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Study 192371-024

Title: A Phase 2, Multi-center, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol Amendment 6 Date: Jan 19, 2017

Statistical Analysis Plan (SAP) Date: June, 20, 2017

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STUDY TITLE

A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol Number:	192371-024
Phase:	2
Name of Investigational Product:	RESTASIS® X
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500
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Serious Adverse Event Reporting Fax Numbers:	[redacted]
Allergan Medical Safety Physician Contact Information:	[redacted]

Allergan Signatory:

[redacted]

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

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: RESTASIS® X (Cyclosporine Ophthalmic [redacted])

Phase: 2

Study Objectives:

Stage 1: To evaluate the safety, exploratory efficacy, and pharmacokinetics of F1 and F2 administered [redacted] in patients with moderate to severe dry eye disease.

Stage 2: To evaluate the safety, exploratory efficacy, and pharmacokinetics of cyclosporine [redacted] in patients with moderate to severe dry eye disease.

[redacted]

Study Design

[redacted]

CFI is a new formulation of CsA [redacted] To fully evaluate F1, F2, and CFI, this phase 2 study will be conducted in 2 stages.

Stage 1 will evaluate, in a paired-eye fashion, the safety, exploratory efficacy, and pharmacokinetics of [redacted] of F1 and F2 in patients with moderate to severe dry eye disease.

[redacted] The dose cohorts for stage 1 are described in detail in Table 1, and the study flow for stage 1 is shown in Figure 1.

[redacted]

Structure:

Stage 1: multicenter, randomized, investigator-masked, dose escalation, vehicle-controlled

- single-dose, paired-eye comparison
- paired-eye comparison, retreatment at week 12 (cohorts 6C and 6D)

Stage 2: multicenter, randomized, investigator-masked, parallel treatment groups, vehicle-controlled

- single dose, bilateral treatment at baseline
- bilateral retreatment at week 12

Duration:

Stage 1: The duration per patient will be approximately 26 weeks (from screening to week 24 visit).

Stage 2: The duration per patient will be approximately 26 weeks (from screening to week 24 visit).

Study Treatment Groups:

Stage 1: Vehicle, F1 and F2

Baseline and retreatment cohort 6C and 6D: F1 and F2

Stage 2: Baseline and retreatment groups: up to 3 dose groups: vehicle, CFI , and CFI

Controls:

Stage 1: sham treatment, vehicle

Stage 2: vehicle

Dosage/Dose Regimen:

Stage 1 will sequentially examine the safety of doses of F1 and F2 administered

y,

[redacted]

[redacted]

Dosing in stage 2 will begin as a bilateral-eye treatment of CFI or vehicle. In the absence of significant safety findings (determined by the investigator) at 12 weeks, patients in treatment group 1 will be retreated with vehicle in both eyes and followed for another 12 weeks. In the absence of significant safety findings (determined by the investigator) at 12 weeks, patients in treatment groups 2 and 3 will be retreated with CFI in both eyes and followed for another 12 weeks. The dose and dose regimen for stage 2 are provided in Table 2.

[redacted]

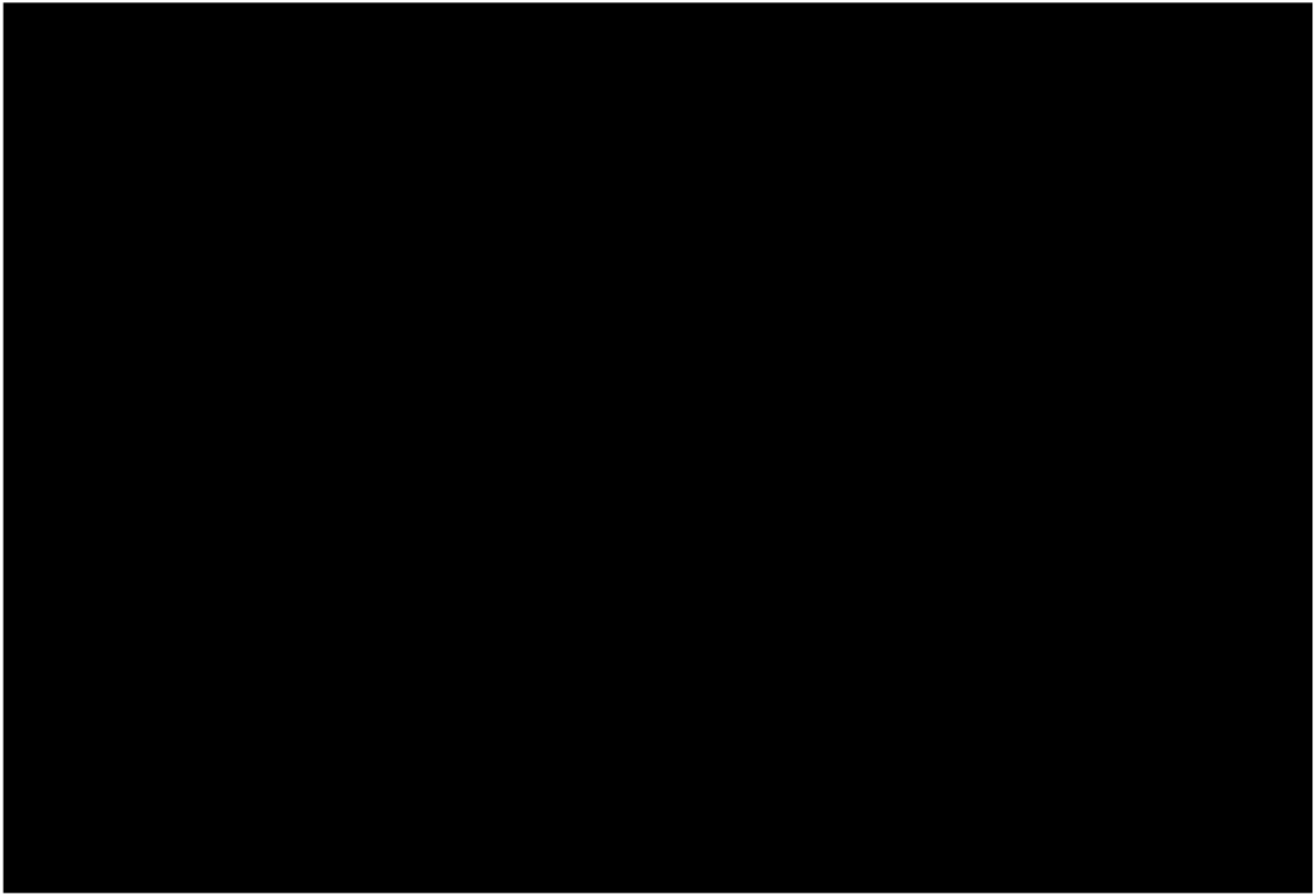
[redacted]

Randomization/Stratification:

Stage 1: Within each cohort, patients will be randomly assigned with respect to the eye, right or left, to receive F1 or F2 (or vehicle for cohort 1). The contralateral eye will receive vehicle [redacted]

Stage 2: Patients will be allocated in a randomized fashion to the treatment groups. This randomization will be stratified by Sjögren's syndrome (presence or absence) at screening.

[redacted]



Study Population Characteristics

Number of Patients:

Up to 87 patients will be enrolled.

Stage 1: Stage 1 will have up to 63 patients and approximately 10 cohorts (cohorts 1 to 6D). The anticipated numbers of patients per cohort are 3 for cohort 1, 4 for cohorts 2, 6C, and 6D, and 8 each for cohorts 3 through 6B.

[redacted]

Condition/Disease:

Stage 1: patients with moderate to severe dry eye disease

Stage 2: patients with moderate to severe dry eye disease

Key Inclusion Criteria:

Stages 1 and 2:

- male or female, at least 18 years of age at screening visit (week -2)
- at baseline visit (day 1), dry eye disease (keratoconjunctivitis sicca) in both eyes, characterized by the following clinical signs:
  - [redacted]
- a[redacted]

Key Exclusion Criteria:

Stages 1 and 2:

- use of topical RESTASIS or any other topical ophthalmic preparation of Cyclosporine (CsA) within 3 months prior to the baseline visit (day 1) and unwilling/unable to discontinue use for 3 months prior to baseline, or anticipated use during the study
- any use of systemic or dermatologic CsA or other calcineurin inhibitors within the 3 months prior to the screening visit (week -2), or anticipated use during the study
- topical ophthalmic use of anti-inflammatory medications (nonsteroidal anti-inflammatory drugs [NSAIDs] or glucocorticoids) within 1 month prior to the screening visit (week -2), or anticipated use during the study
- [redacted]
- any use of topical ocular medication other than artificial tears within 1 month prior to the screening visit (week -2), or anticipated use during the study
- use of contact lenses in either eye within 1 month prior to the screening visit (week -2), or anticipated contact lens wear in either eye during the study
- [redacted]

Stage 2:

- participation in stage 1 of this study

Response Measures

Stage 1:

Safety:

- adverse events
- best-corrected visual acuity (BCVA; manifest refraction at screening and exit visits)
- macroscopic hyperemia assessment and slit-lamp biomicroscopy
- dilated ophthalmic exam
- photographic conjunctival hyperemia assessment
- intraocular pressure (IOP)
- vital signs
- laboratory tests (chemistry, hematology, urinalysis)
- urine pregnancy test (for females of childbearing potential)

Pharmacokinetics:

- ocular pharmacokinetics (assessed from tear samples)
- systemic pharmacokinetics

[redacted]

Health Outcomes:

- Supplemental Dry Eye Patient Reported Outcomes Questionnaire

[redacted]

General Statistical Methods and Types of Analyses:

For both stages 1 and 2, the safety population, consisting of all patients who receive study treatment, will be used for safety analyses. The modified intent-to-treat (mITT) population, consisting of all patients who receive study treatment and have baseline and at least 1 postbaseline assessment for 1 or more of the exploratory efficacy measurements, will be used for exploratory efficacy analyses. In general, continuous variables will be summarized by descriptive statistics including sample size (N), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency count and percentage.

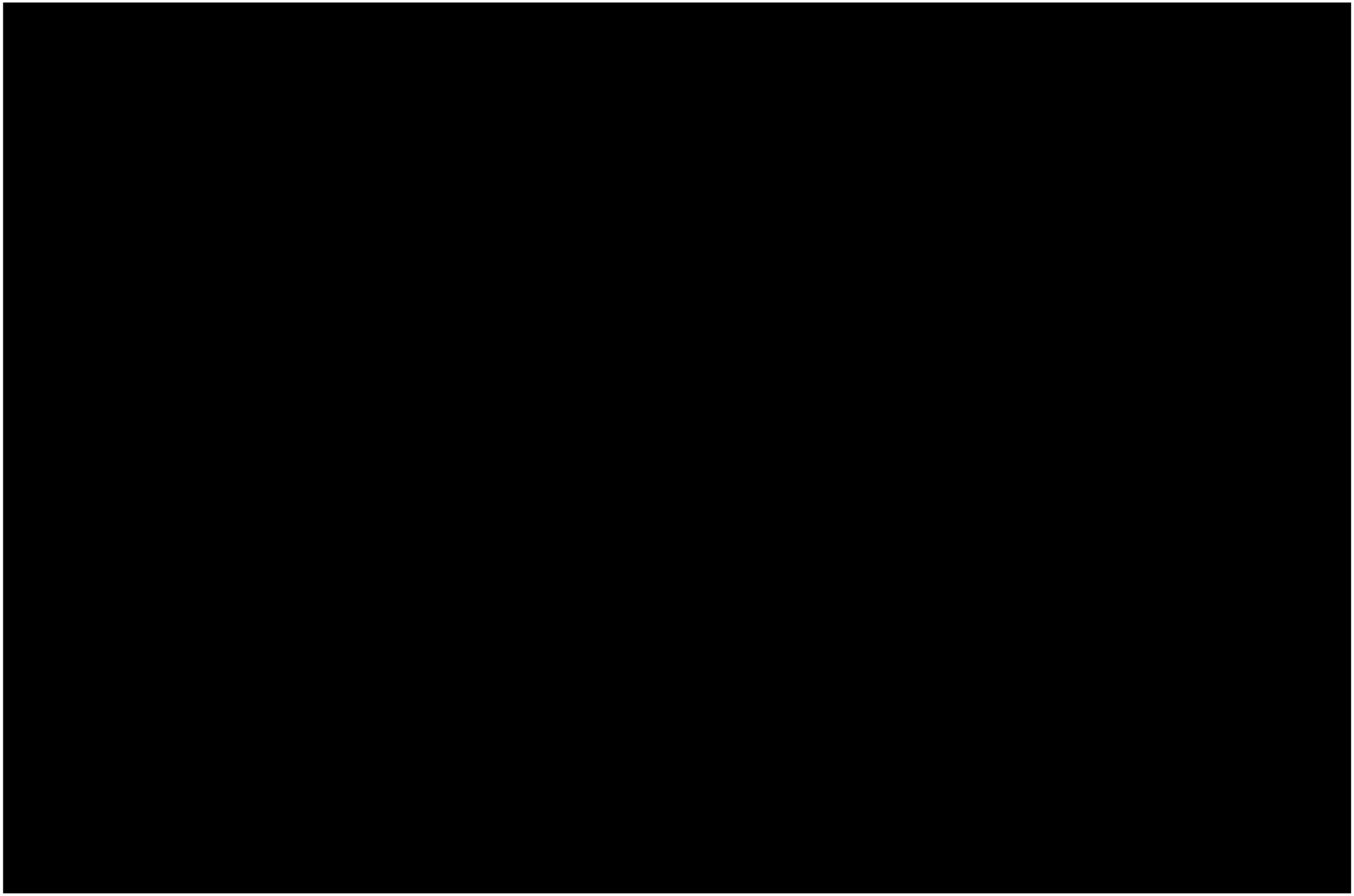
Exploratory efficacy (stage 1 and stage 2) measures will be evaluated. Baseline and change from baseline measure will be assessed. Also, number (percent) of responders may be assessed.

For both stages 1 and 2, a model-independent approach will be used to calculate pharmacokinetic parameters of CsA, if appropriate, for tears and blood. Pharmacokinetic parameters for blood and tears will only be calculated for samples collected from patients who receive study treatment.

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. The number and percentage of patients with treatment-emergent adverse events will be tabulated based on the primary system organ class and the preferred term using the safety population. The adverse events will be classified as ocular versus nonocular adverse events and analyzed separately.

Sample Size Calculation: The sample sizes for stages 1 and 2 were determined empirically.

[redacted]



[redacted]

Treatment and Response Measurements by the Investigators

This study requires a follow-up investigator and a treating investigator. Certain study tests and procedures are assigned to the treating investigator to maintain masking of the follow-up investigator to the study treatments. The treating investigator will conduct RESTASIS X administration, macroscopic regional hyperemia, slit lamp biomicroscopy (eyelids, margins, lashes, and conjunctiva), all dilated ophthalmic examinations, and impression cytology for biomarker analysis. [redacted]. The follow-up investigator or appropriately trained and qualified site personnel will administer all other procedures. See Table 5 for a listing of investigator's procedure assignments.

[redacted]

1 Background and Clinical Rationale

This study represents the first evaluation in patients of the safety, exploratory efficacy, and pharmacokinetics of RESTASIS® X, [redacted] cyclosporine (CsA). The study will be conducted in patients with moderate to severe dry eye disease.

[redacted] (CFI) is a new formulation of CsA [redacted] To fully evaluate F1, F2, and CFI, this phase 2 study will be conducted in 2 stages.

1.1 Study Rationale

Cyclosporine, a cyclic peptide containing 11 amino acids with a total molecular weight of 1202 Daltons, has long been known as a potent immunosuppressant and anti-inflammatory agent that specifically inhibits T lymphocyte proliferation via inhibition of Interleukin-2 (IL-2) expression and cytokine production (Nussenblatt and Palestine, 1986; Petcher et al, 1976). At the molecular level, CsA functions by binding to and forming a complex with cytosolic Cyclophilin A. The CsA:Cyclophilin A complex in turn inhibits the calcium/calmodulin-dependent phosphatase activity of calcineurin that is responsible for dephosphorylation and translocation of nuclear factor of activated T cells (NFATc), a transcription factor required for IL-2 gene expression and T-cell activation (Ho et al, 1996). In addition to NFATc inhibition, CsA negatively regulates inflammation through its ability to bind and inhibit the phosphorylation of Inhibitor of κB (IκB), thereby preventing nuclear translocation of NF-κB, a key transcription factor for multiple proinflammatory cytokine/chemokine genes. Additional molecular mechanisms reported to be inhibited by CsA include c-fos/jun and AP-1 transcription factors, and key inflammation-related intracellular signaling pathways including p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, and extracellular signal-related kinase.

In ophthalmology, prior to its use as a topical treatment for dry eye disease, systemic (intravenous and oral) CsA was used for the treatment of severe posterior segment inflammation (Masuda et al, 1989). Ulcerative keratitis associated with Wegener's

granulomatosis, severe Grave's ophthalmopathy, and graft rejection after keratoplasty have also been successfully treated with systemic CsA (Georganas et al, 1996; Nussenblatt et al, 1991; Prummel et al, 1989; Reinhard et al, 1997). It was found, however, that systemic administration could be accompanied by side effects such as nephrotoxicity and hypertension (Mihatsch et al, 1998). To increase local drug concentrations and avoid systemic side effects, topical ophthalmic CsA was developed. Topical ophthalmic CsA is marketed by Allergan in over 25 countries as RESTASIS (cyclosporine ophthalmic emulsion 0.05%) for increasing tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

Supporting CsA's mechanism of action as an inhibitor of T-cell activation and its applicability for treatment of dry eye disease, Kunert and colleagues (2000) evaluated conjunctival biopsy specimens from 32 patients with dry eye disease: 13 treated with 0.05% CsA, 6 with 0.1% CsA, and 13 with vehicle alone for 6 months. Conjunctival biopsies from patients given topical CsA showed relative decreases in the numbers of cells positive for CD3, CD4, and CD8. In addition, biopsies from patients treated with 0.05% topical CsA showed a significant decrease in the number of cells expressing the inflammatory markers CD11a and human leukocyte antigen type DR (HLA-DR). A reduction in the expression of markers of general inflammation such as CD11a and HLA-DR, suggests that perhaps through its direct inhibitory effect on activated T cells, CsA indirectly reduces the overall magnitude of inflammation, thus contributing to a more quiescent status in the tissue.

