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Study ID: OCUN-023

Title: Prospective, Open-Label, Randomized, Proof of Concept Study Exploring Application of TrueTear™ for the Treatment of Meibomian Gland Disease

Statistical Analysis Plan Amendment 2 Date: 25 Sept 2018

Prospective, Open-Label, Randomized, Proof of Concept Study Exploring Application of TrueTear™ for the Treatment of Meibomian Gland Disease

Final 1.0: 2018-03-07

Amendment 2.0: 2018-9-25

Study Number:	1919-610-019
Development Phase:	Proof of Concept
Product Name:	TrueTear™
Study Statistician:	[redacted]
Sponsor:	Allergan, Plc. *2525 Dupont Drive, Irvine, CA 92610*

1.0 TABLE OF CONTENTS

2.0 LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
AE	Adverse Event
AP	Analysis Plan
ATC	Anatomical Therapeutic Chemical
CFB	Change From Baseline
MedDRA	Medication Dictionary For Regulatory Activities
CS	Clinically Significant
PT	Preferred Term
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOC	System Organ Class
SPEED	Standard Patient Evaluation for Eye Dryness
OSDI©	Ocular Surface Disease Index©
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

3.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the effectiveness and safety data as outlined and/or specified in the final protocol of Study 1919-610-019 (version dated June 1, 2017). Specifications of tables, figures, and data listings are contained in a separate document.

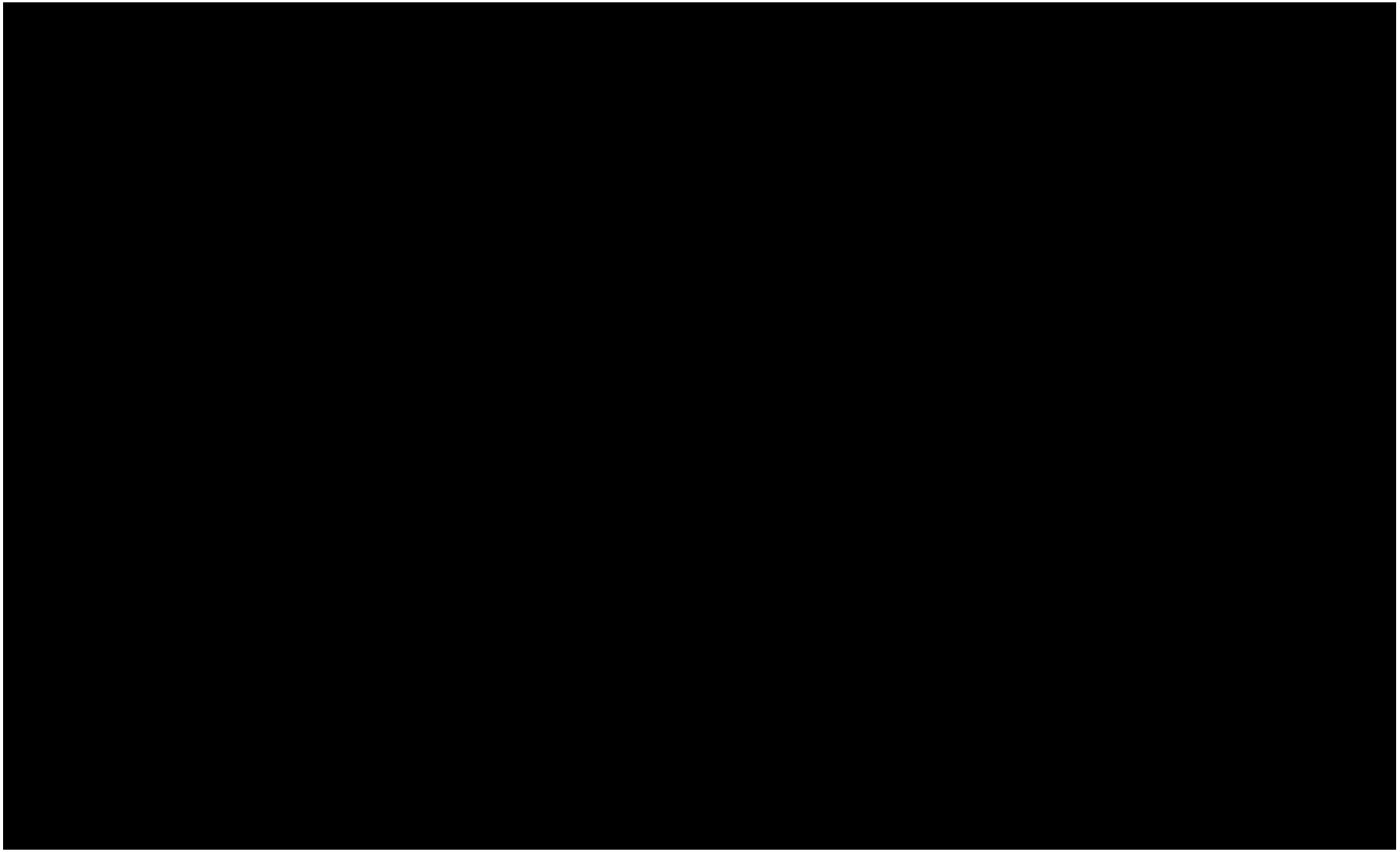
Study 1919-610-019 is a prospective, open-label, randomized, parallel two-arm study conducted at up to two sites in patients at least 22 years of age who have a Standard Patient Evaluation for Dryness (SPEED) [redacted] In at least one eye, the participants need to meet all of the objective measure in the same eye:

