensed their intervention kits (Days 1 [Baseline], 30, and 60), they will be instructed to use 1 to 2 drops in each eye, 3 times per day.

Study intervention compliance will be monitored by: 1) having the participants complete the Study Eye Drop Usage Questionnaire at Day 1 (Baseline) and at each follow-up visit, and 2) having the participants return both their used and unused vials for those participants stratified to the NATF formulation and both their used and unused bottles for those participants stratified to Systane Ultra MD.

The used and unused vials and bottles will be returned at each participant's Day 30, Day 60, and Day 90/Early Exit Visits and the study site's impartial dispenser will keep an accurate record of what is dispensed and returned for each participant throughout the study.

6.5. Concomitant Therapy

The use of any new concomitant medication, prescription or OTC, is to be recorded on the participant's source document at each visit along with the reason the medication is being taken.

At Screening (Day -7), Baseline (Day 1), and at each follow-up visit, study staff will question each participant specifically on the use of concomitant medications. Whenever possible, study staff should notify Allergan immediately if a participant uses any concomitant medications not permitted by the protocol. Participants who used prohibited concomitant medications (see Section 6.5.3), will be discontinued from the study and early termination procedures pertaining to safety assessments are recommended to be followed (see Section 1.3).

6.5.1. Prohibited Treatments and Washout Before the Study

Any systemic medication (including OTC, herbal, prescription, or nutritional supplements) that may affect DED or vision should be stably used for at least 90 days prior to the Screening (Day -7) visit. Systemic medications, which may affect DED or vision, include but are not limited to the following: flax seed oil, fish oil, omega-3 supplements, cyclosporine, antihistamines, cholinergic agents, anticholinergics, antimuscarinics, beta-blocking agents, tricyclic antidepressants, phenothiazines, estrogen, progesterone, and other estrogen derivatives.

Contact lens use is prohibited 90 days prior to the screening (Day -7) visit. Participants are not allowed to have any scheduled or planned ocular or systemic surgery or procedure during the study that, in the investigator's opinion, may inhibit the participant's study participation. Participants are not allowed to receive temporary or permanent occlusion or cauterization of the lacrimal puncta < 6 months prior to the Screening (Day -7) visit.

Participants should not have ocular/ophthalmic surgery or trauma, which could affect corneal sensitivity and/or tear distribution (eg, cataract surgery, LASIK, photorefractive keratectomy, or any surgery involving a limbal or corneal incision) within 12 months prior to the Screening (Day -7) visit.

Participants should not use lid-heating therapy (ie, LipiFlow, iLUX, etc.), Meibomian gland probing, or therapeutic Meibomian gland expression in either eye within 6 months prior to the Screening (Day -7) visit.

Participants should not use TrueTear or other topical ocular medications (OTC or prescription), except the monotherapy for glaucoma or OHT, or cyclosporine topical ophthalmic preparation (eg, RESTASIS or other ophthalmic form) or lifitegrast 5% ophthalmic solution (Xiidra) within 1 month of the Screening (Day -7) visit.

Lastly, nonstudy artificial tear products can only be used before the Screening (Day -7) visit and cannot be used for the remainder of the study.

6.5.2. Permitted Treatments

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. Systemic medications that **do not** cause or affect DED, dry mouth, changes in vision (as per exclusion criterion 2.01) or other ocular changes are considered permissible medications. Use of artificial tear products will be limited to only REFRESH PLUS during the run-in period. Thereafter, use of any artificial tear product, except the assigned study intervention, is prohibited for the duration of the study. Topical ocular medications are not allowed during the study, except for participants meeting all inclusion and exclusion criteria for their use of monotherapy for glaucoma or OHT, or use of a cyclosporine topical ophthalmic preparation (eg, RESTASIS or other ophthalmic form) or lifitegrast 5% ophthalmic solution (Xiidra). Participants using any of these products, should continue to use their drops at the same dose and frequency for the duration of the study. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the following:

- Indication
- Dates of administration including start and end dates
- Dosage information including route, dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact Allergan.

Allergan should be contacted if there are any questions regarding prior or concomitant therapy.

Any medication taken during the study between the date of the first dose (Day 1 [Baseline]) of study intervention and the date of the study exit will be recorded on the source document as a concomitant medication; any medication started after the study exit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Prohibited Treatments During the Study

- Participants are not allowed to have any scheduled or planned ocular or systemic surgery or procedure during the study that, in the investigator's opinion, may inhibit the participant's study participation.
- Participants are not allowed to receive temporary or permanent occlusion or cauterization of the lacrimal puncta during the study.
- After Screening (Day -7), participants should not begin or stop the use of or change dose on any systemic medications (OTC, herbal, prescription, or nutritional supplements) that may affect a dry eye condition or affect vision (eg, may cause blurred vision, cataracts, or glaucoma). ***Sites should look up the potential adverse reactions of each medication to ensure they do not fall within these exclusionary drug families***. The following exceptions are applicable after the Screening Visit (Day -7) for participants that initiate the following to facilitate short-term treatment of systemic conditions such as allergies, cold/flu, and pain/headache:
    - Use of systemic antihistamines for up to 7 consecutive days
    - Use of cold/flu medications used for up to 7 consecutive days
    - Use of over-the-counter pain medications (aspirin, acetaminophen, etc.) for up to 7 consecutive days
- Participants should not use any lid-heating therapy (ie, LipiFlow, iLUX, etc.), Meibomian gland probing, or therapeutic Meibomian gland expression in either eye during the study.
- Participants should not begin or stop any topical ophthalmic medication.

- Participants should not change dose on allowable topical ophthalmic medications per inclusion/exclusion criteria (monotherapy for glaucoma or OHT, cyclosporine topical ophthalmic preparation (eg, RESTASIS or other ophthalmic form) or lifitegrast 5% ophthalmic solution (Xiidra) while enrolled in the study.
- Participants may not use any artificial tear product, except the run-in medication (during the screening period) and the assigned study intervention (after randomization).
- The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

6.5.4. Rescue Medicine

Rescue medicine is not applicable.

6.6. Dose Modification

Dose modification is not applicable.

6.7. Intervention after the End of the Study

No interventions after the end of the study are planned.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant, who signs the ICF and is dosed, ceases participation in the study and the completion of the protocol-defined study procedures and visits, regardless of the circumstances.

Reasons for discontinuation from the study treatment and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
AE	Death
Lack of efficacy	
Lost to follow-up	
Noncompliance with study intervention	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by Allergan	
Study terminated by Allergan	
Withdrawal by participant	

7.1. Discontinuation of Study Intervention

See the SoA (Section 1.3) for data to be collected at the time of early exit.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Participants will be discontinued if they use any prohibited treatments described in Section 6.5.3 of this protocol.
- For participants who discontinue the study early, every effort should be made to have these participants return to the clinical center for completion of the early exit visit. Adverse events leading to a participant's early discontinuation must be followed up as appropriate.
- If the participant withdraws consent for disclosure of future information, Allergan may retain and continue to use any data collected before such a withdrawal of consent.