In nonclinical studies in rabbits and dogs, [redacted] To date, no studies have been completed with RESTASIS X in humans, so its safety, pharmacokinetics, and pharmacology have yet to be determined. In the study described here, RESTASIS X will be evaluated in patients who were previously diagnosed with moderate to severe dry eye disease but have not been treated with topical RESTASIS for at least 3 months prior to entering the study. [redacted]

[redacted]

[redacted]

[redacted]

2 Study Objectives and Clinical Hypotheses

2.1 Study Objectives

The study will be conducted in 2 stages:

Stage 1:

To evaluate the safety, exploratory efficacy, and pharmacokinetics of F1 and F2 administered [redacted] in patients with moderate to severe dry eye disease.

Stage 2:

To evaluate the safety, exploratory efficacy, and pharmacokinetics of CFI administered [redacted] in patients with moderate to severe dry eye disease.

2.2 Clinical Hypotheses

[redacted]

[redacted]

[redacted]

[redacted]

3 Study Design

This study is a multicenter, randomized, investigator-masked, 24-week evaluation of the safety, exploratory efficacy, and pharmacokinetics of [redacted] RESTASIS X in patients with moderate to severe dry eye disease. This study will be conducted in 2 stages.

Stage 1: Single dose, paired-eye comparison, dose escalation, vehicle-controlled, followed by retreatment (cohorts 6C and 6D).

Stage 1 will evaluate the safety and ocular and systemic pharmacokinetics of F1 [redacted] and F2 [redacted]

Stage 1 will begin with cohort 1 (approximately 3 patients) in which patients will be given a [redacted] sham treatment in one eye and [redacted] vehicle in the other eye. [redacted]

significant safety findings [redacted], the remaining 2 patients in cohort 2 will be given a [redacted] vehicle in one eye and [redacted] F1 [redacted]) in the other eye. After 2 weeks of monitoring, and in the absence of significant safety findings [redacted], four patients in cohort 3 will receive [redacted] vehicle in one eye and [redacted] F1 [redacted]) in the other eye. After 2 weeks of monitoring the fourth patient in cohort 3, [redacted]. Four patients in cohort 4 will receive [redacted] of vehicle in one eye and [redacted] F1 [redacted] in the other eye. Two weeks after dosing the fourth patient in cohort 4, [redacted]. In the absence of significant safety findings from the first 4 patients in cohort 4, cohorts 5A and 6A will begin. For cohort 5A, patients will be administered [redacted] F1 [redacted]) in one eye and [redacted] vehicle in the other eye. After 2 weeks of monitoring the first 4 patients in cohort 5A, [redacted] If there are no significant safety findings for the first 4 patients in cohort 5A, the dosing of the remaining 4 patients in cohort 5A will proceed, and then the first 4 patients of cohort 5B will be administered [redacted] of F1 [redacted] in one eye and [redacted] vehicle in the other eye.

For cohorts 6A and 6B, patients will receive [redacted] either F2 or vehicle (see Figure 1 and Table 1). For cohorts 6C and 6D, patients will receive [redacted] of either F1 or F2 and vehicle (see Figure 1 and Table 1). The doses [redacted] associated with cohorts 6A, 6B, 6C, and 6D will be determined [redacted] The progression from cohort 6A to 6B will be conducted in the same manner as for cohorts 3 through 5, with decisions to continue with dosing of a given cohort and/or to escalate to the next higher dose cohort based upon [redacted]

[redacted]

[redacted]

4 Study Population and Entry Criteria

4.1 Number of Patients

The study anticipates enrolling up to 87 patients.

Stage 1: Stage 1 will be conducted at approximately 10 sites and will have up to 63 patients and approximately 10 cohorts (cohorts 1 to 6D). The anticipated number of patients per cohort are 3 for cohort 1; 4 each for cohorts 2, 6C, and 6D; and 8 each for cohorts 3 through 6B.

Stage 2: Stage 2 will be conducted at approximately 15 sites and will have up to 24 patients and 3 treatment groups. The number of treatment groups and number of patients per group will be based on results from stage 1.

4.2 Study Population Characteristics

Stage 1: patients with moderate to severe dry eye disease

[redacted]

4.3 Inclusion Criteria

The following are requirements for entry into the study:

General Inclusion Criteria for Both Stages 1 and 2

1. male or female, at least 18 years of age at screening visit (week -2)

2. at baseline (day 1) visit, dry eye disease (keratoconjunctivitis sicca) in both eyes, characterized by the following clinical signs:

[redacted]

3. [redacted]

4. best-corrected visual acuity (BCVA) of 20/100 or better (Snellen equivalent), using the logarithm of the minimum angle of resolution (LogMAR) in each eye at the screening (week –2) and baseline (day 1) visits

[redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

For Stages 1 and 2:

1. use of topical RESTASIS or any other topical ophthalmic preparation of CsA within 3 months prior to the baseline visit (day 1) and unwilling/unable to discontinue use for 3 months prior to baseline, or anticipated use during the study

2. any use of systemic or dermatologic CsA or other calcineurin inhibitors within 3 months prior to the screening visit (week -2), or anticipated use during study

3. topical ophthalmic use of anti-inflammatory medications (nonsteroidal anti-inflammatory drugs [NSAIDs] and/or glucocorticoids) within 1 month prior to the screening visit (week -2) or anticipated use during study

4. [redacted]

5. [redacted]

6. any use of topical ocular medication other than artificial tears within 1 month prior to the screening visit (week -2), or anticipated use during the study

7. use of contact lenses in either eye within one month prior to the screening visit (week -2), or anticipated use during the study

[redacted]

[redacted]

[redacted]

[redacted]

Stage 2:

35. participation in stage 1 of this study

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Allergan will provide patients with REFRESH PLUS, the only topical artificial tear permitted during the study. Patients will be required to replace any existing artificial tear product with REFRESH PLUS.

During the 2-week period between the screening and baseline visits, REFRESH PLUS should be instilled in both eyes 4 times per day.

Following the baseline visit, REFRESH PLUS can be used up to 4 times per day. Use of REFRESH PLUS should not occur within 6 hours prior to any study visit.

Use of inhaled corticosteroids (as needed) is permitted during the study.

Use of the following systemic medications and supplements is permitted during the study, providing a stable dosing regimen is established (dosing is not stable if a patient starts, stops, or changes dose/drug during the study):

- cholinergic agonists or antihistamines, antimuscarinics, diuretics, tricyclic antidepressants, phenothiazines, cholesterol lowering agents
- systemic vitamins and/or systemic supplements containing omega 3 fatty acids; vitamins A, B, and E; fish oil; or Evening Primrose oil
- hormone replacement therapy program, oral or transdermal contraception use, use of other estrogen or progesterone treatment
- systemic androgen replacement therapy
- systemic inhibitors of steroidogenesis, spironolactone, cyproterone acetate, or other anti-androgen treatment

- oral macrolides, tetracyclines, tetracycline derivative drugs (including doxycycline and minocycline)

- non-ophthalmic retinoids (eg, isotretinoin), non-ophthalmic corticosteroids, or other non-ophthalmic anti-inflammatory medications or immune modulators used for prolonged treatment of systemic immune-mediated diseases

4.5.1.1 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

Women who are not of childbearing potential are either postmenopausal (and with at least 12 consecutive months without menstruation) or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy).

Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause. For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner, or sexual abstinence.

The investigator and each patient will determine the appropriate method of contraception for the patient during their participation in the study.

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug (RESTASIS X/CsA), and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

4.5.2 Prohibited Medications/Treatments

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.

The following medications or classes of medications are prohibited during the study:

- any systemic/dermatological/ophthalmic use of RESTASIS/CsA or other calcineurin inhibitors
- any artificial tear product other than REFRESH PLUS
- use of REFRESH PLUS greater than 4 times per day or within 6 hours prior to a study visit
- use of any topical ocular medication other than REFRESH PLUS
- use of Lacrisert™ (hydroxypropyl cellulose ophthalmic insert) or methylcellulose ocular inserts

The following procedures/treatments are prohibited during the study:

- insertion of punctal plugs
- punctal cautery in either eye
- use of contact lenses in either eye
- use of scleral lenses, or sealed compartment ocular frames
- LipiFlow or other lid-heating therapy, meibomian gland probing or therapeutic gland expression in either eye
- anterior segment surgery or trauma that could affect corneal sensitivity (eg, cataract surgery or any surgery involving a limbal or corneal incision) in either eye
- insertion or removal of glaucoma filtration shunts or devices

4.5.3 Rescue Medications

In the event that rescue medication is required for worsening signs or symptoms of dry eye disease during the course of the study, patients will be provided an appropriate rescue regimen by the investigator/treating clinician, and be monitored through the end of the study.

5 Study Treatments

5.1 Study Treatments and Formulations

[redacted]

5.2 Control Treatments

For cohort 1 in stage 1, the control treatment will be a sham procedure. For cohorts 2 through 6D in stage 1, patients will receive [redacted] vehicle [redacted]) in the contralateral eye. [redacted] For stage 2, patients in treatment group 1 will receive [redacted] vehicle in both eyes.

5.3 Methods for Masking

This study requires a treating investigator and a follow-up investigator. Certain study tests and procedures are assigned to the treating investigator to maintain masking of the follow-up investigator to the study treatments. The treating investigator will conduct RESTASIS X [redacted] administration, macroscopic regional hyperemia, slit lamp biomicroscopy (eyelids, margins, lashes, and conjunctiva), impression cytology for biomarker analysis, and all dilated ophthalmic examinations. The follow-up investigator or appropriately qualified site personnel will administer all other procedures. See Table 5 for a listing of investigator's procedure assignments. The site personnel conducting photographic conjunctival hyperemia assessments may assist with study tasks consistent with the role of the treating investigator. In addition, RESTASIS X kit components will be labeled in a manner that maintains preparation and administration in a masked fashion. In stage 1, follow-up investigators and patients will be masked with regard to the identity [redacted]. In stage 2, follow-up investigators and patients will be masked with regard to the identity and dose [redacted]. For further description of the kits, see Section 9.5.2.

5.4 Treatment Allocation Ratio and Stratification

Stage 1: Within each cohort, each patient will be randomly assigned with respect to the eye, right or left, to receive F1 or F2 (vehicle for cohort 1). The contralateral eye will receive vehicle (sham for cohort 1) (see Table 1).

Stage 2: Patients will be allocated in a randomized fashion to the treatment groups shown in Table 2. This randomization will be stratified by Sjögren's syndrome (presence or absence of Sjögren's syndrome) at screening. Patients in treatment group 1 will be assigned to receive vehicle in both eyes as the baseline treatment, and patients in treatment groups 2 and 3 will be assigned to receive CFI [redacted], respectively, in both eyes as the baseline treatment. Table 6 shows the randomization/stratification groups.

[redacted]

5.5 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of study treatment, each patient who provides informed consent will be assigned a patient number that will serve as the patient identification number on all study documents.

An automated interactive voice response system (IVRS)/interactive web-based response system (IWRS) will be used to manage the randomization, stratification, and treatment assignment.

Stage 1:

For each cohort, Allergan Biostatistics will prepare a scheme that will randomly assign patients with respect to the eye, right or left, to receive F1 or F2 (vehicle for cohort 1) (see Table 1). At baseline, if the patient is eligible to be randomized, the IVRS/IWRS will assign the next available randomization number for that cohort to the patient at the time the investigator requests randomization.

Stage 2:

Allergan Biostatistics will prepare a scheme that will randomly assign patients to 1 of 3 treatment groups (Table 2). The randomization will be stratified by Sjögren's syndrome (presence or absence of Sjögren's syndrome at screening).

At baseline, if the patient is eligible to be randomized, he/she will be assigned to a treatment group through the IVRS/IWRS. Randomization numbers will be assigned in blocks for each Sjögren's stratum (absent/present). Based on the randomization scheme, a randomization number will be assigned to each patient sequentially according to the order of enrollment in the stratum. That is, IVRS/IWRS will assign the next available randomization number to the patient at the time the investigator requests randomization. The treatment-group assignment will be based on an equal allocation ratio across the study (not by site).

For both stages, study medication labeled with medication kit numbers will be shipped to each study site. The IVRS/IWRS will report a medication kit number to use for each patient corresponding to the randomization number. Sites will receive the IVRS/IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

5.6 Treatment Regimen and Dosing

Following a 2-week run-in period whereby signs and symptoms of dry eye disease will be verified and washout of artificial tears other than REFRESH PLUS will be facilitated by run-in with REFRESH PLUS, [redacted] RESTASIS X or vehicle will be initiated. [redacted] Each eye will receive either vehicle or [redacted] RESTASIS X.

5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, and in accordance with the conditions specified in this protocol.

[redacted]

5.8 Preparation of Study Medications/Treatments

A detailed description of the study drug preparation procedure will be provided in the procedure manual. [redacted]

5.9 Treatment Administration

The study drug administration will be conducted in an office setting or in a surgical suite. [redacted]. For stage 1, F1 or F2 will be administered to the study eye per the study protocol. For stage 2, vehicle will be administered to both eyes in treatment group 1, and CFI will be administered to both eyes in treatment groups 2 and 3. A detailed description of the study drug administration procedure will be provided i[redacted]

5.10 Retreatment

In stage 1 of the study, patients in cohorts 6C and 6D will be retreated (at week 12) [redacted].

To help guide the investigator's decision on retreatment, [redacted] unless a ≥ +2 hyperemia grade [redacted] is present, at which time the investigator may elect not to retreat the patient in stage 1. In this case, the

patient will not be retreated in either eye but continue to be observed for safety (see Table 3) for the duration of the study. [redacted]

For stage 2, patients in treatment groups 2 and 3 will be retreated (at week 12) with CFI in both eyes at the same dose used for the baseline (day 1) [redacted] Treatment group 1 patients will be retreated at week 12 with vehicle. If retreatment is not administered, the patient will continue to be observed for safety (see Table 4) and exited at the Week 24/Week 12R/Exit visit.

In stage 2, the investigator can elect to [redacted] if a ≥ +2 hyperemia grade [redacted] is present. [redacted]

[redacted]

[redacted]

6 Response Measures and Summary of Data Collection Methods

6.1 Safety Measures

For stages 1 and 2, the following safety measures will be examined:

- adverse events (ocular and nonocular)
- BCVA
- macroscopic hyperemia assessment and slit-lamp biomicroscopy
- IOP
- dilated ophthalmic exam
- photographic conjunctival hyperemia assessment

- vital signs
- laboratory tests (chemistry, hematology, urinalysis)
- urine pregnancy test

Laboratory test results will be forwarded from the central laboratory to the study site and to Allergan or its designee. The laboratory results from screening will be reviewed prior to randomization. Laboratory tests at screening may be repeated once at the discretion of the investigator and pending discussion with Allergan, to confirm exclusionary status. Study treatment will be performed only if the investigator deems the laboratory results to be acceptable. The most current specimen results will be reviewed prior to randomization. The investigator will review all laboratory results for the clinical significance of any abnormalities. Evaluation and management of abnormal laboratory results should be conducted according to local site practice. Clinically significant abnormalities are to be recorded on an adverse event electronic case report form (eCRF) page.

6.2 Pharmacokinetic Measures

Stage 1:

Ocular and systemic pharmacokinetic samples will be collected (Table 3). For determinations of drug concentration in the tear film, tear samples will be collected from both eyes at baseline (prior to treatment), weeks 1, 4, 8, 12, and 24/12R or Exit for cohorts 2 through 6D. For determination of drug concentration in the circulation, blood samples will be collected at baseline (prior to treatment), weeks 1, 4, 8, 12, and 24/12R or Exit for cohorts 2 through 6D. For cohorts 6C and 6D only, tear and blood samples will be collected post retreatment at weeks 1R, 4R, and 8R, and 24/12R or Exit (see Table 3).

Stage 2:

Ocular drug concentrations will be determined from tears sampled at baseline (prior to treatment), weeks 1, 4, 8, 12, and post-retreatment at weeks 1R, 4R, 8R, and 24/12 R or Exit (see Table 4). For determination of systemic drug concentration, blood samples will be collected at baseline (prior to treatment), weeks 1, 4, 8, 12, and post retreatment at weeks 1R, 4R, 8R, and 24/12R or Exit (see Table 4).

[redacted]

[redacted]

[redacted]

6.3.1 Health Outcomes Measures

In stage 1, a Supplemental Dry Eye Patient Reported Outcomes (PRO) Questionnaire, developed to assess symptoms individually in each eye, will be administered at the study visits indicated in Table 3. In stage 2, the Supplemental Dry Eye PRO Questionnaire and the Dry Eye Treatment Satisfaction PRO will be administered at the study visits indicated in Table 4.

[redacted]

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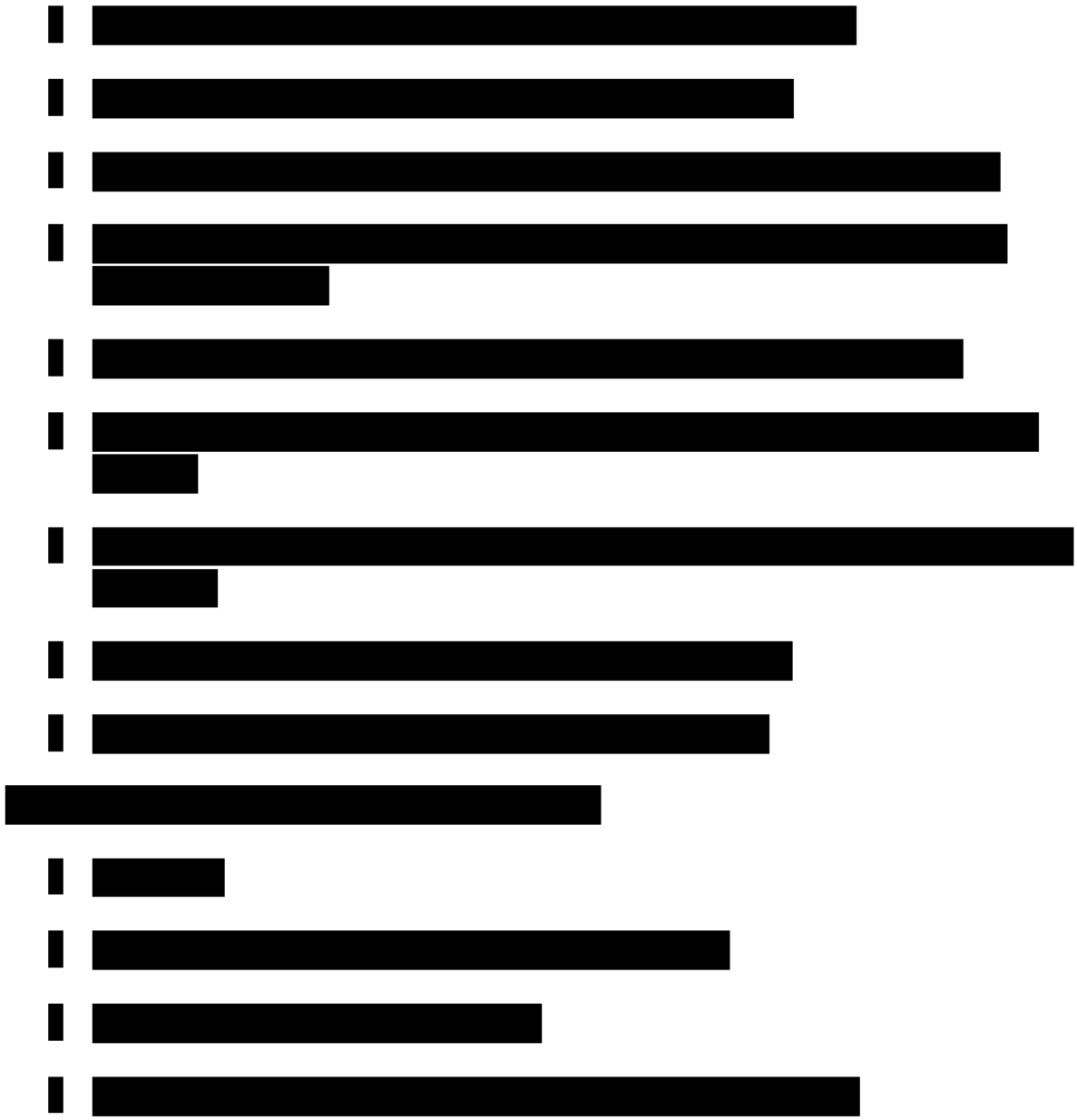

6.5 Summary of Methods of Data Collection

This protocol will use eCRFs with remote data capture through a qualified third-party vendor. Data entered into the eCRF will correspond to, and be supported by, source documentation maintained at the sites. The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. The data will be entered on the eCRFs in a timely manner and on an ongoing basis.