- A basal Schirmer test of ≥ [redacted]
- [redacted]
- [redacted]
- Tear film breakup time (TBUT) [redacted]

The length of this study will be approximately 44 days. Signed informed consent from the patient will be obtained before any study-related procedures are begun. At the Screening Visit, patients who provide written informed consent will be assigned a screening number. At the day of randomization (Day 0), patients meeting the entry criteria will be randomized (1:1 ratio) to either the TrueTear or moist heat compress control treatment groups. Following the initial application of treatment in clinic at Day 0, participants will apply the randomized treatment for approximately 30 days.

Effectiveness and safety assessments will be conducted at the clinic at Screening, Baseline, Day 7, Day 14 and Day 30.

The schedule of evaluations for Study 1919-610-019 is presented in Table 3–1.



4.0 OBJECTIVES

The primary objective of this study is to compare the safety and effectiveness of TrueTear (intranasal tear neurostimulator) to standardized moist heat compress (Thermalon Dry Eye Compress) for the treatment of Meibomian Gland Disease (MGD).

5.0 PATIENT POPULATIONS

5.1 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all randomized patients.

5.2 SAFETY POPULATION

The Safety Population will consist of all patients who initiated at least 1 device application.

5.3 DATA COLLECTED BUT NOT ANALYZED

The following variables collected on the CRF but not addressed in the analysis will be listed in the subject data listing without statistical summary or hypothesis testing: dates that informed consent was signed, dates of informed consent version, reason for unscheduled visits; medical status update, and required examination forms.

6.0 PATIENT DISPOSITION

The frequency (count and percent) of patients randomized, treated, completed study and prematurely discontinued during the study period will be presented for each treatment group and overall. The number of patients screened will be summarized overall only.

The frequency of patients who complete the study period and of patients who prematurely discontinue during the same period will be presented on the ITT Population. The reasons for premature discontinuation from the study period as recorded on the termination pages of the case report forms will be summarized (number and percentage) by treatment group for the ITT Population. All patients who prematurely discontinue during the study period will be listed by discontinuation reason for the ITT Population.

7.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group (<65 vs ≥ 65, race; ethnicity; sex), baseline characteristics (wearing contact lenses before seven days prior to the study) and other disease characteristics (Sjogren's syndrome) will be summarized descriptively by treatment group and overall for the ITT populations. Continuous variables will be summarized by number of patients and mean, SD, Q1/Q3, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients. A subject listing of demographics and baseline characteristics will be provided.

Medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities,* version 20.1 or newer. The number and percentage of patients with Ocular and Non-Ocular medical and surgical histories at baseline in each system organ class and preferred term will be summarized by treatment group for the Safety Population, separately. A subject listing for Surgical and Medical Histories will be provided.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of study treatment.

Both prior and concomitant medications will be coded using The Anatomical-Therapeutic-Chemical classification text from World Health Organization (WHO) Drug Dictionary. The use of prior and concomitant medications will be summarized by the number and percentage of patients in each treatment group for the Safety Population. If a patient took a specific medication multiple times or took multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class. Formulations (including salts, esters, etc) containing the same active ingredient will be pooled under the coded drug name of the base compound. Medications containing multiple active ingredients of different coded drug names will be reviewed during the study and may be pooled under a single coded drug name for analyses. A subject listing for prior and concomitant medications will be provided.

The Anatomical-Therapeutic-Chemical classification text from World Health Organization (WHO) Drug Dictionary, MAR17 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

A listing of randomized data will be presented. A listing of the significant protocol deviations reported will be provided. A significant deviation includes the deviation coded as 'Inclusion/Exclusion and Randomization' and 'Improper Protocol Procedures at Site (missed, repeated, not per protocol)'.

8.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 EXTENT OF EXPOSURE

Exposure to the study treatment for the Safety Population during the study period will be summarized for [treatment duration, calculated as the number of days from the date of the first application dose of study treatment to the date of the last application of study treatment, inclusive. Descriptive statistics will be presented by treatment group and overall.

8.2 MEASUREMENT OF TREATMENT COMPLIANCE

A subject listing will be prepared that provides the treatment assignment for all randomized or treated subjects. The study completion status and the reason selected for subjects that did not complete the study as planned is displayed in the discontinuation listing.

9.0 EFFECTIVENESS ANALYSES

9.1 PRIMARY EFFECTIVENESS PARAMETER(S)

This study does not include any effectiveness measures since it is an exploratory pilot study.

9.2 SECONDARY EFFECTIVENESS PARAMETER(S)

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and other safety measurements defined in the protocol including corrected distance visual acuity or slip lamp biomicroscopy findings. For each safety parameter, the last nonmissing safety assessment before the first dose of study treatment will be used as the baseline for all analyses. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

10.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 20.1 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present one or after the first application of study treatment or was present before the date of the first application of study treatment and increased in severity or became serious on or after the first application of study treatment.

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

The number and percentage of patients reporting TEAEs and treatment-related TEAEs in each treatment group will be tabulated by system organ class and preferred term, separately. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity.

A summary table will be provided for subjects with TEAE, TESAE, death and subjects with TEAEs leading to discontinuation if 5 or more participants reported such events. A subject listing of all AEs will be presented.

11.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

12.0 DETERMINATION OF SAMPLE SIZE

As this is a proof of concept study, no formal calculation of sample size was conducted. Approximately 70 participants will be enrolled to achieve approximately 60 completed.

13.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version [redacted]

14.0 DATA HANDLING CONVENTIONS

14.1 VISIT TIME WINDOWS

The analyses will be based on nominal visits from CRFs.

14.2 DERIVED VARIABLES

14.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of the first treatment, the results from the final non-missing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

14.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

14.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

14.6 MISSING CAUSAL RELATIONSHIP TO STUDY TREATMENT FOR ADVERSE EVENTS

[If the 3-point scale for relationship to study treatment is used (ie, "Not related," "Possibly related," and "Related"), the relevant text below may need to be modified accordingly. For example, "causal relationship" would become "relationship" and "*yes*" would become "*related.*"]

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

14.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date
- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date.

14.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

14.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same, but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same, but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

14.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, impute it as descripted in Section 14.4. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same, but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same, but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

15.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None

16.0 REFERENCES

None

17.0 AMENDMENTS

Date	Revision Number	Primary Author	Description of Change
07 March 2018	1	[redacted]	Initial Approval
25 Sept 2018	2	[redacted]	[redacted] • Administrative changes

ALLERGAN

1919-610-019 Analysis Plan

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]