- See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Any safety concerns should be discussed with Allergan immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screen failure, as applicable.

8.1. Efficacy Assessments

Efficacy assessments include the following: corneal staining, conjunctival staining, Schirmer test (with anesthesia), OSDI score, TBUT, and self-assessed questionnaires/surveys.

Timing and measurement details are provided in Table 8-1.

Table 8-1 Efficacy Assessments

Assessment	Timing	Measurement
Primary Efficacy Measure		
Total staining	• Screening and Days 1, 7, 30, 60, and 90/Early Exit	• Total staining score will be the sum of corneal and conjunctival staining score.
Secondary Efficacy Measure		
Current Symptom Survey	• Screening and Days 1, 7, 30, 60, and 90/Early Exit	• A self-assessed 6-item visual analog scale (VAS) survey that assesses various symptoms of DED disease.
Other Efficacy Measures		
Corneal Staining (modified NEI grading scheme, with fluorescein)	• Screening and Days 1, 7, 30, 60, and 90/Early Exit	• Corneal staining will be assessed in each eye after the evaluation of TBUT, using the modified NEI grading scheme).
Conjunctival staining (Modified NEI grading scheme, with lissamine green)	• Screening and Days 1, 7, 30, 60, and 90/Early Exit	• Conjunctival staining will be assessed in each eye using the modified NEI grading scheme
Schirmer test (with anaesthesia)	• Screening and Days 1, 7, 30, 60, and 90/Early Exit	• Schirmer test with anesthesia will be performed in each eye after all other ophthalmic testing.
TBUT (with fluorescein)	• Screening and Days 1, 7, 30, 60, and 90/Early Exit	• TBUT is the time in seconds required for dry spots to appear on the corneal surface after blinking.
OSDI Questionnaire Score	• Screening and Days 1, 7, 30, 60, and 90/Early Exit	• Participants will be asked to evaluate the frequency of various symptoms, related visual functions, and environmental triggers of DED using a 5-point scale. This is a self-assessed overall evaluation, not per eye.
Study Eye Drop Experience and Tolerability Questionnaire	• Days 7, 30, 60, and 90/Early Exit	• A self-assessed survey that evaluates the immediate, short- and long-term participant experience in comfort and vision with the study intervention, as well as tolerability of the assigned study intervention over the past week in selected performance measures, using a VAS.
Functional Vision Questionnaire	• Days 1, 7, 30, 60, and 90/Early Exit	• A self-assessed questionnaire to assess visual function within the past 3 days.
5-Minute Blurry Vision and Ocular Discomfort Questionnaire	• Days 1 and 90/Early Exit	• A 2-question VAS survey evaluates the participant's blurry vision and ocular discomfort before dosing and at 30 seconds, 1 minute, 90 seconds, and 2, 3, 4, and 5 minutes after dosing.

8.1.1. Primary Efficacy Assessment

8.1.1.1. Total Staining

Total staining score will be determined as the sum of corneal and conjunctival staining scores.

8.1.2. Secondary Efficacy Assessment

8.1.2.1. Current Symptom Survey

At all visits, the Current Symptom Survey will be completed by each participant to measure their ocular symptoms over the past 24 hours. Participants should be instructed to mark a vertical line on the anchored VAS that best captures how their eyes have been feeling over the past 24 hours, except the few minutes immediately after using eye drops. A trained member of the study personnel will then use the provided VAS ruler to convert the participant's response to a numerical value (0 to 100). This is an overall evaluation, not per eye. The questionnaire will read as follows (**Note:** The VAS scales will be an actual scale and not just text as indicated below for the purposes of this protocol):

Think about how your eyes have felt over the past 24 hours. Using the scales provided below, please mark a vertical line at the place that best describes the level of severity you experienced with each of the following symptoms over the past 24 hours:

1. Burning (VAS anchors: 0 = no burning, 100 = maximum burning)
2. Dryness (VAS anchors: 0 = no dryness, 100 = maximum dryness)
3. Irritation (VAS anchors: 0 = no irritation, 100 = maximum irritation)
4. Grittiness/foreign body sensation (VAS anchors: 0 = no grittiness/foreign body sensation, 100 = maximum grittiness/foreign body sensation)
5. Blurry/fluctuating vision (VAS anchors: 0 = no blurry/fluctuating vision, 100 = maximum blurry/fluctuating vision)
6. Overall ocular pain/discomfort (VAS anchors: 0 = no pain/discomfort, 100 = maximum pain/discomfort)

8.1.3. Other Efficacy Assessments

8.1.3.1. Tear Break-up Time (with Fluorescein)

TBUT will be performed on both eyes at all visits.

Slit-lamp settings should be adjusted to a magnification of 10X to 16X using a cobalt blue filter and yellow barrier filter placed directly in front of the objective lens of the slit-lamp. The slit-lamp's light source must be set to high intensity (increased voltage) when the cobalt blue and enhancement filters are in place.

Participants will be asked to tilt their heads slightly back and, starting with the right eye, 5 µL of 2% preservative-free liquid sodium fluorescein will be applied to the lower cul-de-sac using a micropipette and sterile disposable tip. To thoroughly mix the fluorescein with the tear film, the participant will be instructed to blink several times over approximately 15 seconds. The participant will be instructed to blink 3 times naturally, then stare and not blink. Using a stopwatch, TBUT will be measured by the investigator as the time from the last blink until 1 or more black (dry) spots appear in the precorneal tear film (not just local thinning or tear film irregularity). After the first measurement, the participant will be instructed to blink naturally 3 additional times and a second measurement will be taken. The procedure will be repeated for a third measurement. After a 60-second rest period, the entire procedure, starting with instillation of liquid sodium fluorescein will be repeated for the left eye. The time in seconds for each of the 3 measurements will be recorded rounding up to the nearest tenth of a second.

8.1.3.2. Corneal Staining (Modified NEI Grading Scheme, with Fluorescein)

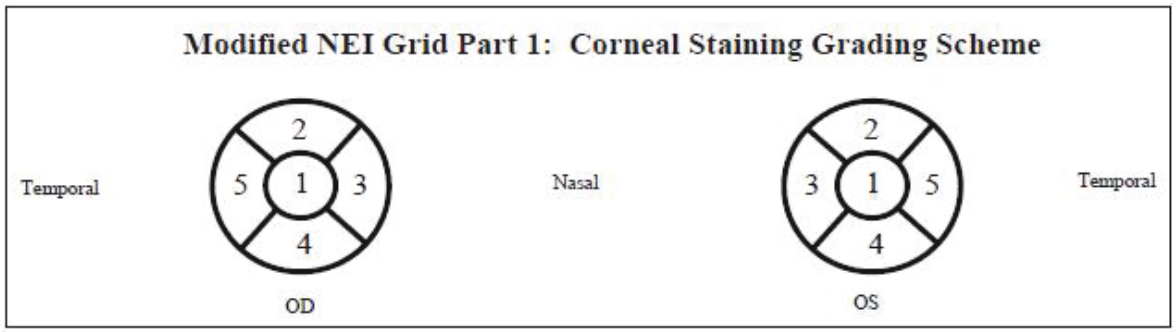
Corneal staining will be evaluated in each eye at all visits.