An IVRS/IWRS will be used to assign patient identification numbers, patient initials, randomize/stratify patients, and manage study medication inventory. Data will be transferred to Allergan on a periodic basis throughout the study.

Qualified laboratories will be used for the analysis of blood and urine samples. Laboratory data will be transferred to Allergan on a periodic basis throughout the study.

A qualified image reading center will be used to collect and analyze photographs taken by the study sites. Photographs will be transferred from the reading center to Allergan on a periodic basis. All digital images will be transferred from the reading center to Allergan at the end of the study.

In the event external data need to be captured within the eCRFs by the vendor, the vendor will handle the data as a site would and the vendor will be responsible for ensuring that these data are properly recorded on each patient's eCRFs and related documents. A vendor representative will also be required to sign for the eCRFs that they have completed.

7 Statistical Procedures

[redacted] An interim database lock of stage 1 will not be conducted until after all patients in cohorts 1 through 6B complete the study and all patients in cohorts 6C and 6D completed at least week 1 following retreatment. An interim database lock of stage 2 will not be conducted until after all patients in stage 2 complete at least week 1 following retreatment. A final database lock will occur after all enrolled patients have completed stage 2 of the study. The statistical analysis plan (SAP) will be developed and finalized before database lock.

7.1 Analysis Populations

The safety population will include all treated patients. This population will be used for the safety analyses. The modified intent-to-treat (mITT) population will be all patients who are treated and have baseline and at least 1 postbaseline assessment for 1 or more of the exploratory efficacy measurements (see Section 6.3). The mITT population will be used for the exploratory efficacy analyses. The population consisting of subjects who received the active study treatment will be used for pharmacokinetic analysis.

7.2 Collection and Derivation of Exploratory Efficacy Assessments

Exploratory efficacy (stage 1 and stage 2) measures (Section 6.3) will be evaluated. Baseline and change from baseline measure will be assessed. Also, number (percent) of responders may be assessed.

7.3 Hypothesis and Methods of Analysis

In general, continuous variables will be summarized by descriptive statistics including sample size (N), mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by frequency count and percentage.

7.3.1 Safety Analyses

Safety measures will be analyzed using the safety population. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. The number and percentage of patients with treatment-emergent adverse events will be summarized. The adverse events will be classified into ocular and nonocular types and will be summarized separately. Detailed methods for the analyses of adverse events and other safety variables will be described in the SAP.

[redacted]

[redacted]

7.4 Subgroup Analyses

Subgroup analyses will be conducted for all safety and efficacy measures by presence and absence of Sjögren's syndrome for stage 2. No other subgroup analyses are planned, but they may be performed for exploratory purposes.

7.5 Sample Size Calculation

The sample sizes for both stages 1 and 2 are determined empirically.

7.6 Interim Analyses

An interim database lock of stage 1 will not be conducted until after all patients in cohorts 1 through 6B complete the study and all patients in cohorts 6C and 6D complete at least week 1 following retreatment. An interim database lock of stage 2 will not be conducted until after all patients in stage 2 completed at least week 1 following retreatment. Statistical analyses will be performed following each database lock to support the design of future clinical studies.

8 Study Visit Schedule and Procedures

[redacted]

[redacted]

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients will be considered for entry into this study by applying the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) at the screening and baseline visits.

8.1.2 Informed Consent and Patient Privacy

The study procedures will be discussed with the patient. Any patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization and other written documentation in accordance with the relevant local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Patients who provide informed consent will be assigned a patient number that will be used on patient documentation throughout the study.

8.2 Washout Intervals/Run-in

For patients not on RESTASIS at the screening visit, there will be a 2-week run-in period with REFRESH PLUS, for use 4 times per day. If patients are using topical RESTASIS at screening, their screening period will be extended to a 13-week period to allow for washout of topical RESTASIS in conjunction with the 2-week run-in with REFRESH PLUS. Any screening diagnostic procedures that were performed at the start of the extended screening period will be repeated within days -14 to -2.

8.3 Procedures for Final Study Entry

During the 2-week run-in period, signs and symptoms of dry eye disease will be verified in both eyes at screening (week -2) and baseline (day 1) visits. Specific scores for qualification tests can be found in the inclusion criteria (Section 4.3).

Female patients of childbearing potential MUST have a negative urine pregnancy test result at screening (week -2) and baseline (day 1) visits. Only eligible patients will be enrolled into the study. A patient is considered to have enrolled in the study at the time of randomization to treatment at baseline (day 1).

See Section 5.5 for the method of assignment to treatment groups/randomization.

8.4 Visits and Associated Procedures

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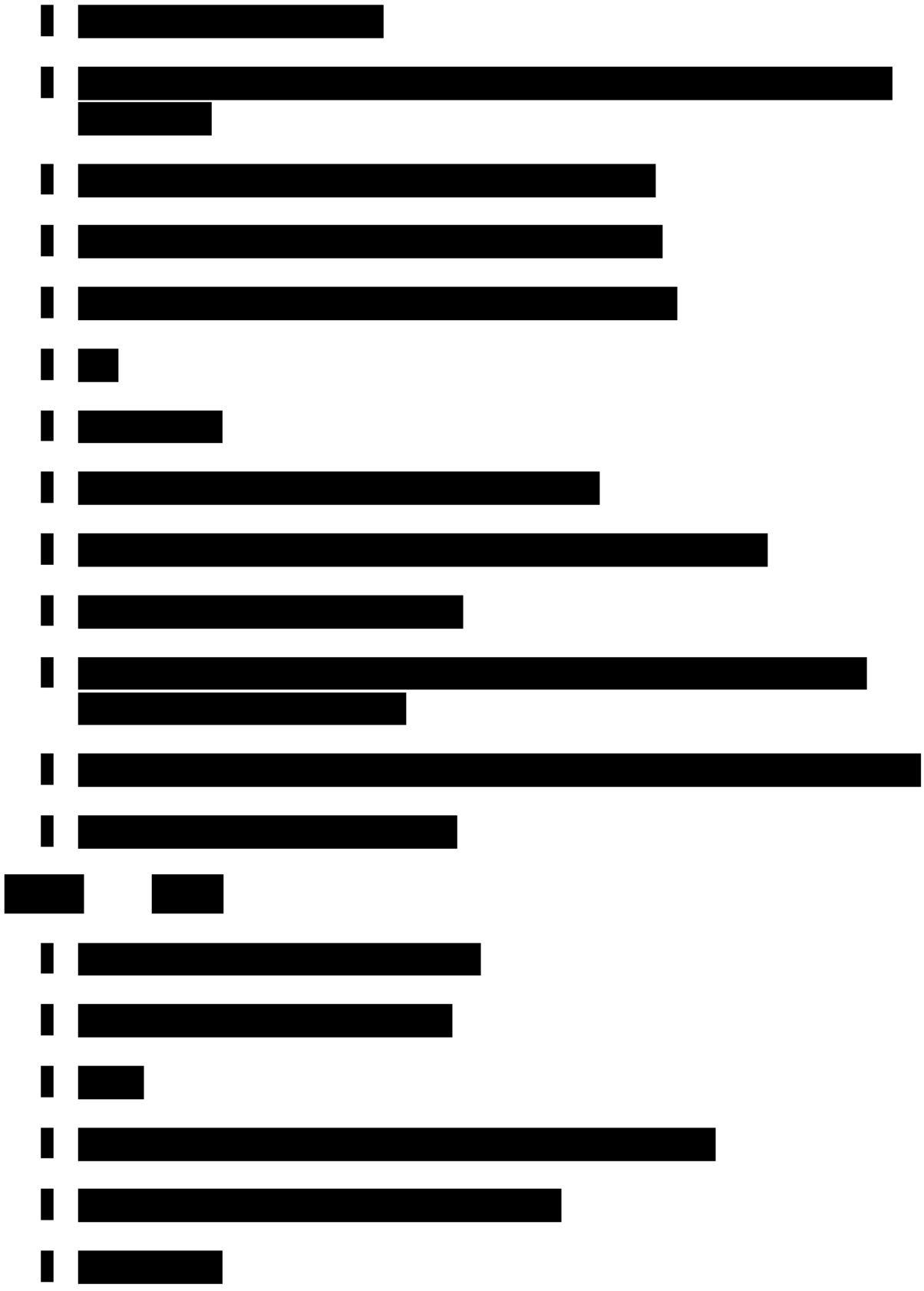

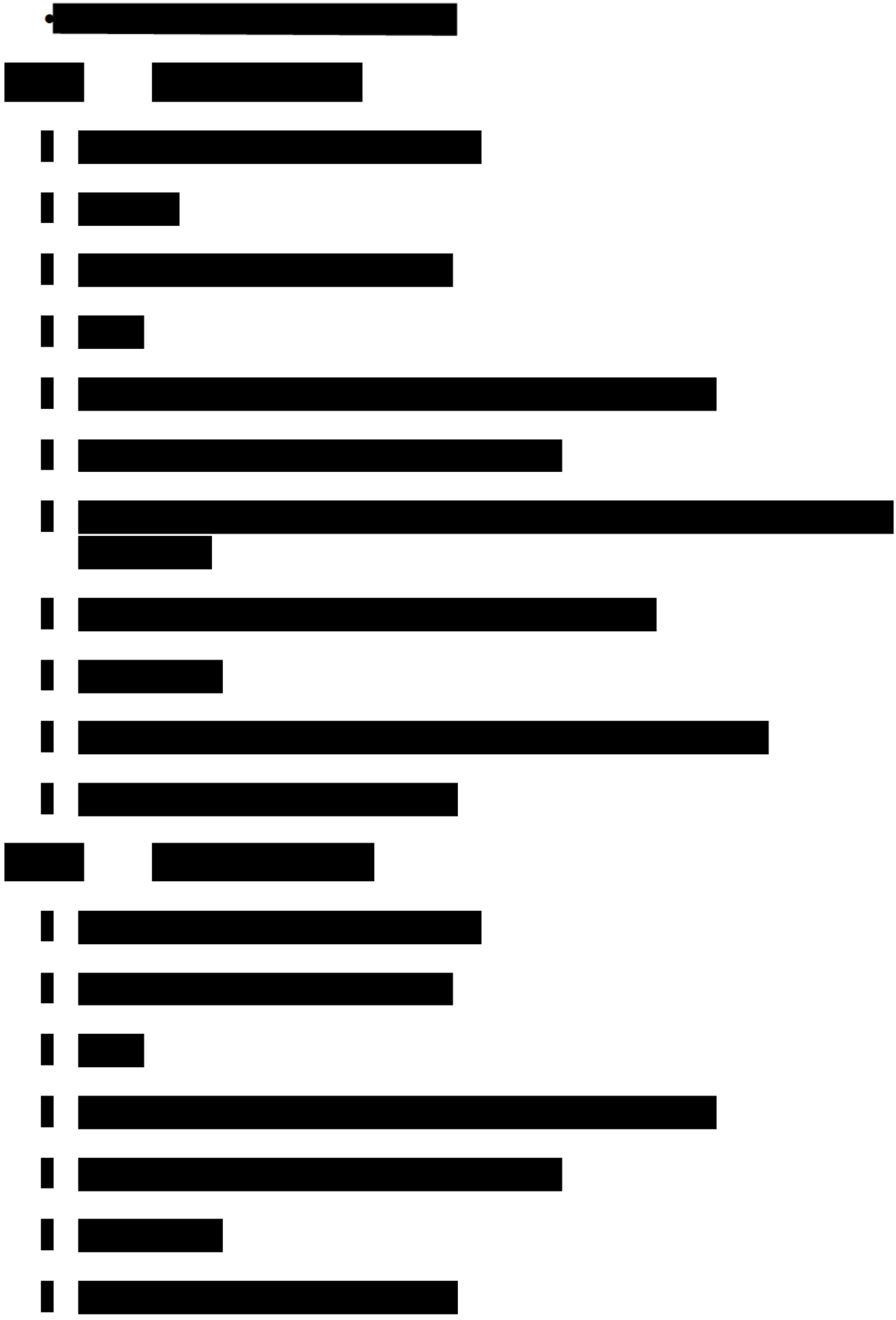

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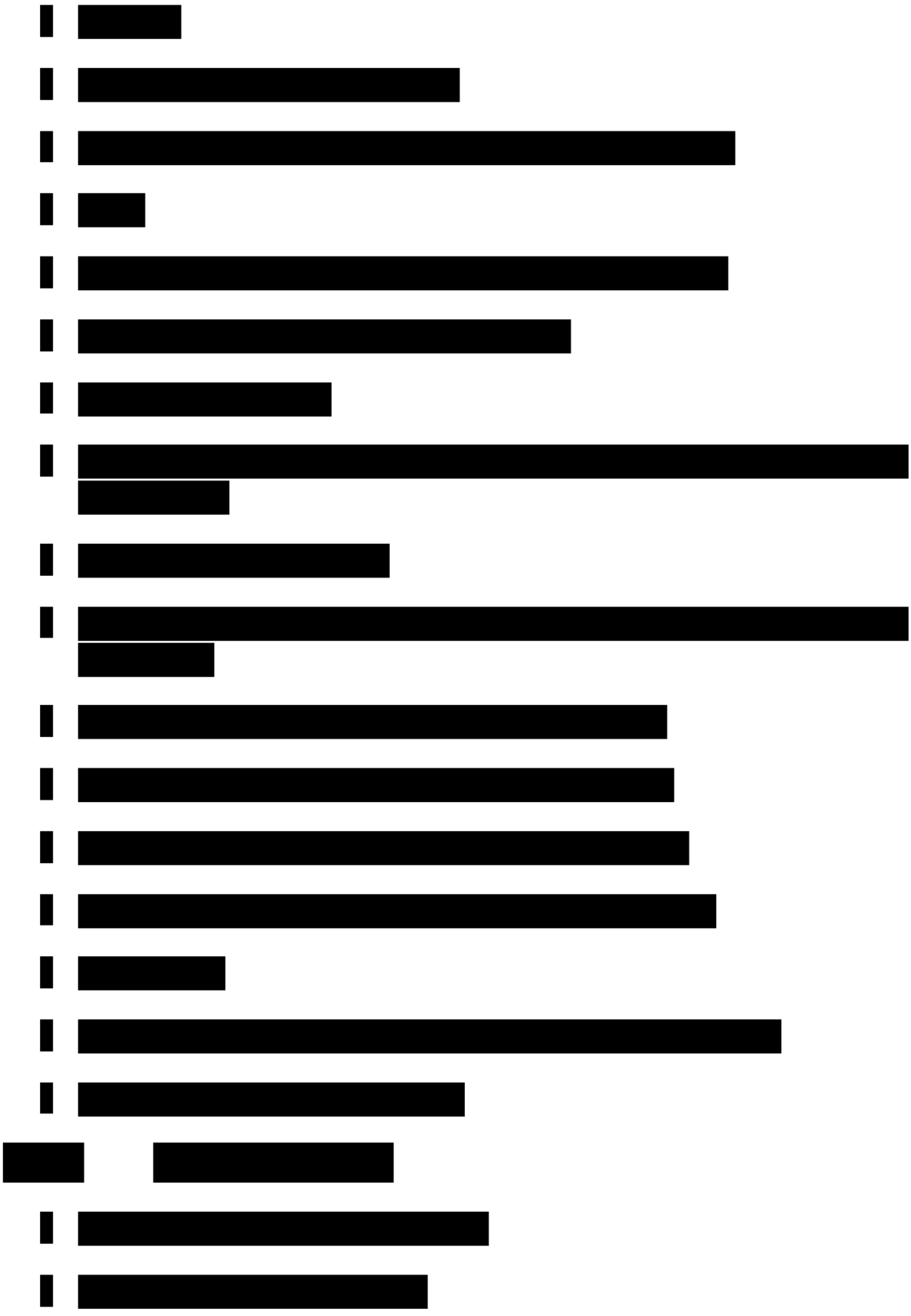