Approximately 3 minutes after instillation of sodium fluorescein and subsequent assessment of TBUT in both eyes (see Section 8.1.3.1), the cornea will be evaluated for staining, starting with the right eye. No additional liquid sodium fluorescein should be instilled.

Fluorescein staining will be evaluated using a slit-lamp with full slit width and approximately 10X to 16X magnification with cobalt blue illumination and a yellow barrier filter to enhance contrast. The yellow barrier filter must be placed *directly in front of the objective lens of the slit-lamp*. The slit-lamp's light source should also be set to high intensity (increased voltage) when the cobalt blue and enhancement filters are in place.

Grading of the resulting corneal staining will be based on the Modified NEI (National Eye Institute/Industry Workshop) grading scheme (Lemp 1995, Pflugfelder 2008). The schematic representations of the 5 corneal regions per eye are shown in Figure 8-1. Each of the 5 areas on the cornea of each eye is to be graded independently (0-5 per region). The upper eyelid is lifted slightly to grade the entire corneal surface. This procedure should then be repeated in the left eye. The total corneal staining score is calculated as the sum of grading score of 5 regions. The maximum possible score for total corneal staining is 25.

Figure 8-1 **Modified NEI Grading Scheme Part 1: Corneal Staining Grading Scheme**



Grade each zone using the dot count scale:

Dot Count	Grade
No staining	0
1 to 5 dots	1
6 to 15 dots	2
16 to 30 dots	3
> 30 dots	4
> 30 dots + confluence	5

8.1.3.3. Conjunctival Staining (Modified NEI Grading Scheme, with Lissamine Green)

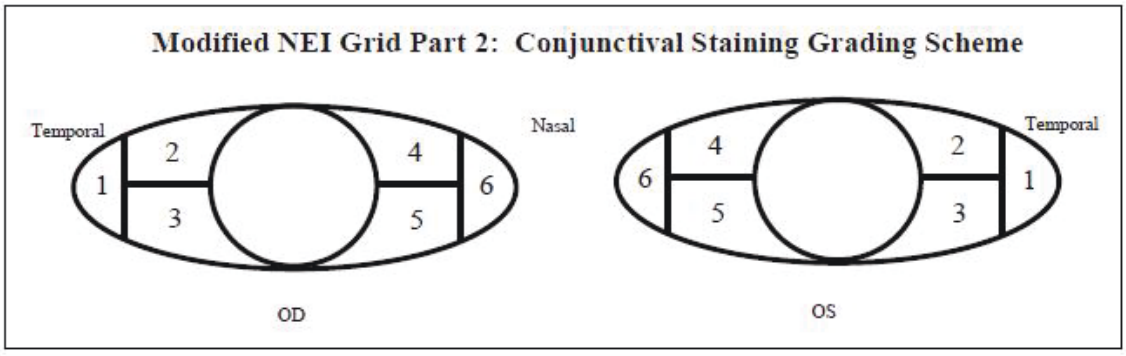
Interpalpebral conjunctival staining will be graded following the corneal staining evaluation at all visits starting with the right eye.

With the sterile lissamine green strip still in the package, the impregnated side of the strip should be grasped, and the outer package torn in half vertically, exposing the white portion of the strip. Grasping the white portion of the strip, the impregnated side of the strip should be moistened with 2 drops of sterile saline solution, allowing the solution to pool into a droplet at the end of the strip. The participant should then be instructed to look up such that 1 drop of lissamine green can be applied to the right eye by gently pulling down on the lower lid and touching the droplet to the bulbar conjunctiva, releasing the droplet. Ensure not to touch the paper strip to bulbar conjunctiva. A second (new) lissamine green strip will then be immediately wetted with 2 drops of sterile saline solution such that a drop of lissamine green can be added to the left eye. To thoroughly mix the lissamine green with the tear film, the participant will be instructed to blink several times over approximately 15 seconds. Approximately 1 minute after instillation and starting with the right eye, grading of the resulting corneal staining will be based on the Modified NEI (National Eye Institute/Industry Workshop) grading scale.

Using the white light of low to moderate intensity, the 6 conjunctival regions (3 nasal and 3 temporal) will be graded using the modified NEI grading scheme (score between 0 and 5 per region) yielding a maximum possible score per eye of 30. The schematic representation of the 6 conjunctival regions per eye is shown in Figure 8-2. To grade the temporal zone, the

participant should be instructed to look nasally; to grade the nasal zone, the participant should be instructed to look temporally.

Figure 8-2 Modified NEI Grading Scheme Part 2: Conjunctival Staining Grading Scheme



Grade each zone using the dot count scale:

Dot Count	Grade
No staining	0
1 to 5 dots	1
6 to 15 dots	2
16 to 30 dots	3
> 30 dots	4
> 30 dots + confluence	5

8.1.3.4. Schirmer Test (with Anesthesia)

The Schirmer test (with anesthesia) should be performed in each eye after completion of both corneal and conjunctival staining at each study visit.

One drop of anesthetic will be instilled into each eye. The participant will be instructed to keep the eyes gently closed for 1 minute. Gentle blotting of the corners of the eye lids with a facial tissue is allowed to catch the over spill, but this should be performed by site staff. Any direct, active blotting of the cul-de-sac is not allowed. After opening the eyes, the participant will be asked to rest with eyes open for approximately 1 additional minute.

The participant will be asked to look up and the Schirmer strips will be placed in each eyelid in the lower cul-de-sac of the junction of the temporal and central one-third of the lower eyelid margin. Once in place, a stopwatch (timer) should be started. To minimize artifacts from this test, participants should gently close their eyelids until 5 minutes have elapsed. Once 5 minutes have elapsed, participants will be asked to open their eyes and the strips are removed. Because the tear front will continue advancing a few millimeters after it has been removed from the eyes, it is important to mark the tear front with a ballpoint pen at precisely 5 minutes. This test is to be conducted in a dimly lit room.

Strip Measuring: Write the letter “R” on the strip used in the OD (right) eye and the letter “L” on the strip used in the OS (left) eye. Each strip has graduated sections on it that will aid in

capturing the appropriate measurement. Record only whole numbers, rounding up to the nearest whole number if the tear front is at or greater than the half millimeter mark.

8.1.3.5. Ocular Surface Disease Index Questionnaire

At all visits, participants will complete an OSDI Questionnaire (see next page). The purpose of this assessment is to capture a range of ocular surface symptoms, including symptoms related to dry eye, their severity, and their impact on the participant's ability to function, scaled into a 0 (no disease) to 100 (maximum severity of disease) score. The OSDI score is calculated as follows:

OSDI = (sum of scores) × 25/(number of questions answered)

OCULAR SURFACE DISEASE INDEX© (OSDI) – *To be completed by the participant*

Please answer the following questions by marking the box that best represents your answer.

Have you experienced any of the following during **the last week?**	All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time	
1. Eyes that are sensitive to light?	☐	☐	☐	☐	☐	
2. Eyes that feel gritty?	☐	☐	☐	☐	☐	
3. Painful or sore eyes?	☐	☐	☐	☐	☐	
4. Blurred vision?	☐	☐	☐	☐	☐	
5. Poor vision?	☐	☐	☐	☐	☐	

Have problems with your eyes limited you in performing any of the following during **the last week**?	All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time	N/A
6. Reading?	☐	☐	☐	☐	☐	☐
7. Driving at night?	☐	☐	☐	☐	☐	☐
8. Working with a computer or bank machine (ATM)?	☐	☐	☐	☐	☐	☐
9. Watching TV?	☐	☐	☐	☐	☐	☐

Have your eyes felt uncomfortable in any of the following situations during **the last week**?	All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time	N/A
10. Windy conditions?	☐	☐	☐	☐	☐	☐
11. Places or areas with low humidity (very dry)?	☐	☐	☐	☐	☐	☐
12. Areas that are air-conditioned?	☐	☐	☐	☐	☐	☐

Participant Signature: _____ ☐☐ ☐☐☐ ☐☐

Day Month Year

8.1.3.6. Study Eye Drop Experience and Tolerability Questionnaire

This questionnaire evaluates the short- and long-term subjective experience in comfort and vision with the study eye drops, as well as the tolerability of the assigned study eye drops over the past week, using a VAS. At Day 1 (Baseline) and all follow-up visits, the Study Eye Drop Experience and Tolerability Survey will be completed by each participant. Participants should be instructed to mark a vertical line on the anchored VAS that best describes their agreement with the statements within the questionnaire. A trained member of the study site personnel will then use the provided VAS ruler to convert the participant's response to a numerical value (0 to 100). This is an overall evaluation, not per eye. The questionnaire will read as follows (**Note:** The VAS scales will be actual scales and not just text as indicated below for the purposes of this protocol.):

Think about your experience with the study eye drops within the first 5 minutes of applying them. Using the scales provided below, please mark a vertical line at the place that best describes your agreement with the following statements:

1. The study eye drops do not cause stinging or burning in my eyes. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
2. The study eye drops provided immediate relief of my eye dryness. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

Now think about your experience with the study eye drops 30 minutes after you applied them. Using the scales provided below, please mark a vertical line at the place that best describes your agreement with the following statements:

3. The study eye drops are very soothing for my eyes. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
4. The study eye drops did not feel sticky. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
5. The study eye drops continued to provide relief of my eye dryness. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

Lastly, think about how you have felt over the last week while using the study eye drops. Using the scales provided below, please mark a vertical line at the place that best describes your agreement with the following statements:

6. The study eye drops provided long-lasting relief of my eye dryness. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

8.1.3.7. Functional Vision Questionnaire

This questionnaire evaluates the functional vision as a consequence of using the study eye drops over the past 3 days in selected performance measures using a VAS. At Day 1 (Baseline) and all follow-up visits, the Functional Vision Questionnaire should be completed by each participant to obtain functional vision ratings from participants for selected performance measures. All measurements will be done on an anchored VAS. Participants should be instructed to mark a

vertical line on the anchored VAS that best describes their agreement with the statements within the questionnaire. A trained member of the study personnel will then use the provided ruler to convert the participant's response to a numerical value (0 to 100). This is an overall evaluation, not per eye. Participants will be asked 19 questions. The questionnaire will read as follows (**Note:** The VAS scales will be actual scales and not just text as indicated below for the purposes of this protocol):

Think about your vision over the past 3 days. You will be asked several questions about your general vision, then questions on specific activities such as watching television (TV), using a computer, using a cell phone and reading a book or magazine. If a particular question does not apply to you, you may check N/A (not applicable) where specified. Using the scales provided below, please mark a vertical line at the place that best describes your agreement with the following statements:

GENERAL VISION – Over the past 3 days:

1. My vision was blurry. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
2. I needed to blink frequently because of blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
3. My eyes got tired because of blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

WATCHING TV – Over the past 3 days:

4. I have clear vision when watching TV. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
5. I can watch TV for as long as I would like. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
6. I **never** stop watching TV due to blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
7. I enjoy watching TV more as I have less blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

USING A COMPUTER – Over the past 3 days:

8. I have clear vision when looking at my computer screen. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
9. I can read the computer screen as fast as I would like. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
10. I can use my computer for as long as I would like. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
11. I **never** stop using my computer due to blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

USING A CELL PHONE – Over the past 3 days:

12. I have clear vision when looking at my cell phone. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
13. I **never** have a problem using my cell phone due to blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
14. I can use my cell phone more as I have less blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

READING A BOOK OR MAGAZINE – Over the past 3 days:

15. I have clear vision when reading. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
16. I can read as fast as I would like. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
17. I can read for as long as I would like. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
18. I **never** stop reading due to blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)
19. I enjoy reading more as I have less blurry vision. (VAS anchors: 0 = strongly disagree, 100 = strongly agree)

8.1.3.8. 5-Minute Blurry Vision and Ocular Discomfort Questionnaire

The 5-Minute Blurry Vision and Ocular Discomfort Questionnaire will be used to assess the degree of the participant's blurry vision and ocular discomfort. The questionnaire will be completed by each study participant at Day 1 (Baseline) and Day 90/Early Exit before the study eye drop instillation and at 30 seconds, 1 minute, 90 seconds, 2 minutes, 3 minutes, 4 minutes, and 5 minutes after instillation of one drop of the assigned study eye drop in each eye by the impartial dispenser. Participants should be instructed to mark a vertical line on the anchored VAS that best describes the amount of blurry vision, respective ocular discomfort they are experiencing at each timepoint. A trained member of the study site personnel will then use the provided VAS ruler to convert the participant's response to a numerical value (0 to 100). This is an overall evaluation, not per eye. The questionnaire will read as follows (**Note:** The VAS scales will be an actual scale and not just text as indicated below for the purposes of this protocol.):

Using the 2 sets of scales below, you will be asked to rate the amount of blurry vision and ocular discomfort you are experiencing before the instillation and over the 5 minutes immediately after instillation of the study eye drop.

The amount of blurry vision you are experiencing can range from "No Blurry Vision" (Score of 0) to "Extreme Blurry Vision" (Score of 100) and this may change over the 5 minutes you are rating.