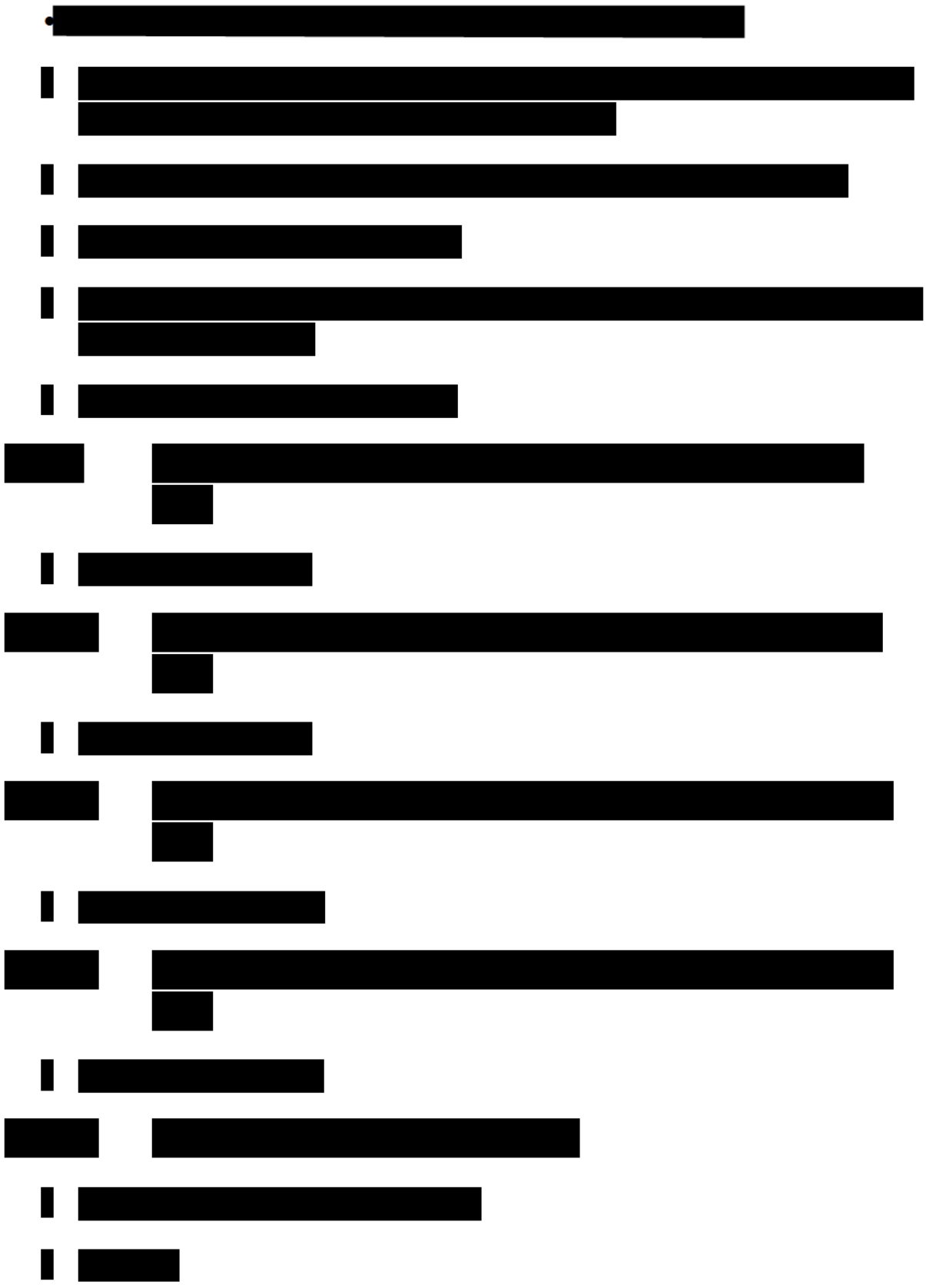

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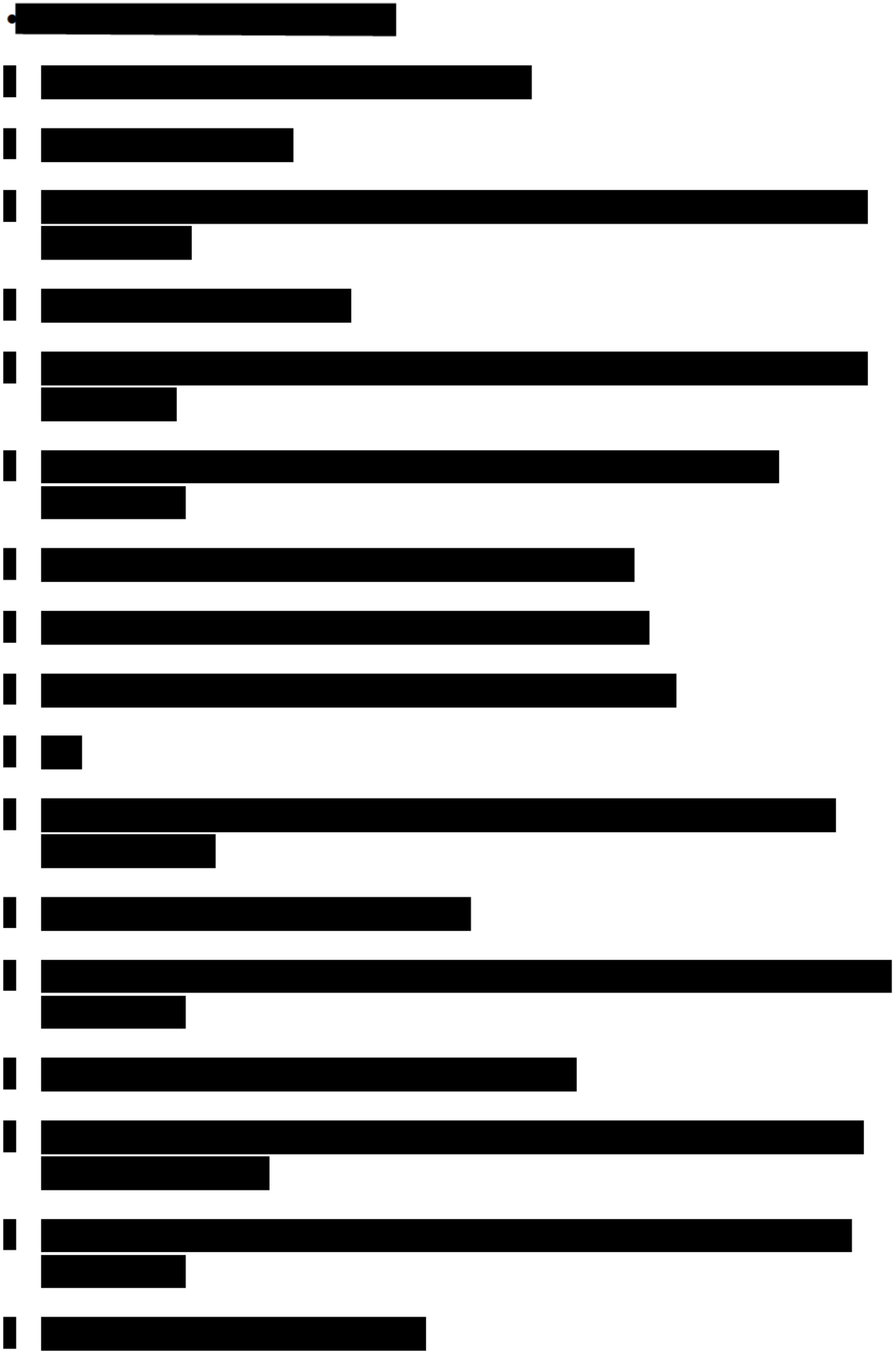

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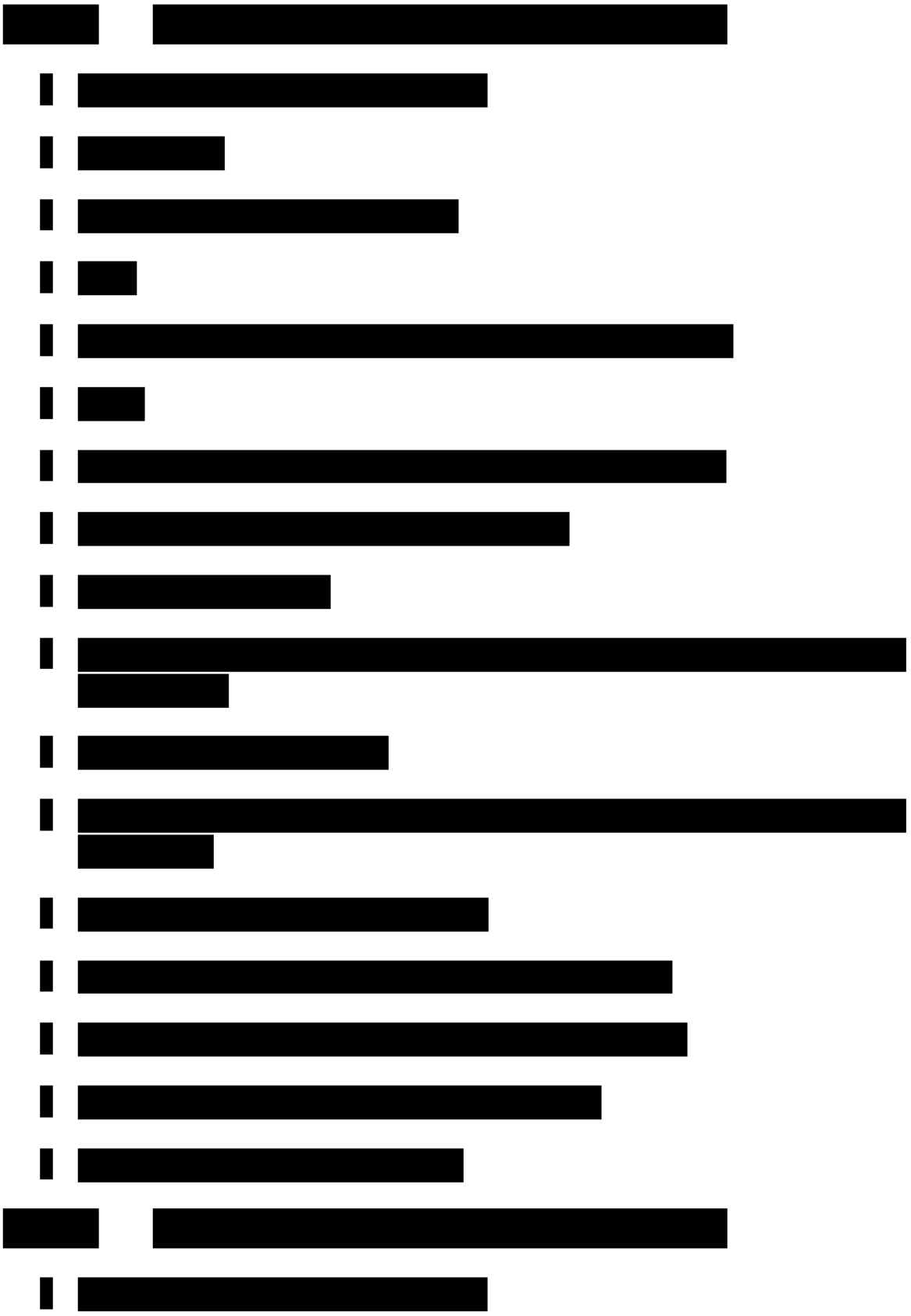

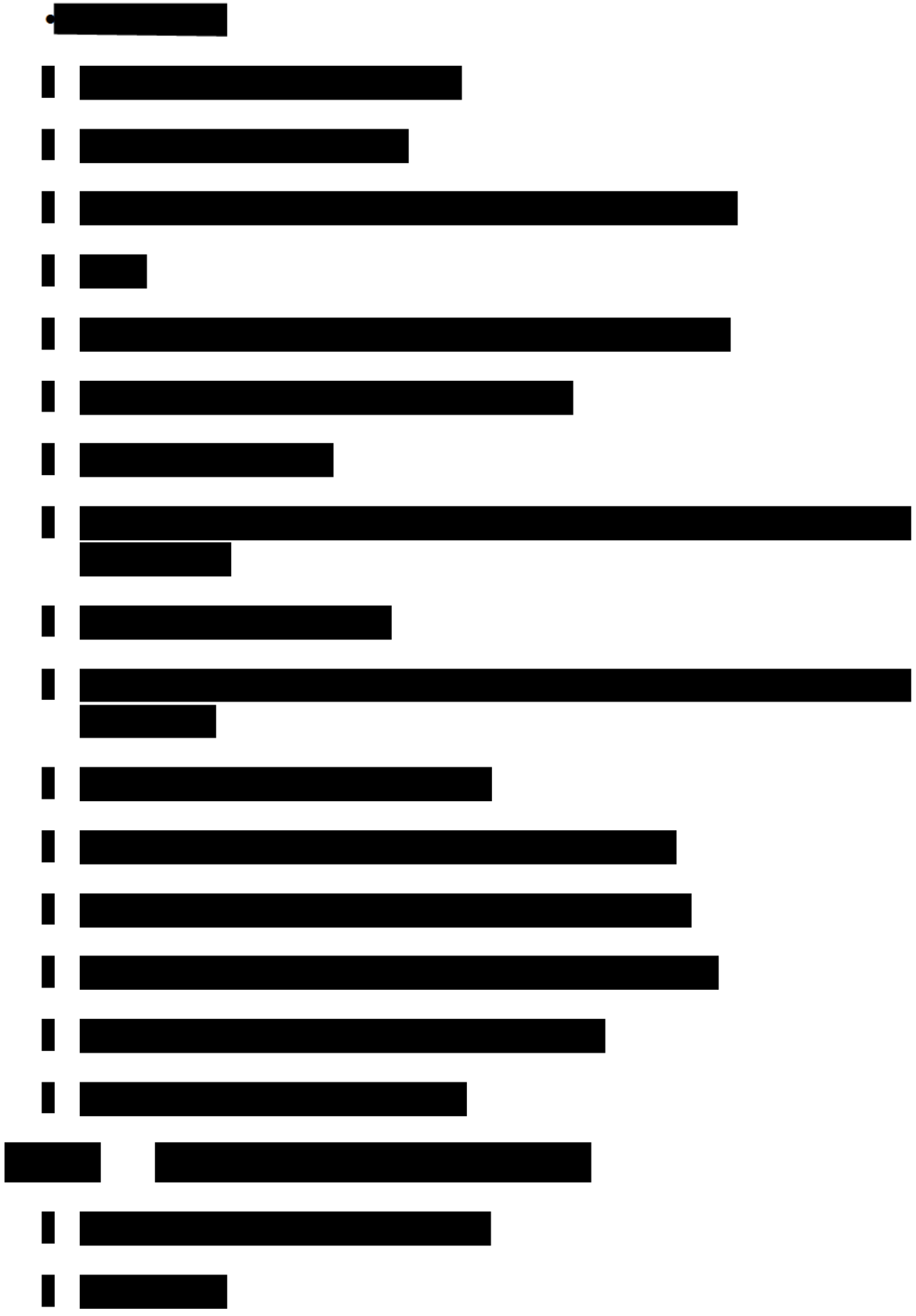

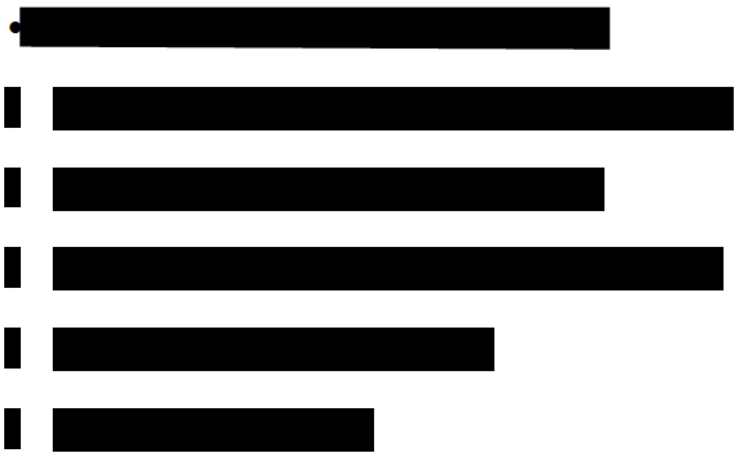

8.5 Instructions for the Patients

Patients are to be instructed not to instill REFRESH PLUS within 6 hours prior to a study visit.

Patients will be instructed to strictly follow the study visit schedule and to report all changes in condition to the investigative site.

Instruction should be given to the patient to maintain a stable dose whenever possible of any chronically used concomitant medication. Patients should be instructed to communicate any changes to their medication or any new medications at their next study visit. Patients should also be reminded to contact the study site if they are experiencing any ocular or nonocular medical changes between study visits, or if they have had any medical procedures (including diagnostic procedures) performed between study visits.

8.6 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise, at the discretion of the investigator. Additional examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study.

If a patient is seen for an unscheduled visit, an assessment and record of adverse events should be completed. Additional evaluations should be performed as necessary, and the appropriate eCRFs should be completed.

8.7 Compliance With Protocol

Patients will be scheduled for follow-up visits and these should occur as closely as possible to the day specified in the visit schedule.

At each postbaseline visit, the investigator or designee will ask patients if they have been compliant with use of only REFRESH PLUS (up to 4 times per day, both eyes), used any concomitant medications, or have had any medical procedure performed since the previous visit.

8.8 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time; these patients will be encouraged to return for the week 24/12R or Exit visit and have exit procedures completed when possible.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate eCRF.

8.9 Withdrawal Criteria

The investigator and Allergan have the right to withdraw a patient from the study at any time for any reason. When possible, the decision to withdraw a patient from study treatment or the study should be discussed with Allergan.

Patients should be discontinued from the study if any of the following criteria are met:

- patient develops (or has an exacerbation of) any medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk or compromises the patient's ability to participate in the study
- patient is unwilling or unable to continue to comply with study procedures

Patients who are withdrawn early from the study during a study visit should have the exit procedures completed when possible.

8.10 Study Termination

The study may be stopped at a study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason, with appropriate notification.

8.11 Adverse Events

Adverse events occurring during the study will be recorded on the adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

8.12 Definitions

8.12.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and 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. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

8.12.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. See Section 8.14 for procedures for reporting a serious adverse event.

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Preplanned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

8.12.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

8.12.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

8.13 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local

regulations, and the governing health authorities. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

8.14 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 12 weeks after the last dose of study drug must be immediately reported, but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan (or Agent of Allergan) as listed on the Allergan Study Contacts Sheet and recorded on the serious adverse event form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of the protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

8.15 Procedures for Unmasking of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned

and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unmasking study medication. The investigator should inform the sponsor (Allergan Medical Safety Physician) of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel calling into the IVRS or IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

9 Administrative Items

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines, eg, the ICH Guideline on GCP.