The amount of ocular discomfort you are experiencing can range from "No Ocular Discomfort" (Score of 0) to "Extreme Ocular Discomfort" (Score of 100) and this may change over the 5 minutes you are rating.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Currently Corrected Distance Visual Acuity

At all visits, corrected visual acuity will be measured using a logarithmic visual acuity chart with Sloan letters for testing at 3 meters (9 feet, 10 inches). One chart is provided with right, left, and center acuity targets, and will be used as described below. Make sure the participant is tested using his/her current distance correction, if applicable. (Note: Participants should use the same distance correction, if required, at each visit, whenever possible). *To provide standardized assessments of visual acuity during the study, all visual acuity assessments should be consistently carried out using the same lighting conditions during the entire study.* Note: Test under normal office-like lighting conditions such that the chart is evenly lit without glare. Attach the chart to the wall at approximately eye level to the average height of a seated participant. Mark a spot on the floor (eg, with tape) that is 3 meters from the chart. Using this mark as a reference, position the participant so his/her eyes are 3 meters from the chart.

Begin by first testing the right eye. Occlude the left eye. The participant should be asked to start on the top line of the bottom right chart (20/50 equivalent). Participants should be told to read the letters from left to right on each line and that the chart has letters only, no numbers. If the participant reads a number, he/she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The participant should be asked to read slowly so as to achieve best identification of each letter and not to proceed to the next letter until he/she has given a definite answer.

If the participant changes a response (eg, "that was a C not an O") before he/she has read aloud the next letter, then the change must be accepted. If the participant changes a response after having read the next letter, then the change will not be accepted. The examiner must not point to specific letters during the test.

When the letters become difficult to read, or if the participant identifies a letter as one of 2 letters, he/she should be asked to choose one letter and, if necessary, to guess. Participants should be encouraged to continue trying even when letters become difficult to read. Stop testing when 3 or more errors are made on the same line. Use the supplied source document worksheet to mark the letters missed for each line and to enter the number of letters correctly read for each line.

If a participant cannot read the 20/50 equivalent line when instructed, verify that the proper current correction is in place. If the participant is still unable to read the 20/50 equivalent line, have him/her read from the top of the full center chart, letter by letter, and record the number of letters missed and the number of letters correctly read for each line in the source document.

Test the left eye following the same procedures outlined above, except have the participant start on the top line of the bottom left chart (20/50 equivalent). This strategy minimizes letter memorization.

8.2.2. Best-Corrected Distance Visual Acuity

Best-corrected visual acuity will be measured at Day -7 (Screening) and Day 90/Early Exit visits using the same logarithmic visual acuity chart with Sloan letters for testing at 3 meters (9 feet, 10 inches) that will be used for the currently corrected distance visual acuity. The LogMar chart will be viewed using a trial frame holding the best-corrected distance endpoint manifest refraction. (Measuring acuity using the phoropter is acceptable so long as the chart distance is 3 meters.)

Sphere, cylinder, and axis will be determined and a consistent endpoint should be used, which is generally the least minus sphere that provides the participant's best measured acuity. Visual acuity should be determined using the same procedure used for currently corrected distance visual acuity. The phoropter may be either a plus or minus cylinder design. Values generated should be recorded directly from the phoropter without conversion.

Whenever possible, the same individual should perform the refraction and the same examination lane should be used.

8.2.3. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy (***without*** pupil dilation) will be performed on both eyes at all visits during the study. Observations for the slit-lamp biomicroscopy examination will be graded as described below. Findings other than those listed below should be recorded under “other” for the appropriate location of the finding.

The following will be examined at each visit:

- Eyelid/eyelid margins/lashes
- Conjunctiva
- Cornea
- Anterior Chamber

EYELID / EYELID MARGINS / LASHES

Erythema

0	(None)	No erythema
+ 0.5	(Trace)	Localized, minimal (trace) flush reddish color
+ 1	(Mild)	Localized, mild, flush reddish color
+ 2	(Moderate)	Diffuse reddish color encompassing the entire lid margin
+ 3	(Severe)	Deep diffuse reddish color of lid margins and superior and/or inferior eyelid

Edema (eyelids)

0	(None)	No edema
+ 0.5	(Trace)	Localized, minimal (trace) swelling
+ 1	(Mild)	Localized, mild swelling
+ 2	(Moderate)	Diffuse, moderate swelling
+ 3	(Severe)	Diffuse, severe swelling

CONJUNCTIVA (BULBAR AND PALPEBRAL)

Hyperemia

0	(None)	No hyperemia
+ 0.5	(Trace)	Minimal (trace) flush, reddish color
+ 1	(Mild)	Mild flush, reddish color
+ 2	(Moderate)	Bright red color
+ 3	(Severe)	Deep, bright diffuse redness

Edema

0	(None)	No edema
+ 0.5	(Trace)	Localized, minimal (trace) swelling
+ 1	(Mild)	Localized, mild swelling
+ 2	(Moderate)	Diffuse, moderate swelling
+ 3	(Severe)	Diffuse, severe swelling

CORNEA

Edema

0	(None)	No edema
+ 0.5	(Trace)	Localized, minimal (trace) epithelial haze
+ 1	(Mild)	Dull glass appearance of epithelium that may include fine localized microcystic changes
+ 2	(Moderate)	Dull glass appearance of epithelium with large number of cystic changes with or without stromal edema
+ 3	(Severe)	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

ANTERIOR CHAMBER

For the measurements of cells and flare based on standardized uveitis nomenclature, the following settings should be used:

- 1 × 1 mm slit
- Highest slit-lamp voltage
- Illumination angle of 45 degrees
- High magnification
- Low ambient lighting
- Same grader and slit-lamp whenever possible

Cells

0	=	0 cells
+ 0.5	=	1 to 5 cells (trace)
+ 1	=	6 to 15 cells
+ 2	=	16 to 25 cells
+ 3	=	26 to 50 cells
+ 4	=	> 50 cells

Flare

0	=	None: no flare seen
+ 1	=	Faint: faint flare seen
+ 2	=	Moderate: iris and lens details clear
+ 3	=	Marked: iris and lens details hazy
+ 4	=	Intense: fibrin or plastic aqueous

8.2.4. Urine Pregnancy Test

Women of childbearing potential will have urine pregnancy tests performed at the Screening (Day -7) and Day 90/Early Exit visits. At each visit, the investigator should discuss contraceptive use compliance with WOCBP. Additional details are provided in Appendix 6.

8.2.5. Intraocular Pressure (with Anesthesia and Fluorescein)

After the Schirmer test with anesthetic is administered, IOP will be measured for each eye at Screening (Day -7) and Baseline (Day 1) and at all follow-up visits for participants with glaucoma or OHT only. Measurements should be taken using a Goldmann applanation tonometer affixed to a slit-lamp with the participant seated. Additional sodium fluorescein can be applied if needed. The participant and slit-lamp should be adjusted so that the participant's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting neckwear should be loosened. Both eyes will be tested, with the right eye preceding the left eye. The measurer looks through the binocular viewer of the slit lamp at low power. The tension knob is preset at a low pressure value (4 to 6 mm Hg). The measurer follows the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to

the cardiac cycle. When this image is reached, the measurer takes his/her fingers off the tension knob and records the IOP reading along with the date and time of day in the source document.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

AEs will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

All AEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent, will be recorded on the source document and transcribed onto the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken to not introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.3.5. Pregnancy

- If a pregnancy is confirmed after the participant has received the study intervention, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through their Day 90/Early Exit visit.
- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and through the duration of the pregnancy.