9.1 Protection of Human Patients

9.1.1 Compliance With Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

9.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

9.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

9.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

9.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

9.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

9.3.1 Patient Privacy

Written authorization and other documentation in accordance with the relevant local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act [HIPAA] Standards for Privacy of Individually Identifiable Health Information).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

9.4 Documentation

9.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRFs serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- patient's name
- patient's contact information
- date that the patient entered the study and patient number
- study title and/or protocol number of the study and the name of Allergan
- A statement that informed consent was obtained (including the date). A statement that written authorization or other local patient privacy required documentation for this study has been obtained (including the date).
- dates of all patient visits
- medical history including childbearing potential (if female)
- ophthalmic history
- All concurrent medications: list all prescription and nonprescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.
- study variables (eg, vital signs, manifest refraction and visual acuity worksheets, IOP measurements, Schirmer's test, biomicroscopy and ophthalmoscopy results, macroscopic hyperemia assessment, HRT-Rostock printouts, staining results, tear film break-up time)
- patient questionnaires
- occurrence and status of any adverse events

- Procedural notes of study treatment preparation and procedure should include the following: date and start/stop time of study treatment preparation, date and time of the procedure, [redacted], and complications, if any.

- date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation

- results of laboratory tests performed by the site (eg, results of urine pregnancy tests, see Section 11.1.23)

9.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

9.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

9.4.4 Retention of Documentation

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

9.4.4.1 Study Site

The study site should retain the essential documents to be kept at the study site, such as source documents, contracts, informed consent form, protocol, records on control of the investigational product, or other study-related documents until either item 1 or 2 listed below, whichever is later. However, when Allergan requires that these documents are to be retained for longer period, the study site should discuss with Allergan regarding the period and method of preservation. The record retainer designated for each record should be responsible for the preservation.

1. The date of approval for manufacturing and marketing applications of the relevant investigational products (in case of discontinuing its development, until at least 3 years after the date of development discontinuation)

2. The day at least 3 years after the date of the termination or completion of the clinical study

The study site and the record retainer should take measures in such a way that these records are not lost or abandoned during the designated period of preservation and that they are presented upon request.

9.4.4.2 Institutional Review Board

The IRB should retain all relevant records such as standard operating procedures (SOPs), membership lists (including qualifications of the members), submitted documents, minutes of meetings, and correspondence until either item 1 or 2 listed below, whichever is later.

1. The date of approval for manufacturing and marketing applications of the relevant investigational products (in case of discontinuing its development, until at least 3 years after the date of development discontinuation)

2. The day at least 3 years after the date of the termination or completion of the clinical study

When the study site or Allergan requests the SOPs and membership lists, the IRB should comply with the request.

9.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

9.5.1 Labeling/Packaging

All study medication will be packaged, labeled, and supplied by Allergan. The investigational materials will be packaged in identically appearing containers consistent with all applicable regulations. The medication will be identified as an investigational compound. The kit number will be identified on the unit label.

9.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator. A unit is defined as a kit. [redacted]

9.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

9.6 Monitoring by the Sponsor

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct onsite visits to review, audit, and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

9.7 Handling of Biological Specimens

All samples will be returned to Allergan or Allergan designee at the completion of the study. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.

9.7.1 Blood and Urine Samples for Safety Analysis

Samples of blood (nonfasting) and urine will be evaluated for blood chemistry, hematology (including complete blood count with differential and hemoglobin A1c [HbA1c]), and urinalysis at a centralized clinical laboratory [redacted] with certification from a recognized accreditation agency. Details of sample collection are found in Attachment 11.1.22 and in the procedure manual.

9.7.2 Blood Samples for Pharmacokinetic Analysis

Blood samples obtained at the study sites will be analyzed for CsA concentrations by an Allergan-qualified laboratory [redacted] using a validated method. This laboratory has been qualified by Allergan's Bioanalytical Sciences department to conduct analysis of clinical samples. Details of sample collection and handling are found in Attachment 11.1.21 and in the procedure manual.

9.7.3 Tear Samples

Tear samples obtained at study sites will be analyzed for CsA concentrations by [redacted] using a qualified method. Details of sample collection and handling are found in Attachment 11.1.20 and in the procedure manual.

All samples will be stored at the clinical site or at [redacted] until shipment to the bioanalytical laboratory.

9.7.4 Impression Cytology Samples

Impression cytology samples may be submitted to 1 or more laboratories for processing and storage prior to forwarding to analytical laboratories for analysis. All laboratories should

meet GLP requirements. Details of sample collection, handling, storage, and shipping procedures are found in Attachment 11.1.16 and in the procedure manual.

9.8 Publications

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.

10 References

Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea. 2003;22:640-650.

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11 Attachments

11.1 Examination Procedures, Tests, Equipment, and Techniques

These tests may not be described in the order in which they are to be conducted. Refer to the Schedule of Visits and Procedures (Table 3 and Table 4) and Section 8.4 for the order in which procedures should be conducted for each visit. Certain study tests and procedures are assigned to the treating investigator to maintain masking of the follow-up investigator to the study treatments. See Table 5 for assignments of procedures and tests by investigator. When not specified, procedures and tests may be done by either the follow-up investigator or appropriately trained and qualified site personnel.

11.1.1 Vital Signs

Systolic and diastolic blood pressure will be measured using an appropriate sphygmomanometer after patients have been at rest (seated) for at least 5 minutes. Blood pressure will be recorded in mm Hg.

Pulse rate will be measured in bpm after the patient has been in a resting state (seated) for at least 5 minutes. Pulse will be counted for 30 seconds, multiplied by 2, and recorded in bpm.

11.1.2 Pregnancy Test

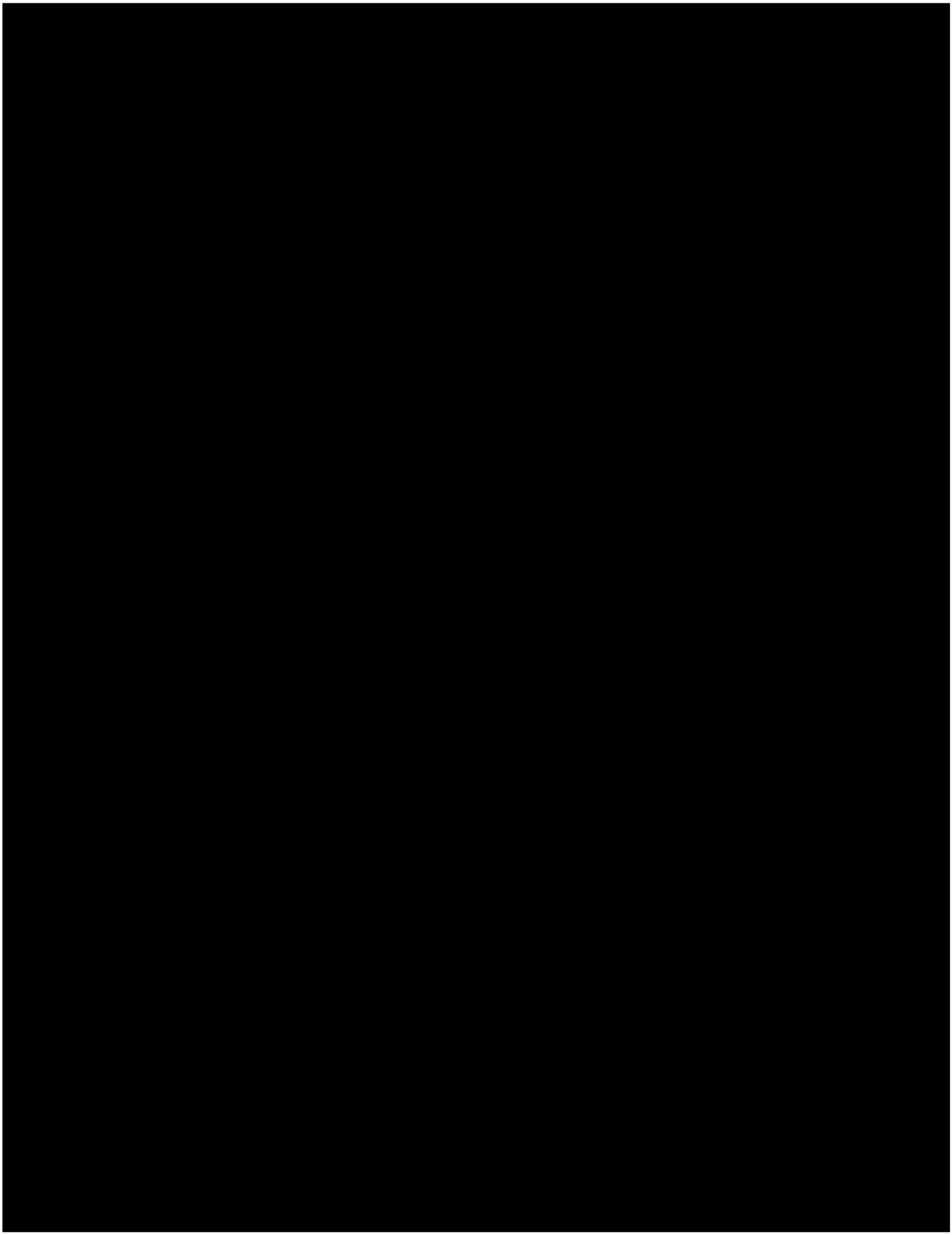
Female patients of childbearing potential will have urine pregnancy tests performed. Pregnancy test kits will be provided by an Allergan-designated supplier and will be administered according to the instructions provided with the tests.

11.1.3 Ocular Surface Disease Index

The OSDI© questionnaire consists of 12 questions regarding ocular symptoms, environmental triggers, and vision-related functioning in patients with dry eye disease (Schiffman et al, 2000). The patient will be asked to rate each symptom using a 5-point scale (0 to 4), where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; and 4, all of the time. Seven questions related to visual functioning allow a response of "N/A" (not applicable); no more than 3 of these 7 questions may be answered as N/A for the questionnaire to be evaluable. The total OSDI score is calculated as: ([sum of scores for all questions answered] X 100)/([total number of questions answered] X 4).

An example of the questionnaire follows.

- [redacted]



[redacted]

11.1.8 Best-corrected Visual Acuity

Manifest refraction will be performed at screening and used for BCVA at all subsequent visits until exit. In patients who are retreated, manifest refraction will be repeated at retreatment

and used for BCVA until exit. If there is a decrease in BCVA, the manifest refraction should be repeated as confirmation. Visual acuity (in Snellen equivalents) will be measured for each eye using a logarithmic visual acuity chart for testing at 10 feet (3 meters). Since most examination rooms do not allow for a 10 feet (3 meters) testing distance, the results from the manifest refraction may be placed in a trial frame and visual acuities measured. The chart should be set at approximately eye level to the average height of a seated patient. Mark a spot on the floor (eg, with tape) that is 10 feet away from the chart. The test distance and illumination for the chart must be kept constant throughout the study.

Begin by testing the right eye. The patient is asked to read each letter, line by line, left to right, beginning with line 1 at the top. The patient should be told that the chart has letters only, no numbers. If the patient reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The patient is not to proceed to the next letter until she/he has given a finite answer.

If the patient 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 patient changes a response after having read the next letter, then the change is not accepted. The examiner must not point to specific letters on the chart during the test.

When the letters become difficult to read, or if the patient identifies a letter as 1 or 2 letters, he/she should be asked to choose one letter and, if necessary, to guess. Record the visual acuity as the lowest line read with **one or no mistakes**. Record the acuity in Snellen equivalent units (eg, 20/63). Repeat for the left eye.

The pinhole method for measuring visual acuity is not acceptable.

11.1.9 Macroscopic Bulbar Hyperemia

The macroscopic (gross) bulbar hyperemia grading should be completed prior to any other eye examinations. Macroscopic bulbar hyperemia grading will consist of both global and regional hyperemia assessments. The global assessment will be done by the follow-up investigator and the regional (quadrant) assessment will be done by the treating investigator. Macroscopic hyperemia assessments will be done under consistent illumination by comparing the appearance of the bulbar conjunctiva to standard photographs (Allergan bulbar conjunctival hyperemia grading guide).

0	(None)	=	Normal. Vessels of bulbar conjunctiva easily observed
+0.5	(Trace)	=	Trace flush, reddish-pink color
+1	(Mild)	=	Mild flush, reddish color
+2	(Moderate)	=	Bright red color
+3	(Severe)	=	Deep, bright diffuse redness

The gross macroscopic hyperemia evaluation should be performed by the same evaluator in the same facility with consistent lighting throughout the entire study, whenever possible.

11.1.10 Photographic Conjunctival Hyperemia Assessment

A Canfield camera will be used at all study sites for ocular surface photography. Images will be uploaded to a reading center to evaluate global and regional hyperemia scores. The global hyperemia scores will be determined from interpalpebral images, and regional hyperemia scores will be determined from 4 quadrant images. The site personnel conducting photographic conjunctival hyperemia assessment will not perform other tasks for the study other than those outlined in Section 5.3. See the procedure manual for further details.

11.1.11 HRT3-Rostock — Ocular Surface Imaging

The Heidelberg Retinal Tomograph 3 (HRT3) is a confocal laser scanning system. The addition of the Rostock Cornea Module (Rostock) converts the HRT3 to a confocal microscope for in vivo histological views of the ocular surface. The HRT3-Rostock will be used at select study sites and in select patients. Additional details can be found in the procedure manual.

11.1.12 Slit-lamp Biomicroscopy Examinations

Findings other than those listed below should be recorded under "other" for the appropriate location of the finding.

11.1.12.4 Anterior Chamber (conducted by follow-up investigator)

For the measurements of cells and flare based on standardized uveitis nomenclature (SUN Working Group, 2005), the following settings should be used:

- 1 x 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

11.1.12.5 Iris/Pupil (conducted by follow-up investigator)

The iris/pupil will be evaluated for pathology. If pathology is present, it will be described.

11.1.13 Dilated Ophthalmic Examinations (conducted by treating investigator)

Use biomicroscopic examination, indirect lenses, direct/indirect ophthalmoscopy, etc as appropriate to visualize. Dilating drops should not be administered until slit lamp biomicroscopy and IOP measurements are completed.

11.1.13.1 Lens

Lens Status

Lens status will be assessed as phakic, pseudophakic, or aphakic. The lens (including the posterior capsule for patients who have undergone lens extraction) will also be evaluated for pathology. If pathology is present, it will be described.

Cataract Assessment (phakic eyes only)
Under dilated examination, the presence and severity of nuclear, cortical and posterior subcapsular cataract lens opacities will be evaluated. At the first dilated examination, each type of cataract, if present, will be graded using the scale below. At the last follow-up dilated examination, each type of cataract will be assessed for change from first dilated exam and if changed, the current severity will be graded using the scale below:

0	=	None
+1	=	Mild
+2	=	Moderate
+3	=	Severe

11.1.13.2 Vitreous

The vitreous will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

11.1.13.3 Fundus

The fundus (posterior pole; periphery, when dilated) will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

11.1.13.4 Optic Nerve

The optic nerve will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

Cup/disc ratio will be reported using a 0.0 to 1.0 scale. The Armaly chart provided by Allergan provides a pictorial scale of cup/disc ratio of 0.0 to 0.8. Note if the condition is not evaluable.

11.1.14 Intraocular Pressure

IOP should be measured only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. Measurements will be taken using a Goldmann applanation tonometer affixed to a slit lamp with the patient seated. The patient and slit lamp should be adjusted so that the patient'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 s/he 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.

11.1.15 Schirmer's Tear Test with Anesthesia

Procedure

This test is to be conducted in a dimly lit room. Instill 1 drop of anesthetic into each eye and wait approximately 4 minutes. Gentle blotting of the corners of the eyelids with a facial tissue is allowed to catch the over spill. Any direct, active blotting of the cul-de-sac will not be allowed. Ask the patient to look up and draw the lower lid gently downward and temporally. Hook the rounded bent end of the sterile strip into the lower cul-de-sac at the temporal one-third of the lower eyelid margin. Start the timer. To minimize artifacts from this test, patients should gently close their eyelids until 5 minutes have elapsed, patients then 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 ball point pen at precisely 5 minutes.

Strip Measuring

Write the letter "R" on the strip used in the right (OD) eye and the letter "L" on the strip used in the left (OS) 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. Once marked, each strip will be affixed to the source document (marked side up), in the space provided, and covered completely with transparent tape. The measurement is then to be captured on the source document and transcribed onto the eCRF.

11.1.16 Impression Cytology for Biomarker Analysis (conducted by treating investigator)

Prior to initiation of impression cytology, each site must ensure the availability of a 4° C refrigerator for immediate storage of samples.

Conjunctival epithelial cells will be collected via impression cytology from each eye from 2 locations around the superior–temporal bulbar conjunctiva. Sample collection, handling, storage, and shipping details can be found in the procedure manual.

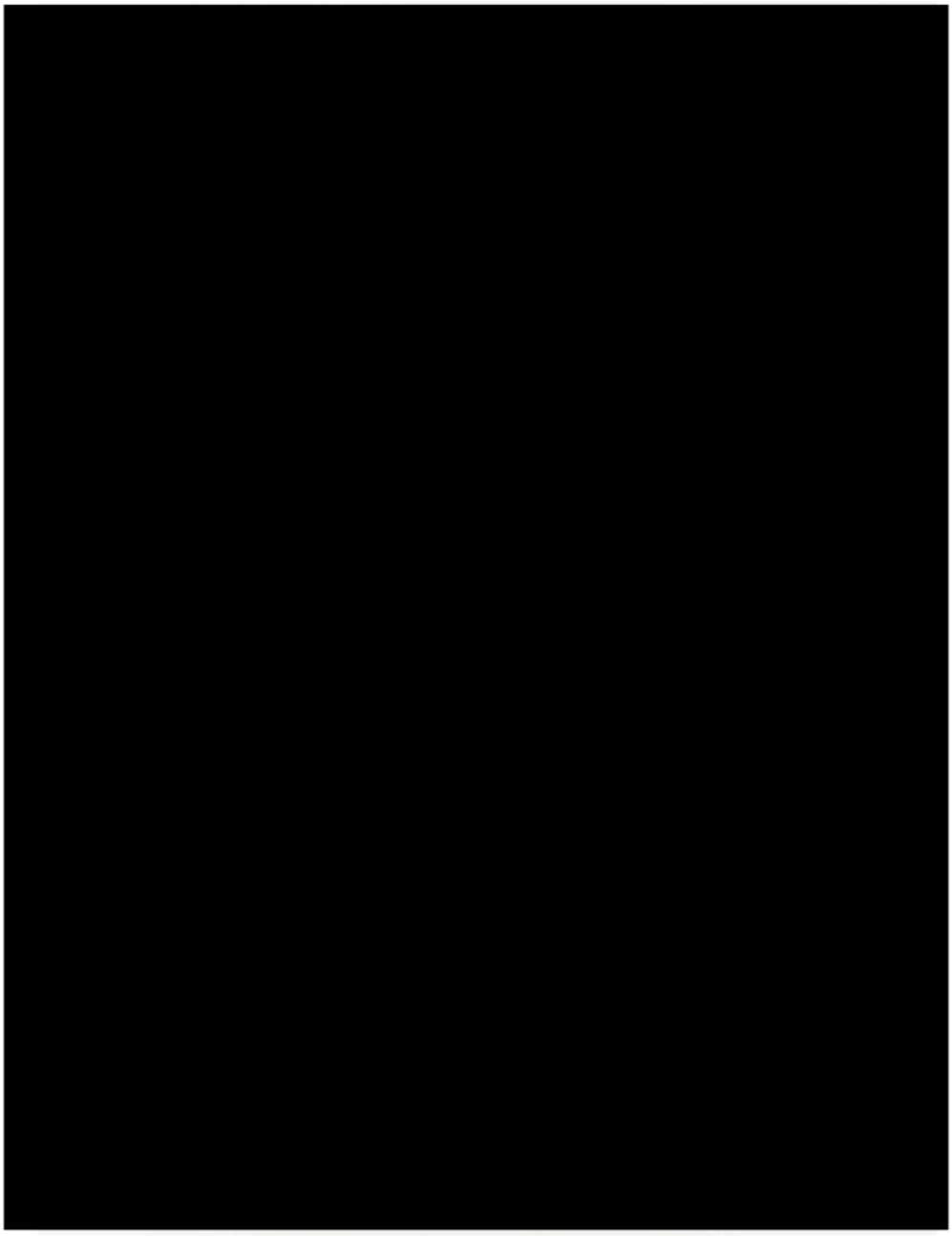
[redacted]

11.1.18 Corneal Sodium Fluorescein Staining

The examination will be performed by the follow-up investigator with the slit lamp at 10X magnification. A fluorescein strip will be moistened with balanced salt solution and the strip will be gently touched against the superior bulbar conjunctiva of the right eye. A stopwatch will be started immediately after application. The corneal staining will be graded approximately 2 minutes after instillation of the fluorescein. Evaluate the entire cornea for staining using the supplied yellow barrier filter placed directly in front of the objective lens

of the slit lamp. The slit lamp's cobalt blue filter must be used to illuminate the cornea. Corneal fluorescein staining should be evaluated as close to the 2-minute timepoint as possible. Refer to the Oxford Scheme (Bron et al, 2003; DEWS, 2007) outlined in the laminated chart provided to grade the staining. Although the scheme depicts the grading of conjunctival staining, only corneal fluorescein staining is to be graded. Once grading of the right eye is complete, the entire procedure will be repeated for the left eye.

For grades 0 to 2, the dot count will be collected and recorded.



11.1.19 Lissamine Green Conjunctival Staining

Ophthalmic lissamine green stain will be applied to the inferior cul-de-sac of the right eye. A stopwatch should be started immediately after application. The patient will be instructed to blink several times.

Using white light of low to moderate intensity, the follow-up investigator will grade only the visible conjunctiva, without holding the eye open. Conjunctiva to be evaluated are within the

interpalpebral region of the nasal and temporal zones. Refer to the Oxford scheme of staining to grade. Grade staining independently in each of the 2 areas of the conjunctiva (2 areas each: temporal [a] and nasal [b]) as shown in the diagram below based upon a 6-point scale (0, 1, 2, 3, 4, 5). Grading should be done within approximately 3 minutes of instillation of the lissamine green stain. The staining values obtained from the Oxford scheme (Section 11.1.18) are then to be captured on the source document (as shown in the diagram below) and transcribed onto the eCRF.

The procedure is then repeated for the left eye.

11.1.20 Pharmacokinetic Tear Samples

Prior to tear sample collection, each site must ensure the availability of dry ice for immediate storage of tear samples prior to transfer to a freezer.

Tear samples will be obtained using a single use, sterilized microcapillary tube for each collection per patient. Tear collection will continue until a maximum of 5 µL is collected from each eye or until 5 minutes have elapsed (per eye). Complete handling, labeling, and packaging instructions are provided in the procedure manual.

11.1.21 Pharmacokinetic Blood Samples

All blood samples for pharmacokinetic analysis will be collected as described in the procedure manual.

11.1.22 Blood and Urine Sample Collection

Prior to blood and urine sample collection, each site must ensure the availability of dry ice for immediate storage of samples prior to transfer to a freezer. The nonfasting blood and urine samples should be sent on dry ice to [redacted] for analysis on the same day that they are collected. Patient number should be left blank on the lab requisition form for the baseline visit.

Blood and urine samples will be collected under normal conditions. Normal phlebotomy procedures will be followed for collection of blood samples. Tubes for blood sample collection for pharmacokinetic measures will be filled first. All blood and urine sample collection tubes should be appropriately labeled. Refer to the procedure manual for additional details.

Specimen Collection kits

A specimen collection kit has been designed for each visit requiring laboratory data within the protocol. Each kit is labeled with the pharmaceutical company name, protocol number, investigator number and visit. For the content of each kit, specimen collections, and shipping instructions, please refer to the [redacted]. All necessary venipuncture and shipping materials are provided in the kits. Supplies not included in the kits are: tourniquets, cotton swabs and Band-Aids®.

Safety labs will be collected nonfasting. All blood and urine specimens will be shipped by the site to the central laboratory. Refer to the central laboratory manual for instruction on sample collection, processing, storage, and shipment procedures. The central laboratory will analyze all blood and urine specimens.

11.1.23 Blood and Urine Sample Analysis

Hematology parameters will include hematocrit, hemoglobin, HbA1c, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets, red blood cell (RBC) count, RBC morphology, total white blood cell (WBC) count, and differential (neutrophils, bands, lymphocytes, monocytes, basophils, and eosinophils).

Serum chemistry parameters will include albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartase aminotransferase (AST), gamma-glutamyl transferase (GGT), bicarbonate, calcium, chloride, creatinine, creatine kinase, direct bilirubin, glucose, indirect bilirubin, magnesium, phosphorous, potassium, sodium, total bilirubin, total cholesterol, total protein, urea nitrogen, and uric acid. The urine will be analyzed for specific gravity, pH, color, protein, glucose, blood, bilirubin, and microscopic examination (WBC, RBC, epithelial cells, bacteria, mucus, casts, crystals).

11.2 RESTASIS X Administration

RESTASIS X administration should be conducted by the treating investigator. [redacted]

11.3 Handling of Biological Specimens

Additional details for handling, processing, and shipping biological specimens are in the procedure manual.

11.4 Glossary of Abbreviations

Term/Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-12h}	area under the concentration-time curve from 0 to 12 hours
BCVA	best-corrected visual acuity
CFI	cyclosporine [redacted]
CFR	Code of Federal Regulations
C_{max}	maximal concentration
CsA	cyclosporine
DET	dry eye test
[redacted]	[redacted]
eCRF	electronic case report form
F1	[redacted]
F2	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA-DR	human leukocyte antigen type DR
HRT3-Rostock	Heidelberg retinal tomograph with Rostock cornea module
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IκB	Inhibitor of κB
IL-2	Interleukin-2
IOP	intraocular pressure
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web-based response system
LogMAR	logarithm of the minimum angle of resolution

MedDRA	Medical Dictionary for Regulatory Activities
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mITT	modified intent-to-treat
N	sample size
NFATc	nuclear factor of activated T cells
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index
OU	both eyes
PRO	patient-reported outcome
RBC	red blood cell
SOP	standard operating procedure
TBUT	tear film break-up time
VAS	visual analog scale
WBC	white blood cell

11.5 Protocol Amendment 1 Summary

Title: A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol 192371-024 Amendment 1

Date of Amendment: March 2014

Amendment Summary

This summary includes changes made to Protocol 192371-024 (approved December 2013). Based on additional information from clinical sites and investigators, this protocol is amended to: 1) modify sample storage conditions, 2) indicate that 2 investigators (follow-up and treating) will be dividing the procedures and clarify who will be performing various study activities, and 3) clarify several study activities, methods for masking, [redacted]

The following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Tables 3 and 4 (Summary)	Separated [redacted] slit-lamp biomicroscopy exams into separate line items	Procedures tables updated for clarity and to match existing text in Section 8.4
Summary, Tables 3 and 4, and 12.1.12	Changed terminology from "dilated fundoscopic exam" to "dilated ophthalmic exam"	More accurately reflects the procedure
3.2	Clarified language around stage 1 and 2 activities; added that ad hoc review of masked or unmasked data may occur at any time during the study, in order to evaluate unexpected safety findings	[redacted] ad hoc review of unexpected findings may occur at any time.
summary (page 16), Table 4, 6.3, 8.4, 12.1.10	HRT3 parameters changed to "ocular surface" instead of "cornea and conjunctival".	"Ocular surface" more accurately reflects the collection of HRT3 parameters being evaluated.
Summary	Changed numbering of key inclusion criteria to bullet points	Need to avoid different numbers for the same inclusion criteria when comparing between the summary and Section 4.3

Section	Revision	Rationale
4.3	Inclusion criteria numbering changed so each item has a unique number in the list. Only the last item in the list changed from 1 to 8.	Unique numbers are needed in order to uniquely capture the reason for screening failures in the database.
4.4	Exclusion criteria numbering changed so each item has a unique number in the list. Only the last item in the list changed from 1 to 35.	Unique numbers are needed in order to uniquely capture the reason for screening failures in the database.
6.4, 12.1.15, 12.1.19, 12.1.21	Remove sample storage temperatures for impression cytology, blood, and tear pharmacokinetic samples. Specified immediate storage at 4° C is needed for impression cytology biomarker samples.	Remove specifics regarding storage temperatures; now providing in procedure manual only.
6.4, 12.1.18	Lissamine Green test strips have been replaced with instillation of Lissamine Green solution. Repeat of procedure added for the left eye.	Lissamine Green test strips have been removed from the market.
Tables 3, 4, and 5; 5.3, 8.4, 12.1.6, 12.1.8, 12.1.9, 12.1.11, 12.1.12, 12.1.15, 12.1.17, 12.2	Changed from a third party individual (now termed the treating investigator) doing [redacted], to the treating investigator [redacted] RESTASIS® X administration, macroscopic regional hyperemia, slit lamp biomicroscopy (eyelid, eyelid margins, lashes; and conjunctival hyperemia, edema, and [redacted]l hemorrhage), impression cytology for biomarker analysis, and dilated ophthalmoscopy. Added a new table (Table 5) to clarify roles, and clarified that the study will require a follow-up investigator and a treating investigator.	To maintain masking of the follow-up investigator, the third-party investigator (now termed the treating investigator) [redacted] will now also perform assessments [redacted]
6.5	In the event external data need to be captured within the eCRFs by the vendor, the vendor will handle the data as a site would and the ~~site~~ vendor will be responsible for ensuring that these data are properly recorded.	The vendor will take responsibility for external data capture within the eCRFs, not the site.

Section	Revision	Rationale
10.4.1	In source documents section, procedural notes of study treatment is changed accordingly: [redacted]	[redacted]
10.4.1	Removed randomization number from the patient's record information	The patient's source documents do not need the randomization number.
10.7.2, 10.7.3	Added that details of pharmacokinetic sample collection and handling are found in the attachments and in the procedure manual.	Reference to other information was needed.
10.7.3	Change location of tear sample analysis from Allergan bioanalytical sciences department to [redacted]	Analysis location now matches that for blood samples.
12.1.3	Inserted new version of the OSDI questionnaire	Provided an example of the version that will be used in the study
12.1.8	Added sentence: "Regional hyperemia scores will also be determined by slit lamp microscopy and scoring each of the 4 quadrants of the conjunctiva."	Scoring of conjunctival hyperemia will be done by quadrants, as well as by gross examination.
12.1.17	Removed DET from sentence describing fluorescein strips	DET is only used for the TBUT procedure.

11.6 Protocol Amendment 2 Summary

Title: A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol 192371-024 Amendment 2

Date of Amendment: June 2014

Amendment Summary

This summary includes changes made to Protocol 192371-024 Amendment 1 (approved March 2014). Based on additional information from clinical sites and investigators, this protocol is amended to: 1) clarify OSDI requirements for study entry, 2) clarify sequence of contacts to IVRS/IWRS for patient numbers and randomizations, and 3) provide flexibility for the method of lissamine green instillation based upon recent difficulties with sourcing lissamine reagents.

The following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Summary, 4.3	[redacted]	Clarified that OSDI score requirements must be met at both screening and baseline visits.
6.4, 12.1.18	Lissamine green stain is replacing Lissamine green solution.	Lissamine green solution has been difficult to obtain.
Tables 3 and 4; 8.4.1.1, 8.4.1.2, 8.4.1.9, 8.4.2.1, 8.4.2.2, 8.4.2.8, 8.4.2.14	Contact IVRS/IWRS at the screening visit was moved to after written informed consent, and specified that it will be used for patient number assignment. Specified that IVRS/IWRS contact for Stage 1 is at baseline (for randomization) and week 24 (for study exit), and for Stage 2 contact is at baseline (for randomization and treatment allocation), week 12 (for treatment allocation), and at week 24 (for study exit).	Patient number assignment is needed for all patients prior to the tests and procedures performed at screening. Clarified the purposes of other IVRS/IWRS contacts.

Section	Revision	Rationale
Table 5, 12.1.16	Clarified that grading of TBUT should be done by the follow-up investigator. However, instillation of fluorescein for the TBUT exam should be done by the treating investigator or qualified personnel that assist the treating investigator.	For the TBUT exam, fluorescein is applied to the superior conjunctiva, thus potentially exposing the site [redacted] Having either the treating investigator or qualified personnel that assist the treating investigator apply the fluorescein will preserve masking for the follow-up investigator to the study treatment.
5.3	The site personnel conducting photographic conjunctival hyperemia assessments ~~will not perform other tasks for the study~~ may assist with study tasks consistent with the role of the treating investigator.	Clarified role of site personnel conducting photographic conjunctival hyperemia assessment.
Summary, 7.3.3	Pharmacokinetic parameters for blood and tears will only be calculated for samples collected from patients who receive study treatment. ~~Pharmacokinetic parameters for tears will only be calculated for samples collected from drug treated eyes of patients who receive study treatment.~~	Modified to analyze tear samples from both drug treated and untreated (contralateral) eyes of patients.

11.7 Protocol Amendment 3 Summary

Title: A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol 192371-024 Amendment 3

Date of Amendment: September 2014

Amendment Summary

This summary includes changes made to Protocol 192371-024 Amendment 2 (approved June 2014). [redacted]

The following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Summary	In the Dosage/Dose Regimen section, the change is: For cohorts 3 and 4, [redacted] –will evaluate available data 2 weeks after treatment of the fourth patient in each cohort and then again 2 weeks after treatment of the last patient in each cohort. [redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
Summary, Sections 1.1, 5.1, 5.2	The word [redacted]" was removed from descriptions of the vehicle and the study treatment.	The vehicle may not contain a [redacted] formulation in the future.
Section 3	[redacted] patients in cohort 4 ~~(approximately 8 patients)~~ will receive [redacted] vehicle in one eye and [redacted] RESTASIS® X [redacted] in the other eye. ~~Four~~ [redacted]	[redacted]
Section 3.2	[redacted]	[redacted]
Section 5.8	Added the text "Periodically throughout the study, the [redacted] may be contacted and asked to provide feedback (via a survey) on the feasibility and potential clinical barriers of the study drug [redacted]	[redacted]

11.8 Protocol Amendment 4 Summary

Title: A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol 192371-024 Amendment 4

Date of Amendment: February 2015

Amendment Summary

This summary includes changes made to Protocol 192371-024 Amendment 3 (approved September 2014). This protocol is amended to increase the highest dose cohort to [redacted] and to include [redacted] The number of cohorts in Stage 1 is increased from 4 to 9, with 2 additional dose levels of [redacted] now included. [redacted] The approximate number of patients in the study has been increased from 53 to 138. Stage 1 will have approximately 63 patients, and Stage 2 will have approximately 75 patients. The [redacted] to be used in Stage 2 will be recommended [redacted] based on safety data from Stage 1.

Section	Revision	Rationale
Summary: Study Design, Study Treatment Groups, Dosage/Dose Regimen	In Stage 1, 2 dose levels were added [redacted] RESTASIS X will be evaluated. [redacted]. Up to 3 doses of F2 will be evaluated; actual doses [redacted] to be used in Stage 2 will be determined by data from Stage 1, [redacted]	Additional cohorts were added to accommodate the 2 new dose levels. [redacted]
Table 1	Rows were added for Cohorts 5A to 6D	Details for the 5 new cohorts in Stage 1 were added.
Table 2, footnote b	The maximum possible dose is [redacted] per eye, [redacted].	The highest dose will require a larger volume [redacted].

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Section	Revision	Rationale
Table 2	[redacted]	[redacted]
Summary	[redacted]	Safety and tolerability data that is evaluated [redacted] will drive the decisions of what doses [redacted] are appropriate to test.
Figure 1	The schematic was updated to illustrate the additional cohorts and decision points in Stage 1. [redacted]	For illustration of other changes.
Section 1.2	Text describing the nonclinical safety and pharmacokinetics of the F2 [redacted] per eye, and of the F1 [redacted] per eye, is described in rabbits and dogs. Safety margins are also described.	Nonclinical data support the safety of F1 ([redacted] and F2 [redacted]
Section 3	The study design for cohorts 5A through 6C is described. The [redacted] per eye dose will be administered by [redacted], while the [redacted] dose will be administered [redacted]. Decisions to continue dosing a given cohort and/or to escalate to the next higher dose cohort is based upon [redacted] review of data following 2 weeks of monitoring of the first 4 patients in a given cohort.	Additional cohorts and dose volumes were added to accommodate the 2 new dose groups.
Section 3.2	[redacted]	[redacted]
Section 4.1	The number of sites used for Stage 1 has been increased to 10, and the number of sites for Stage 2 has been increased to 15. The number of patients has been increased to 63 and 75 for Stages 1 and 2, respectively.	Additional cohorts require additional sites and patients.
Sections 5.1, 5.2	[redacted]	[redacted]

Section	Revision	Rationale
Section 5.6	Additional dose groups of [redacted] were added.	For consistency with other earlier sections.
Section 7	Added: A database lock may also be performed for all patients in stage 2 at 4 weeks following retreatment (ie, Week 4R).	An additional data analysis was added at Week 4R for administrative purposes.
Section 8	Changes to the number of cohorts, dose groups, highest dose group, [redacted] are made throughout.	For consistency with other earlier sections.