- If a pregnancy is reported, the investigator should inform the sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.6. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 3 categories as follows:

- Wrong study intervention
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong participant (ie, not administered to the intended participant)

8.4. Treatment of Overdose

Treatment of overdose is not applicable to this study.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

8.8.1. Study Eye Drop Usage Questionnaire

The 2-question Study Eye Drop Usage Questionnaire will be completed by each participant at Day 1 (Baseline) and all follow-up visits to capture the date and time of their last study eye drop instillation and their overall compliance to study drop usage.

Question 1: “What date and time did you last use your study eye drops?”

Question 2: “In general, did you use your study eye drops 3 times a day?” (yes / no)

Sites should review each participant’s response to ensure that the last instillation of their study eye drops was ≥ 4 hours from the start of completing this questionnaire and that they are generally using their study eye drops 3 times per day. Should either of the participant’s responses

be out of compliance, the site should discuss with the participant to ensure they dose correctly from that point forward.

8.9. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

One database lock is planned for the study and will occur at the completion of the study. Detailed statistical analyses will be described in the analysis plan, which will be finalized prior to database lock.

9.1. Statistical Hypotheses

The null and alternative hypotheses for the primary efficacy endpoint are:

Superiority

- H_0: The NATF (011516X) is not superior to Systane Ultra MD as measured by the mean change from baseline in total staining score at Day 90.
- H_A: The NATF (011516X) is superior to Systane Ultra MD as measured by the mean change from baseline in total staining score at Day 90.

Noninferiority

- H_0: The NATF (011516X) is inferior compared to Systane Ultra MD as measured by the mean change from baseline in total staining score at Day 90.
- H_A: The NATF (011516X) is noninferior compared to Systane Ultra MD as measured by the mean change from baseline in total staining score at Day 90.

9.2. Sample Size Determination

The primary efficacy variable is change from baseline in total staining score at Day 90. Based on the assumption of noninferiority test for a between-group difference (ie, the noninferiority margin) of 2.3 units in mean change from baseline in total staining at Day 90 with no inherent treatment difference with common standard deviation of 5.98, 170 participants will be required in each intervention to detect the above intervention difference with a power of 90% or greater at the 1-sided 1.25% significance level. Assuming a 15% dropout rate, 200 participants will be randomized for each arm with a total of 400 participants.

9.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

- The intent-to-treat (ITT) population includes all randomized participants. Participants will be summarized according to the randomized study intervention.
- The per-protocol (PP) population includes all randomized participants who have no protocol deviations affecting the primary analysis. Participants will be summarized according to the randomized study intervention.

- The safety population includes all treated participants who receive/take ≥ 1 administration of study intervention. Participants will be summarized according to the study intervention they actually received.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

All data will be summarized with descriptive statistics and/or frequency tables. In general, nominal categorical data will be analyzed using Pearson's chi-square test or Fisher's exact test. Continuous variables will be analyzed using analysis of variance (ANOVA) models, mixed-effects model repeated measures (MMRM), or t-tests.

9.4.1. Efficacy Analyses

The efficacy analyses will be based on the ITT and PP population.

9.4.1.1. Analysis Endpoints

The primary and secondary efficacy endpoints are listed below and analyses will be defined in the following sections. All analyses for other efficacy/effectiveness endpoints listed below will be defined in the SAP.

Primary efficacy endpoint:

- Change from baseline in total staining score at Day 90

Secondary efficacy endpoint:

- Change from baseline in Current Symptom Survey (composite of all symptoms) at Day 90

Other efficacy endpoints:

- Change from baseline in corneal staining score
- Change from baseline in conjunctival staining score
- Change from baseline in total staining score other than Day 90
- Change from baseline in Current Symptom Survey (composite of all symptoms) other than Day 90
- Change from baseline in individual symptom scores from Current Symptom Survey
- Change from baseline in Schirmer test
- Change from baseline in TBUT
- Change from baseline in Functional Vision Questionnaire, 5-Minute Blurry Vision, and Ocular Discomfort Questionnaire

- Study Eye Drop Experience and Tolerability Questionnaire

In addition to those endpoints listed above, other analyses of exploratory efficacy such as responder analyses will be defined in the SAP.

9.4.1.2. Primary Analyses

The primary efficacy variable is the change from baseline in total staining score at Day 90.

The primary efficacy analysis will be performed in the ITT population using MMRM. The differences and the intervals will be constructed with the least squares means from the MMRM model with treatment, visit, visit by treatment interaction, and baseline total staining stratum, and baseline total staining stratum by visit interaction as the fixed effects. In order to control the overall type I error rate in the primary efficacy analysis, the sequential procedures will be performed. Under this procedure, the noninferiority will be performed first and the superiority test will be performed next only if the null hypothesis of noninferiority is rejected. To test the hypothesis of noninferiority, a 2-sided 95% confidence interval will be constructed for the difference in the mean change from baseline in total staining at Day 90. If the upper limit of 2-sided CI is less than 2.3 units, then the NATF tear formulation will be considered noninferior to Systane Ultra MD at the 2.3 unit margin. To test the hypothesis of superiority, a 2-sided test for superiority will be performed at the 0.05 significance level.

The primary efficacy variable will also be analyzed similarly on PP population as a sensitivity analysis.

9.4.1.3. Secondary Analyses

The secondary efficacy variable is the change from baseline in Current Symptom Survey total score (composite of all symptoms) at Day 90. The secondary efficacy variable will be analyzed using MMRM.

9.4.1.4. Other Efficacy Analyses

Other efficacy analyses include comparing the NATF (011516X) with Systane Ultra MD at each scheduled visit on corneal staining, conjunctival staining, total staining score other than Day 90, Current Symptom Survey (composite of all symptoms) other than Day 90, individual symptom scores from Current Symptom Survey, Schirmer test, TBUT, Functional Vision Questionnaire, 5-Minute Blurry Vision and Ocular Discomfort Questionnaire, and Study Eye Drop Experience and Tolerability Questionnaire.

Change from baseline of selected continuous other efficacy variables will be analyzed using MMRM. Detailed methods for the analysis of other efficacy variables will be described in the SAP.

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP.

The safety variables include AEs, biomicroscopy, currently corrected distance visual acuity, BCDVA, and IOP. All safety analyses will be conducted on the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs. For each AE reported, the number and percent of participants will be tabulated. Separate tables will be generated for pretreatment AEs and treatment-emergent AEs. All AEs will be presented in the listings. Detailed analysis methods will be provided in the SAP.