11.9 Protocol Amendment 5 Summary

Title: A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol 192371-024 Amendment 5

Date of Amendment: April 2016

Amendment Summary

This summary includes changes made to Protocol 192371-024 Amendment 4 (approved February 2015). This amendment includes evaluation of RESTASIS® X retreatment at week 12 in stage 1, the safety of an alternate vehicle [redacted], bilateral treatment of both eyes with either vehicle or RESTASIS® X, and a Dry Eye Treatment Satisfaction Questionnaire in stage 2.

The following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Title Page	[redacted]	[redacted]
Summary, Study Objectives and Sections 2.1, 6.3, and 7.3.2	"Exploratory" was deleted from the description of pharmacodynamics for stage 2	Pharmacodynamics will only be exploratory in stage 1
Summary, Clinical Hypotheses and Section 2.2	For stage 1: In patients with moderate to severe dry eye disease, at least 1 dose of [redacted] RESTASIS® X will demonstrate an acceptable safety profile with retreatment dosing.	Patients in 2 cohorts will receive retreatment
	For stage 2: In patients with moderate to severe dry eye disease and 1 or more concomitant systemic immune-mediated diseases, at least 1 dose of [redacted] RESTASIS® X will demonstrate an acceptable safety, pharmacodynamic, and pharmacokinetic profile with both single dosing and retreatment.	For clarification

Section	Revision	Rationale
Summary, Study Design and Sections 3 and 3.1	The study design was modified to allow for additional doses to be examined and for retreatment in cohorts 6C and 6D in stage 1 of the study and to include an alternate vehicle in stage 2	To evaluate additional doses and the safety of retreatment in stage 1, and to evaluate another vehicle in stage 2
Summary, Structure and Controls	Added retreatment for cohorts 6C and 6D in stage 1 of the study, and added a vehicle treatment group and replaced sham with vehicle treatment in stage 2 of the study	To evaluate the safety of retreatment and another vehicle
Summary, Study Treatment Groups	Stage 1: Vehicle, RESTASIS® X F1 [redacted], and RESTASIS® X F2 [redacted] 1 [redacted] Stage 2: RESTASIS® X (~~approximately 3~~ [redacted] and 4 dose groups: vehicle, low, medium, and [redacted] high will be based on results from stage 1 [redacted]	To allow for additional doses to be evaluated in stages 1 and 2 of the study
Summary, Controls	Stage 1: sham ([redacted] treatment, vehicle [redacted] Stage 2: ~~sham~~ [redacted] ~~treatment~~ vehicle	To evaluate another vehicle
Summary, Dosage/Dose Regimen	Stage 1 will sequentially examine the safety of doses [redacted] of RESTASIS X administered [redacted]	To allow for additional doses to be evaluated in stage 1 of the study
	For cohorts 3 through ~~6C~~6B, the DRC will evaluate available ~~safety~~ data 2 weeks after treatment of the fourth patient in each cohort and then again 2 weeks after treatment of the last patient in each cohort. For cohorts 6C and 6D, respectively using [redacted], in the absence of significant safety findings (determined by the investigator), patients will undergo retreatment in the same location, with the same [redacted], and dose at week 12 and will be followed for another 12 weeks. Two weeks following retreatment of the last patient in both cohorts 6C and 6D, [redacted] evaluate available data and recommend whether to allow retreatment (in stage 2) in the same [redacted].	[redacted]
	Dosing in stage 2 will begin as a ~~pair~~ bilateral-eye treatment of RESTASIS® X or vehicle ~~versus sham for 12 weeks~~. For treatment groups 2 to 4, the DRC may recommend initial dose selection [redacted] In the absence of	To evaluate another vehicle

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Section	Revision	Rationale
	significant safety findings (determined ~~per patient~~ by the investigator) at 12 weeks, patients in treatment group 1 will be retreated with vehicle in both eyes and followed for another 12 weeks. In the absence of significant safety findings (determined ~~per patient~~ by the investigator) at 12 weeks, patients in treatment groups 2 to 4 will be retreated with RESTASIS® X in both eyes and followed for another 12 weeks.	
Summary, Table 1	Columns were added for retreatment at week 12; for cohort 6A, [redacted] (F2), and the total dose was changed from TBD to [redacted] for cohort 6B, the volume per location was changed from TBD to [redacted] and the total dose was changed from TBD to [redacted] for cohort 6C, [redacted] and the total dose was changed from TBD to [redacted] and for cohort 6D, [redacted] and the total dose was changed from TBD to [redacted]	To define specific doses for cohorts 6A through 6D
Table 2	Study eye was changed to right eye, contralateral eye was changed to left eye, a vehicle treatment group of 8 patients was added to receive vehicle in both eyes at baseline and at the week 12 retreatment; the baseline treatment in the left eye was changed from sham to RESTASIS® X for treatment groups 2 through 4, the number of patients in the remaining treatment groups was changed from TBD to 25, enrollment was changed from approximately 75 to 83 patients, footnote c was added to explain how to retain masking for groups 2 to 4, and footnote d was added to describe the location of the retreatment [redacted]	To evaluate another vehicle [redacted]

Section	Revision	Rationale
Summary, Randomization/ Stratification	Patients will be ~~equally~~ allocated in a randomized fashion to the treatment groups. This randomization will be stratified by Sjögren's syndrome (presence or absence) at baseline. ~~Within each treatment group, patients will also be randomly assigned with respect to the eye, right or left, to receive RESTASIS® X (termed the study eye) at baseline. The contralateral eye will receive sham treatment.~~	Within each treatment group in stage 2, both eyes will receive the same treatment
Summary, Visit Schedule	Week 2 was corrected to week 1 for stage 2	Correction
Summary, Figures 1 and 2	Figures 1 and 2 were revised to reflect changes in study design in stages 1 and 2	For consistency with the protocol
Summary, Number of Patients and Section 4.1	The total number of patients to be enrolled was changed from approximately 138 to approximately 146, the number of patients to be enrolled and cohorts in stage 1 was changed from approximately 63 to up to 63 and from up to 9 to approximately 10, and the number of patients to be enrolled in stage 2 was changed from approximately 75 to approximately 83 and from up to 3 to 4 treatment groups	To accommodate the number of patients being treated in cohorts 6C and 6D and the addition of the vehicle treatment group in stage 2 of the study
Summary, Inclusion Criteria	[redacted]	[redacted]
Summary, Health Outcomes	The Dry Eye Treatment Satisfaction Questionnaire was added for stage 2	To evaluate patient satisfaction with dry eye treatment
Summary, General Statistical Methods and Section 7.3.1	~~Ocular adverse events and other ocular evaluations will be summarized using eye as the experimental unit. Nonocular adverse events and other nonocular assessments (such as vital signs) will be summarized using patient as the experimental unit.~~	Detailed statistical methods will be provided in the analysis plan
Summary, Table 3	Table was revised to include 12-week retreatment for patients in cohorts 6C and 6D	For consistency with the protocol
Summary, Tables 3 and 4	Footnotes were revised to specify how REFRESH PLUS should be used at screening and after the baseline visit, and a footnote was added clarifying that the follow-up investigator should perform the retreatment assessment	For clarification

Section	Revision	Rationale
Summary, Table 4	The Dry Eye Treatment Satisfaction Questionnaire was added, the minimum 20-minute rest period for tear film restabilization prior to tear sampling was removed from screening, the row for RESTASIS® X administration in the randomized eye was deleted, RESTASIS® X bilateral administration was added for day 1, the week 2 and 2R visits were changed to week 1 and 1R, the procedures were reorganized, [redacted]	For consistency with the protocol
Section 3.2	[redacted]	[redacted]
Section 4.3	[redacted]	To ensure enrollment of qualified eyes that demonstrate moderate to severe dry eye
Section 4.5.1	Specified that REFRESH PLUS should be instilled in both eyes 4 times per day during the 2-week period between the screening and baseline visits and that following the baseline visit REFRESH PLUS can be used up to 4 times per day	For clarification
Section 4.5.1.1	Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause. The investigator and each patient will determine the appropriate method of contraception for the patient during ~~Female patients of childbearing potential will be required to have a negative urine pregnancy test at screening and baseline. In addition, in stage 2, female patients of childbearing potential will be required to have a negative urine pregnancy test at 12 weeks, prior to retreatment~~ their participation in the study.	To be consistent with current protocol template
Section 5.2	Cohort 6C was changed to 6D	To allow for additional doses to be examined in stage 1 of the study
	For stage 2, patients in treatment group 1 will receive ~~a sham procedure at baseline in the contralateral eye~~ [redacted] of vehicle in both eyes.	To examine another vehicle [redacted]

Section	Revision	Rationale
Section 5.4	Stage 2: Patients will be ~~equally~~ allocated in a randomized fashion to the treatment groups shown in Table 2. The randomization will be stratified by Sjögren's syndrome (presence or absence of Sjögren's syndrome)~~. Within each~~ at baseline. Patients in treatment group~~, patients~~ 1 will ~~also~~ be assigned ~~with respect to the eye, right or left,~~ to receive vehicle in both eyes as the baseline treatment, and patients in treatment groups 2 through 4 will be assigned to receive RESTASIS® X in both eyes as the baseline treatment ~~(in the study eye). The contralateral eye will receive sham treatment at baseline~~.	Within each treatment group in stage 2, both eyes will receive the same treatment
	The study eye at baseline column was removed from Table 6	Within each treatment group in stage 2, both eyes will receive the same treatment, and to be consistent with Table 2
Section 5.4, Table 6	Added a vehicle treatment group in stage 2 of the study	To examine another vehicle [redacted]
Section 5.5	Allergan Biostatistics will prepare a scheme that will randomly assign patients ~~(in an equal allocation ratio)~~ to 1 of ~~up to 3~~ 4 treatment groups (Table 2). ~~The randomization will also assign the eye, right or left, to receive RESTASIS® X as the baseline treatment.~~	To examine another vehicle [redacted]
Section 5.6	Each eye will receive either vehicle ~~(for stage 1 only)~~ or [redacted] of RESTASIS® X.	Vehicle treatment will also be in stage 2 of the study and to allow for doses in between [redacted]
Section 5.7	Prior to use, all components should be stored [redacted]	To reflect current storage recommendations
Section 5.9	For stage 1, RESTASIS® X will be administered to the study eye per the study protocol. For stage 2, vehicle will be administered to both eyes in treatment group 1, and RESTASIS® X will be administered to both eyes in treatment groups 2 to 4.	To be consistent with the protocol
Section 5.10	Added retreatment information for stage 1 of the study; clarified that patients in treatment groups 2 to 4 will be retreated (at week 12) with RESTASIS® X, added a sentence that patients in treatment group 1 will receive vehicle in both eyes, and instructed the investigator [redacted]	To be consistent with the protocol
Section 6.2	Cohort 6C was changed to 6D and added a sentence that tear and blood samples will be collected post retreatment for cohorts 6C and 6D for stage 1	To be consistent with the protocol

Section	Revision	Rationale
	For stage 2: For determination of systemic drug concentration ~~in the circulation~~, blood samples will be collected at baseline (prior to treatment), weeks 1~~2~~, 4, 8, 12, and post retreatment at weeks 1~~2~~R, 4R, 8R, and 12R ~~week~~ (24) (see Table 4).	Systemic concentrations will be analyzed only from drug-treated patients
Section 6.3.1	The Supplemental Dry Eye PRO Questionnaire and the Dry Eye Treatment Satisfaction PRO were added for stage 2	To evaluate patient satisfaction with dry eye treatment
Section 6.4	[redacted]	To reflect current storage recommendations
Section 7	~~A d~~Database snapshots and unmasking of the stage 1 treatments ~~may~~ will be performed ~~after the completion of~~ during stage 1. ~~A statistical analysis plan will be approved prior to unmasking the stage 1 data. A database lock snapshot may also be performed after all patients in during stage 2 have completed the Week 4 post retreatment visit (ie., week 4R). A separate analysis plan for stage 2 will be approved prior to the unmasking of stage 2 data.~~	[redacted]
Sections 7.3.1 and 7.3.2	The descriptions of the safety and pharmacodynamic analyses were streamlined	Details will be provided in the analysis plan
Section 7.3.3	For stage 2, to enable only bioanalysis of samples from patients who receive [redacted] the randomization codes will be made available based on Allergan internal procedures.	For clarification
Section 7.6	~~A database snapshot of stage 1 may be performed. An interim analysis of masked or unmasked data may be performed after all patients completed the week 4 post retreatment visit of stage 2 for administrative purposes to support the design of future clinical studies.~~ No interim analyses are planned.	No formal interim analysis is planned
Section 8	Changed the number of doses to be evaluated in stage 1 of the study from [redacted] the number of treatment groups in stage 2 from [redacted] and sham treatment to vehicle, and added a sentence regarding cohorts 6C and 6D	To allow for additional doses to be examined in stage 1 and to examine another vehicle [redacted] in stage 2 of the study
Sections 8.4.1 and 8.4.2	Identified procedures that must be performed in a specific order	To ensure accurate data collection
Section 8.4.1.2	• administer RESTASIS® X or vehicle in randomized eye (must not be done before blood and tear sample collection)	To examine another vehicle [redacted]
Sections 8.4.1.8 to 8.4.1.12	Added procedures for cohorts 6C and 6D	To be consistent with the protocol
Sections 8.4.1.4 and 8.4.1.6 to	• tear sample for pharmacokinetic analysis	To be consistent with the protocol

Section	Revision	Rationale
8.4.1.8	(cohorts 2 to 6~~C~~D) • blood sample for systemic pharmacokinetic analysis (cohorts 2 to 6~~C~~D)	
Section 8.4.2.2	• Dry Eye Treatment Satisfaction Questionnaire • administer RESTASIS® X or vehicle bilaterally	To evaluate patient satisfaction with dry eye treatment and to examine another vehicle [redacted]
Section 8.4.2.7	• Dry Eye Treatment Satisfaction Questionnaire • administer RESTASIS® X or vehicle bilaterally (must not be done before blood and tear sample collection)	To evaluate patient satisfaction with dry eye treatment and to examine another vehicle [redacted]
Sections 8.4.2.9 to 8.4.2.13	"Only for Retreated Patients" was deleted from the title	The expectation is that all patients will be retreated
Section 8.4.2.14	• Dry Eye Treatment Satisfaction Questionnaire	To evaluate patient satisfaction with dry eye treatment
Section 9.5.2	For stage 1, cohort 1, [redacted] for stage 2, treatment group 1, a kit will contain [redacted]	To accommodate for the treatment of both eyes with either vehicle or RESTASIS® X
Section 11.1.6	A section describing the Dry Eye Treatment Satisfaction Questionnaire and how it should be administered was added	To evaluate patient satisfaction with dry eye treatment
Section 11.1.11	~~Images will be sent to Allergan for analysis.~~	Images will be sent to the reading center for analysis

11.10 Protocol Amendment 6 Summary

Title: A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol 192371-024 Amendment 6

Date of Amendment: January 2017

Amendment Summary

This summary includes changes made to Protocol 192371-024 Amendment 5 (approved April 2016). This amendment includes evaluation of a new formulation of RESTASIS X cyclosporine [redacted] (CFI) in stage 2, a total of 3 treatment groups in stage 2, addition of exploratory efficacy measurements and analyses to stage 2, and analysis of data from cohorts 6C and 6D at 1 week after retreatment. In addition, the requirement for patients in stage 2 to have 1 or more concomitant systemic immune mediated diseases in stage 2 of the study were deleted.

The following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Summary, Study Objectives and Section 2.1	For stage 1: [redacted] For stage 2: [redacted]	[redacted]

Section	Revision	Rationale
Summary, Clinical Hypotheses and Section 2.2	For stage 1: In patients with moderate to severe dry eye disease, at least 1 dose of [redacted] ~~RESTASIS® X~~ F1 or F2 will demonstrate an acceptable safety profile with unilateral single dosing. In patients with moderate to severe dry eye disease, at least 1 dose of [redacted] ~~RESTASIS® X~~ F1 or F2 will demonstrate an acceptable safety profile with unilateral retreatment. For stage 2: In patients with moderate to severe dry eye disease ~~and 1 or more concomitant systemic immune-mediated diseases~~, at least 1 dose of [redacted] l ~~RESTASIS® X~~ CFI will demonstrate an acceptable safety, exploratory efficacy~~pharmacodynamic~~, and pharmacokinetic profile with both single dosing and retreatment.	Clarified the formulation(s) to be studied in each stage and that the i[redacted] will be unilateral in stage 1. Changed pharmacodynamics to exploratory efficacy for stage 2. Deleted the requirement for patients in stage 2 to have 1 or more concomitant systemic immune-mediated disease.
Summary, Study Design and Section 1	[redacted] cyclosporine (CsA) (RESTASIS X) will be evaluated in this clinical study: F1 and F2. [redacted] To fully evaluate F1, F2, and CFI, this phase 2 study will be conducted in 2 stages.	To clarify [redacted] RESTASIS X and to provide the rationale for the evaluation of a new Restasis X formulation [redacted]
Summary, Study Design	Stage 1 will evaluate, in a paired-eye fashion, the safety, exploratory efficacy, and pharmacokinetics of a unilateral [redacted] ~~RESTASIS® X~~ F1 and F2 in patients with moderate to severe dry eye disease. [redacted]	Added exploratory efficacy for stage 1. [redacted] Removed redundant text.

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Section	Revision	Rationale
Summary, Study Design	For stage 1: Stage 1 will begin with 2 sequential cohorts in which the safety of the [redacted] vehicle, and [redacted] the lowest dose [redacted] of ~~RESTASIS® X~~ F1 will be evaluated. Based on review of available data from each cohort by the [redacted] ill proceed. Two weeks following randomization of the fourth patient in the F1 [redacted] cohort, [redacted] Cohorts 6C and 6D will begin in parallel using F1 and F2 [redacted] respectively, [redacted] In the absence of significant safety findings (as determined by the investigator), patients will be retreated [redacted] at 12 weeks and followed for another 12 weeks.	For clarification.
	[redacted] ~~will evaluate available data~~ and recommend whether to allow retreatment in stage 2 [redacted]	To be consistent with current protocol.

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Section	Revision	Rationale
	For stage 2: [redacted]	[redacted]
Summary, Study Treatment Groups	For stage 1, revised text as follows: Vehicle, [redacted] and ~~RESTASIS® X~~ [redacted] F2 [redacted] For stage 1, added the following: Baseline and retreatment cohort 6C and 6D: F1 [redacted] F2 [redacted]	For clarification.
Summary, Study Treatment Groups	For stage 2, revised text as follows: Baseline and retreatment groups: ~~RESTASIS® X~~ up to [redacted] dose groups: vehicle, CFI [redacted], and CFI [redacted]	To clarify treatments to be administered in stage 2.

Section	Revision	Rationale
Summary, Dosage/Dose Regimen	For stage 1: Stage 1 will sequentially examine the safety of doses [redacted] of ~~RESTASIS® X~~ F1 and F2 administered as a unilateral [redacted]	Clarified that the i[redacted] will be unilateral in stage 1.
	For cohorts 6C and 6D, respectively using [redacted] the absence of significant safety findings (determined by the investigator), patients will undergo retreatment as outlined in the [redacted] ~~with the same [redacted], formulation, and dose~~ at week 12 and will be followed for another 12 weeks.	To allow reference to more detail within the [redacted]
	[redacted]	To reflect the retreatment visit schedule. For clarification.
	[redacted]	
Summary, Dosage/Dose Regimen, Table 1	Replaced RESTASIS® X [redacted] with F1 or F2 in the table and footnotes, and removed definitions for F1 and F2 from below the table.	For clarification.
	Revised footnote e as follows: Patients in cohorts 6C and 6D will be retreated at 12 weeks with both vehicle and F1 or F2, respectively ~~RESTASIS® X~~ (see Section 5.10), according to the [redacted] ~~ith the same volume, formulation, and dose. .; 2 weeks after retreatment of the last patient in cohorts 6C and 6D~~ [redacted]	To allow reference for more detail within the [redacted] To reflect the visit schedule.

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Section	Revision	Rationale
Summary, Dosage/Dose Regimen	Dosing in stage 2 will begin as a bilateral-eye treatment of CFI or vehicle. [redacted] n the absence of significant safety findings (determined by the investigator) at 12 weeks, patients in treatment group 1 will be retreated with vehicle in both eyes and followed for another 12 weeks. In the absence of significant safety findings (determined by the investigator) at 12 weeks, patients in treatment groups 2 and ~~to~~43 will be retreated with ~~RESTASIS® X~~ CFI in both eyes and followed for another 12 weeks.	To clarify treatments to be administered and the number of treatment groups in stage 2.
Summary, Dosage/Dose Regimen, Table 2	Modified table title as follows: Dosage/Dose Regimen – Stage 2: Baseline~~Single~~ Dose and Retreatment in Patients With Moderate to Severe Dry Eye Disease ~~With One or More Concomitant Systemic Immune-mediated Diseases~~ Revised the table to show 2 active treatment groups [redacted] rather than 3 active treatment groups (low, medium, and high). Changed active treatment to CFI.	Deleted the requirement for patients in stage 2 to have 1 or more concomitant systemic immune-mediated diseases based on feedback from a global advisory board. Clarified treatments to be administered in stage 2.

Section	Revision	Rationale
	Revised Table 2 footnotes as follows: ~~Table reflects planned dosing regimen assuming 3 doses from stage 1 are safe and well tolerated.~~ [redacted] ~~cannot be selected from stage 1, additional treatment groups may be added to stage 2.~~ [a] Up to~~Approximately 24~~83 patients will be enrolled for stage 2. [redacted]	Revised footnotes to reflect modified stage 2 design and visit schedule. Revised the number of patients to be enrolled in stage 2 based on the change in the number of treatment groups to be evaluated in stage 2.
Summary, Dosage/Dose Regimen	Revised text as follows: For stage 1 ~~both Stages 1 and 2~~, the number of treatment groups, doses, [redacted] ~~RESTASIS® X to be used,~~ [redacted] The actual number of treatment groups and doses for stage 2 will be [redacted] based on results from stage 1.	For clarification.

Section	Revision	Rationale
Summary, Randomization/ Stratification and Sections 5.4 (including Table 6), and 5.5	Replaced RESTASIS® X with F1 or F2 (stage 1) or CFI (stage 2). Clarified number of treatment groups and patients in stage 2. This randomization will be stratified by Sjögren's syndrome (presence or absence) at ~~baseline~~screening.	For clarification. Moved blood sample collection for NicOx/Immco Sjögren's diagnostic from baseline to screening to allow for evaluation of the results before randomization/stratification.
Summary, Visit Schedule	For stage 1, revised text as follows: Cohorts 1 through 6B: screening/qualification visit (week -2); baseline (day 1), day 2, weeks 1, 2, 4, 8, 12, and 24/12R or Exit ~~for cohorts 1 through 6B, plus retreatment day 1 (1R) and weeks 1, 4, 8, and 24/exit (1R, 4R, 8R, 12R) for patients in cohorts 6C and 6D~~ Cohorts 6C and 6D: screening/qualification visit (week -2), baseline (day 1), day 2, weeks 1, 4, 8, and 12 (retreatment visit), post-retreatment follow-up visits (day 1R, weeks 1R, 4R, 8R, and 24/12R or Exit) For stage 2, revised text as follows: Stage 2: screening/qualification visit (week -2), baseline (day 1), day 2, weeks 1, 4, 8, and 12 (retreatment visit), post-retreatment ~~safety~~ follow-up visits (day 1R, weeks 1R, 4R, 8R, and 24/12R ~~(24/exit)~~ or Exit	For clarification.
Summary, Visit Schedule, Figure 1	[redacted] Revised the fifth bullet as follows: [redacted]	For clarification. For clarification.
Summary, Visit Schedule, Figure 2	Modified Figure 2 title as follows: Stage 2 Study Flow – Baseline~~Single~~ Dose and Retreatment in Patients With Moderate to Severe Dry Eye Disease ~~With One or More Concomitant Systemic Immune-mediated Diseases~~ Also, replaced the figure and footnotes with an updated version showing the revised study design for stage 2 of the study.	For illustration of changes to the study design for stage 2.

Section	Revision	Rationale
Summary, Number of Patients and Section 4.1	Revised the number patients to be enrolled in stage 2 to up to 24 patients in up to 3 treatment groups, with a total of up to 87 patients to be enrolled in the study overall (stages 1 and 2).	Revised the number of patients to be enrolled in stage 2 based on the change in the number of treatment groups to be evaluated in stage 2.
Summary, Condition/ Disease and Section 4.2	Removed the requirement for patients in stage 2 to have 1 or more concomitant systemic immune-mediated diseases.	Deleted the requirement for patients in stage 2 to have 1 or more concomitant systemic immune-mediated diseases based on feedback from a global advisory board.
Summary, Key Inclusion Criteria and Section 4.3	[redacted]	Revised text based on feedback from a global advisory board.
Summary, Response Measures, Stage 1 and Stage 2, Safety	Deleted ocular symptoms (visual analog scale).	Corrected error.
Summary, Response Measures and Sections 6.1 and 6.3	[redacted] Efficacy" measures. Added patients symptoms [redacted] "	For clarification.

Section	Revision	Rationale
Summary, General Statistical Methods and Types of Analyses	Changed "pharmacodynamic" to "exploratory efficacy" measurements and analyses. Added the following text: Exploratory efficacy (stage 1 and stage 2) measures will be evaluated. Baseline and change from baseline measure will be assessed. Also, number (percent) of responders may be assessed.	For clarification.
Summary, Table 3	Simplified cross reference to Section 8.4.1.	For clarification.
[redacted]	[redacted]	[redacted] Procedure Manual. To reflect visit schedule.

Section	Revision	Rationale
Summary, Table 4 and Sections 8.4.2, 8.4.2.1 to 8.4.2.12 (as applicable to each section)	Simplified cross reference to Section 8.4.2 in Table 4. Moved adverse events to follow collection of concomitant medications and procedures at the beginning of each study visit. Moved sodium fluorescein corneal staining, Oxford scale to occur after tear sampling for pharmacokinetic analysis. Moved the HRT3-Rostock ocular surface imaging assessement to after impression cytology and revised schedule such that this assessment will only be performed at screening and week 24/12R or Exit. Deleted the specification that the HRT3-Rostock imaging will be in "select patients." Corrected footnote letter associated with blood sample collection for systemic pharmacokinetic analysis. Moved collection of a blood sample for Sjögren's diagnostic from baseline to screening. Deleted the original footnote l from Table 4: [redacted]	For clarification. Made revisions to the order of procedures to be followed in stage 2. Moved blood sample collection for NicOx/Immco Sjögren's diagnostic from baseline to screening to allow for evaluation of the results before randomization/stratification.

Section	Revision	Rationale
Section 1	This study represents the first evaluation in patients of the safety, ~~pharmacodynamics~~exploratory efficacy, and pharmacokinetics of RESTASIS® X, a [redacted] The study will be conducted in patients with moderate to severe dry eye disease, ~~with or without concomitant systemic immune-mediated conditions.~~ [redacted] To fully evaluate F1, F2, and CFI, this phase 2 study will be conducted in 2 stages.	For clarification.
Section 1.1	To date, no studies have been ~~conducted~~completed with RESTASIS® X in humans, so its safety, pharmacokinetics, and pharmacology have yet to be determined.	To reflect current ongoing study.

Section	Revision	Rationale
Section 1.2	[redacted]-(CsA) was evaluated in pivotal nonclinical studies under Good Laboratory Practice (GLP) conditions. [redacted]	For clarification. To provide additional background data from Study TX14092.

Section	Revision	Rationale
[redacted]	[redacted] Changed pharmacodynamics to efficacy for stage 1.	For clarification.
	For stage 1, made additional edits as follows: ~~Two weeks following~~ [redacted]	For clarification.

Section		
	[redacted] The actual number of treatment groups and doses for Stage 2 will be recommended [redacted]	
	For stage 2, revised the text as follows: Stage 2 will first evaluate the safety, exploratory efficacy, and pharmacokinetics of bilateral [redacted] of ~~vehicle~~ [redacted] CFI and its vehicle ~~and 3 different doses (low, medium, and high) of RESTASIS® X~~ in patients with moderate to severe dry eye disease ~~and 1 or more concomitant systemic immune-mediated diseases. Pharmacodynamic measures will also be collected. The number of treatment groups, doses,~~ [redacted] ~~RESTASIS® X to be used,~~ [redacted] ~~following review of available data from stage 1.~~ Dosing in stage 2 will begin with 3 treatment groups enrolling in parallel. Up to ~~Approximately~~ 2483 patients (8 per group) will be randomized into 34 treatment groups (vehicle, ~~low, medium, and high dose of RESTASIS® X~~ CFI [redacted] and CFI [redacted] (Table 2). For treatment group 1, patients will be administered [redacted] l vehicle in both eyes. For treatment groups 2 and 3~~through 4~~, patients will be administered ~~RESTASIS® X~~ CFI [redacted] g, respectively, in both eyes and monitored for 12 weeks. [redacted] At week 12, in the absence of significant safety findings (as determined by the investigator), patients will be retreated in both eyes. At week 12, patients in treatment group 1 will again be administered vehicle in both eyes, while patients in treatment groups 2 and 3~~to 4~~ will be retreated with the same dose of [redacted] ~~RESTASIS® X~~	Updated to reflect the modified study design for stage 2.

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Section	Revision	Rationale
	CFI in both eyes.	
Section 3.2	[redacted]	[redacted]
Sections 5.4, 5.5, and Table 6	For stage 1, replaced RESTASIS X with F1 or F2. Revised text to reflect 3 rather than 4 treatment groups in stage 2 and to indicate the CFI 5 [redacted] doses to be used. [redacted] Removed the requirement for 50% of subjects to have Sjögren's syndrome.	For clarification. Updated to reflect the modified study design for stage 2. Moved Sjögren's testing from baseline to screening to allow for evaluation of the results before randomization/stratification. Removed the requirement for 50% of subjects to have Sjögren's syndrome.
Sections 5.9, 5.10, 8, and 9.5.2	For stage 1, replaced RESTASIS X with F1 or F2. Revised text to reflect 3 rather than 4 treatment groups in stage 2 and to indicate the CFI [redacted] to be used.	For clarification. Updated to reflect the modified study design for stage 2.
Section 5.10	[redacted]. Corrected typographical error. Clarified that treatment group 1 patients will be retreated at week 12 with vehicle. Added the following text: If retreatment is not administered, the patient will continue to be observed for safety (see Table 4) and exited at the Week 24/Week 12R/Exit visit.	To reflect the post-retreatment visit schedule.

Section	Revision	Rationale
Section 6.2	Deleted the following statement: ~~Systemic drug concentrations will be determined for all patients in all treatment groups beginning at baseline~~. For stage 2, made the following correction: "Ocular drug concentrations will be determined from tears sampled at baseline (prior to treatment), weeks 1~~2~~, 4, 8, 12, and post-retreatment at weeks 1R, 4R, 8R, and 24/12 R or Exit (see Table 4).	To eliminate redundancy. To correct a typographical error.
Section 6.3.1	[redacted]	For clarification.
Section 7	Database snapshots and unmasking of the stage 1 treatments will be performed during stage 1.~~—~~[redacted] An interim database lock of stage 1 will not be conducted until after all patients in cohorts 1 through 6B complete the study and all patients in cohorts 6C and 6D completed at least week 1 following retreatment. An interim database lock of stage 2 will not be conducted until after all patients in stage 2 complete at least week 1 following retreatment. A final database lock will occur after all enrolled patients have completed stage 2 of the study. The statistical analysis plan (SAP) will be developed and finalized before database lock.	Updated to include details for interim database locks.
Section 7.1	The modified intent-to-treat (mITT) population will be all patients who are treated and have baseline and at least 1 postbaseline assessment for 1 or more of the ~~pharmacodynamic~~exploratory efficacy measurements (see Section 6.3). The mITT population will be used for the ~~pharmacodynamic analyses~~exploratory efficacy analyses. The population consisting of subjects who received the active study treatment will be used for pharmacokinetic analysis.	For clarification.

Section	Revision	Rationale
Section 7.2	Changed heading from pharmacodynamic to exploratory efficacy assessments. Revised text as follows: ~~Stage 2 pharmacodynamic~~Exploratory efficacy (stage 1 and stage 2) measures (Section 6.3) will be evaluated ~~for trends~~. Baseline and change from baseline ~~to each postbaseline~~ measure will be assessed. Also, number (percent) of responders may be assessed.	For clarification.
Section 7.3	~~Descriptive~~In general, continuous variables will be summarized by descriptive statistics includ~~e~~ing sample size (N), mean, standard deviation, median, minimum and maximum ~~for continuous~~. Categorical variables, will be summarized by frequency count and percentage ~~for categorical variables~~.	For clarification.
Section 7.3.1	The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. ~~Treatment~~The number and percentage of patients with treatment-emergent adverse events will be summarized. The adverse events will be classified into ocular and nonocular types and will be summarized separately. Detailed methods for the analyses of adverse events and other safety variables will be described in the SAP ~~analysis plan~~.	For clarification.
Section 7.3.2	[redacted]	For clarification.
Section 7.6	~~No interim analyses are planned.~~ An interim database lock of stage 1 will not be conducted until after all patients in cohorts 1 through 6B complete the study and all patients in cohorts 6C and 6D complete at least week 1 following retreatment. An interim database lock of stage 2 will not be conducted until after all patients in stage 2 completed at least week 1 following retreatment. Statistical analyses will be performed following each database lock to support the design of future clinical studies.	Added interim analyses.

Section	Revision	Rationale
Section 8	For stage 1, changed "RESTASIS X" to "F1 or F2." Stage 2 will enroll patients with moderate to severe dry eye disease. ~~and 1 or more concomitant immune-mediated diseases (at least 50% of patients will have Sjögren's syndrome). Four.~~ Three dose groups will be enrolled in parallel, with patients randomized across dose groups; all patients will receive ~~RESTASIS® X~~CFI or vehicle treatment in both eyes. Screening and run-in with REFRESH PLUS will be similar to stage 1. At week 12, patients will be retreated with the same dose of ~~RESTASIS® X~~CFI or vehicle in both eyes unless safety results preclude retreatment.	For clarification. Deleted the requirement for patients in stage 2 to have 1 or more concomitant systemic immune-mediated diseases based on feedback from a global advisory board. Removed the requirement for 50% of subjects to have Sjögren's syndrome. For clarification of the number of dose groups and formulation to be used in stage 2.
	Deleted the following text: ~~The scheduled examinations for a given timepoint should be performed in the order shown (from top to bottom) in the schedule of visits and procedures (Table 3 and Table 4) and in Section 8 below~~	For clarification.
Section 8.4.1	~~Per protocol, procedures~~ Procedures at each visit should generally be, but are not required to be, performed in the order listed in Table 3 (Schedule of Visits and Procedures). ~~Every effort should be made to follow this order to ensure that the performance of particular procedures do not affect the results of subsequent assessments. , However, should~~ Should the site need to reorder some of the procedures to fit ~~into~~ their standard practices, the following procedures MUST be completed in the order shown below due to potential impact on the subsequent assessments:	For clarification.
Section 8.4.1	Removed blood sampling for pharmacokinetic analysis.	To eliminate redundancy.

Section	Revision	Rationale
Section 8.4.2	~~Per protocol, procedures~~Procedures at each visit should generally be, but are not required to be, performed in the order listed in Table 4 (Schedule of Visits and Procedures). ~~Every effort should be made to follow this order to ensure that the performance of particular procedures do not affect the results of subsequent assessments. However, should~~ Should the site need to reorder some of the procedures to fit ~~into~~ their standard practices, the following procedures MUST be completed in the order shown below due to the potential impact on the subsequent assessments:	For clarification.
Sections 8.4.2.8, 8.4.2.9, 8.4.2.10, and 8.4.2.11	Added (– Retreated Patients Only) to the section headings.	For clarification.
Section 8.12.1	Deleted "(ie, pharmacodynamics)."	For clarification.
Section 9.5.2	For stage 1, cohort 1, a kit will contain [redacted] for stage 1, cohorts 2 to 6D, a kit will [redacted] for stage 2, treatment group 1, a kit will [redacted] for stage 2, treatment groups 2 and 3, a kit will contai [redacted]	For clarification.
Section 10	Added the following reference: Neoral® (package insert). East Hanover, NJ: Novartis Pharmaceutical Corporation; 2015.	For completeness.
Section 11.1.16	Conjunctival epithelial cells will be collected via impression cytology from each eye ~~for efficacypharmacodynamic analyses~~ from 2 locations around the superior–temporal bulbar conjunctiva.	For clarification.
Section 11.2	Deleted the brief description of the [redacted].	To allow reference to more detail within the [redacted]

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Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
19-Jan-2017 07:56 GMT-080	[redacted]	Clinical Development Approval