Other safety variables, including biomicroscopy findings, currently corrected distance visual acuity, BCDVA, and IOP, will also be analyzed.

9.4.2.1. Adverse Events

An AE will be considered a treatment-emergent adverse event (TEAE) if:

- The AE began on or after the date of the first dose of study intervention; or
- The AE was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first dose of study intervention

An AE will be considered a treatment-emergent SAE if it is a TEAE that additionally meets any SAE criteria.

The number and percentage of participants reporting TEAEs in each study intervention group/during the study will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants reporting treatment-related TEAEs in each study intervention group/during the study will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with SAEs and participants with AEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Appendix 2.

9.4.3. Other Safety Analyses

All other safety variables will be analyzed with descriptive statistics. Detailed methods for the analysis of other safety variables will be described in the SAP.

9.4.3.1. Subgroup Analyses

The primary efficacy variable will also be analyzed by stratification factor.

9.5. Interim Analyses

Not applicable.

9.5.1. Data Monitoring Committee

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council on Harmonisation (ICH)/International Organization for Standardization (ISO)/Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the United States National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, GCP: Consolidated Guidance and records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB according to the IRB's reporting requirements.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/ self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient 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 or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• See Section 8.3.3.

Reporting of SAEs

SAE Reporting within 24 hours
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.3. Appendix 3: Abbreviations

Abbreviation	Definition
AE	adverse event
ANOVA	analysis of variance
BCDVA	best-corrected distance visual acuity
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
DED	dry eye disease
eCRF	electronic case report form
EDS-VAS	Eye Dryness Score - Visual Analog Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IOP	intraocular pressure
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intent-to-treat
IxRS	interactive response system
KCS	keratoconjunctivitis sicca
LASIK	laser-assisted in situ keratomileusis
MD	multidose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
N/A	not applicable
NCI	National Cancer Institute
OD	right eye
OHT	ocular hypertension
OS	left eye
OSDI	Ocular Surface Disease Index® Questionnaire
OTC	over-the-counter
NATF	new artificial tear formulation
NEI	National Eye Institute
PP	per-protocol
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SoA	schedule of activities
TBUT	tear break-up time
TEAE	treatment-emergent adverse event
US	United States
VAS	visual analog scale
vs	versus
WOCBP	woman of childbearing potential

10.4. Appendix 4: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. Clinical Data Interchange Standards Consortium (CDISC) terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
AE	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Noncompliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)

CDISC Submission Value	CDISC Definition
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.5. Appendix 5: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Study information	Study Title	A Multicenter, Single-masked, Randomized Study to Compare the Efficacy and Safety of a New Artificial Tear Formulation (011516X) with Systane® Ultra Multidose for 90 Days in Participants with Dry Eye Disease
	Clinical Study Sponsor	Allergan Sales LLC
	Study Phase Classification	Phase 3 study
	Study Indication	DED
	Study Indication Type	Treatment
	Study Type	Efficacy Safety
	Study Length	Approximately 90 days
	Planned Country of Investigational Sites	United States
	Planned Number of Subjects	400
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	DED
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	Not specified
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not specified

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	011516X
	Intervention Type	Drug
	Pharmacological Class of Investigational Therapy	Artificial tear
	Dose per Administration	1 to 2 drops in each eye
	Dose Units	Drop
	Dosing Frequency	3 times per day
	Route of Administration	Topical eye drop
	Current Therapy or Treatment	Artificial tear product
	Added on to Existing Treatments	No
	Control Type	Active
	Comparative Treatment Name	Systane Ultra Multidose
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Study Is Randomized	Yes
	Randomization Quotient	1:1
	Study Blinding Schema	Single-masked
	Stratification Factor	Total ocular staining score of the study eye (mild/moderate = score of 6 to 25 vs severe = score of 26 to 43)
	Adaptive Design	No
	Study Stop Rules	None

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraception Guidance:

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-1.

Table 10-1 Highly Effective and Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device Combinations of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a negative highly sensitive urine pregnancy test at screening.
- Additional pregnancy testing should be performed at study exit, and as required locally.
- Pregnancy testing will be performed when pregnancy is otherwise suspected.
- Urine pregnancy testing will be used unless the study site requires the use of serum testing, in which case serum testing will be used.

Collection of Pregnancy Information:

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Allergan within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to Allergan. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to Allergan as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- If a pregnancy is confirmed after the participant has received study treatment, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the end-of-study visit.

10.7. Appendix 9: Study Schedule Supplement

10.7.1. Screening (Day -7 [-3 days])

- Written informed consent and written documentation in accordance with the relevant country and local privacy requirements
- Demographic information
- Medical and ophthalmic histories
- Inclusion/exclusion criteria assessment
- Self-assessed surveys/questionnaires: Current Symptom Survey and OSDI Questionnaire
- Adverse event assessment
- Prestudy medication assessment
- Urine pregnancy test (for WOCBP only)
- Currently corrected distance visual acuity, BCVA, biomicroscopy, TBUT (with fluorescein), corneal staining (modified NEI grading, with fluorescein), conjunctival staining (modified NEI grading scheme, with lissamine green), Schirmer test (with anesthesia), and IOP (with anesthesia and fluorescein using a Goldmann applanation tonometer)
- Access IxRS
- Dispense run-in medication (if the patient meets the required Day -7 [Screening] qualifications)

Patients who fulfill all inclusion and exclusion criteria should be dispensed the run-in medication, REFRESH PLUS. They should be given instructions regarding the method of instillation and the dose regimen to be followed.

10.7.2. Baseline (Day 1)

- Inclusion/exclusion criteria assessment
- Medical and ophthalmic histories
- Concomitant medication assessment
- Adverse event assessment

- Self-assessed surveys/questionnaires: Study Eye Drop Usage Questionnaire, Current Symptom Survey, OSDI Questionnaire, and Functional Vision Questionnaire
- Currently corrected distance visual acuity, biomicroscopy, TBUT (with fluorescein), corneal staining (modified NEI grading, with fluorescein), conjunctival staining (modified NEI grading scheme, with lissamine green), Schirmer test (with anesthesia), and IOP (with anesthesia and fluorescein using a Goldmann applanation tonometer, only for participants with glaucoma or OHT)
- Monitor return of unused run-in medication and confirmation of run-in medication accountability
- Access IxRS
- Randomization
- Predose and postdose 5-Minute Blurry Vision and Ocular Discomfort Questionnaire
- Dispense study medication (if the participant qualifies for the study)

10.7.3. Day 7 (±3 days)

- Self-assessed surveys/questionnaires: Study Eye Drop Usage Questionnaire, Current Symptom Survey, OSDI Questionnaire, Study Eye Drop Experience and Tolerability Questionnaire, and Functional Vision Questionnaire
- Adverse event assessment
- Concomitant medication assessment
- Currently corrected distance visual acuity, biomicroscopy, TBUT (with fluorescein), corneal staining (modified NEI grading, with fluorescein), conjunctival staining (modified NEI grading scheme, with lissamine green), Schirmer test (with anesthesia), and IOP (with anesthesia and fluorescein using a Goldmann applanation tonometer, only for patients with glaucoma or OHT)

10.7.4. Days 30 and 60 (±7 days)

- Self-assessed surveys/questionnaires: Study Eye Drop Usage Questionnaire, Current Symptom Survey, OSDI Questionnaire, Study Eye Drop Experience and Tolerability Questionnaire, and Functional Vision Questionnaire
- Adverse event assessment

- Concomitant medication assessment
- Currently corrected distance visual acuity, biomicroscopy, TBUT (with fluorescein), corneal staining (modified NEI grading, with fluorescein), conjunctival staining (modified NEI grading scheme, with lissamine green), Schirmer test (with anesthesia), and IOP (with anesthesia and fluorescein using a Goldmann applanation tonometer, only for patients with glaucoma or OHT)
- Monitor return of used and unused study intervention and confirmation of study intervention accountability
- Access IxRS
- Dispense study intervention

10.7.5. Day 90/Early Exit (±7 days)

- Self-assessed surveys/questionnaires: Study Eye Drop Usage Questionnaire, Current Symptom Survey, OSDI Questionnaire, Study Eye Drop Experience and Tolerability Questionnaire, and Functional Vision Questionnaire
- Adverse event assessment
- Concomitant medication assessment
- Urine pregnancy test (for WOCBP only)
- Currently corrected distance visual acuity, BCVA, biomicroscopy, TBUT (with fluorescein), corneal staining (modified NEI grading, with fluorescein), conjunctival staining (modified NEI grading scheme, with lissamine green), Schirmer test (with anesthesia), and IOP (with anesthesia and fluorescein using a Goldmann applanation tonometer, only for patients with glaucoma or OHT)
- Access IxRS
- Predose and postdose 5-Minute Blurry Vision and Ocular Discomfort Questionnaire
- Monitor return of used and unused study intervention and confirmation of study intervention accountability

10.8. Appendix 10: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC.

Amendment 1 (February 2020)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in Protocol Amendment 1 is to remove the evaluation of a second new artificial tear formulation (NATF) formulation (011533X) from the study.

Section Number and Name	Description of Change	Brief Rationale
Title Page, Section 1 Synopsis, Figure 1-1, Section 2.1 Study Rationale, Section 2.2 Background, Section 2.3 Benefit/Risk Assessment, Section 3 Objectives and Endpoints, Section 4.1 Overall Design, Section 4.2, Scientific Rationale for Study Design, Section 6.1 Study Interventions Administered, Section 6.1.3 Instructions for Use and Administration, Section 6.3 Measures to Minimize Bias: Randomization and Masking, Section 6.4 Study Intervention Compliance, Section 9.1 Statistical Hypotheses, Section 9.4.1.4 Other Efficacy Analyses, Section 10.5 Appendix 5: Study Tabular Summary	Removed the NATF formulation 011533X arm from the study.	Administrative decision to focus development efforts and resources on a single formulation.
Section 1 Synopsis, Section 4.1 Overall Design, Section 5 Study Population, Section 9.2 Sample Size Determination, Appendix 5 Study Tabular Summary	Changed the total number of participants from approximately 600 to approximately 400 to be randomized in order to have 340 participants (170 participants in each arm) complete the study through Day 90, assuming an approximate 15% dropout rate.	Because the study is changing from a 3-arm to a 2-arm study, a smaller number of participants will be required.
Section 1 Synopsis, Section 4.1 Overall Design, Section 5 Study Population, Appendix 5 Study Tabular Summary	Changed the number of study sites from up to 40 sites to approximately 28 sites.	Because the study is changing from a 3-arm to a 2-arm study and a smaller number of participants will be required, a smaller number of sites will be required.

Section Number and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Revised inclusion criterion 2.01 as follows: At the Screening (Day -7) and Baseline (Day 1) visits, at least 1 eye must qualify with both of the following ocular staining scores ~~and the same eye must qualify at both visits~~:	For clarification.
Section 5.2 Exclusion Criteria	Added the following exclusion criterion 1.02: At the Screening (Day -7) or Baseline (Day 1) visits, one or both eyes have • Corneal staining score of 5 in any of the 5 zones or a total score of <5 or > 19 based on the modified NEI grading scheme (score range = 0 to 5; graded in 5 zones of the cornea for a total score range of 0 to 25) or • Conjunctival staining score of 5 in any of the 6 zones based on the modified NEI grading scheme (score range = 0 to 5 per zone)	For clarification.
Section 8.1.3.2 Corneal Staining (Modified NEI Grading Scheme, with Fluorescein)	Revised the following text; Fluorescein staining will be evaluated using a slit-lamp with full slit width and approximately 10X to 16X magnification with cobalt blue illumination and a yellow barrier filter to enhance contrast.	For clarification.
Section 8.1.3.3 Conjunctival Staining (Modified NEI Grading Scheme, with Lissamine Green)	Revised the following text: Using the white light of low to moderate intensity, t~~T~~he 6 conjunctival regions (3 nasal and 3 temporal) will be graded using the modified NEI grading scheme (score between 0 and 5 per region) yielding a maximum possible score per eye of 30.	For clarification.

Section Number and Name	Description of Change	Brief Rationale
Section 9.1 Statistical Hypotheses	Revised the following text: • H_0: The NATF (011516X) is ~~not non~~inferior compared to Systane Ultra MD as measured by the mean change from baseline in total staining score at Day 90.	For clarification.
Section 9.4.1.2 Primary Analyses	Revised the following text: In order to control the overall type I error rate in the primary efficacy analysis, the ~~Hochberg Bonferroni reverse fixed sequence~~sequential procedures will be ~~used since~~ performed. Under this procedure, the ~~null hypotheses of~~ noninferiority ~~are nested in~~ will be performed first and the ~~null hypotheses of~~ superiority~~. Under this procedure,~~ test will be performed next only if the null hypothesis of ~~superiority is rejected using Hochberg test the null hypothesis of~~ noninferiority is ~~automatically rejected, and if the null hypothesis of superiority is not rejected using Hochberg procedure the null hypothesis of noninferiority is tested using Bonferroni test. For each NATF tear formulation, test for superiority will be performed first by applying Hochberg's procedure at 0.05 significance level~~ rejected. To test the hypothesis of noninferiority, a 2-sided ~~97.5~~95% confidence ~~intervals~~interval will be constructed for the difference in the mean change from baseline in total staining at Day 90. If the upper limit of 2-sided ~~CIs~~CI is less than 2.3 units, then the NATF tear formulation will be considered noninferior to Systane Ultra MD at the 2.3 unit margin. To test the hypothesis of superiority, a 2-sided test for superiority will be performed at the 0.05 significance level.	Because the study is changing from a 3-arm to a 2-arm study, the primary analysis methods were updated.

11. References

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