Official Title: Effect of Cequa™ in Subjects with Dry Eye Disease That Is Currently Inadequately Controlled While on Cyclosporine 0.05% Ophthalmic Emulsion

Document: Statistical Analysis Plan (SAP)

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Statistical Analysis Plan

Effect of Cequa® in Subjects with Dry Eye Disease That Is Currently Inadequately Controlled While on Cyclosporine 0.05% Ophthalmic Emulsion

Study Phase Phase IV
Product Name: Cequa®
Study/Protocol Number: OTX101-2019-001
Formulation: Cyclosporine 0.09% ophthalmic emulsion
Sponsor: Sun Pharmaceuticals Industries, Ltd.
Date: 25 JAN 2023

This document presents the statistical analysis plan (SAP) for Sun Pharma Industries Ltd., Protocol No. OTX101-2019-001, Effect of Cequa® in Subjects with Dry Eye Disease That Is Currently Inadequately Controlled While on Cyclosporine 0.05% Ophthalmic Emulsion.
Dry eye disease is a common, multifactorial, ophthalmologic disorder of the tears and ocular surface characterized by symptoms of burning, stinging, itching, grittiness, scratchiness, foreign body sensation, dryness, stickiness, and tired eye sensation. The onset of symptoms is usually gradual, bilateral, and chronic. Symptoms typically become more bothersome later in the day and are intensified by various environmental factors.
The goal of this study is to evaluate the clinical benefits of switching to CsA 0.09% ophthalmic solution in subjects whose DED is inadequately controlled while on CsA 0.05% ophthalmic emulsion. This analysis plan is based on the final protocol (Version 1.0) dated 11 FEB 2020. The SAP provides the description of the analyses for the Final Analysis.

Study Objectives:

This study will be carried out with the intention to answer specific questions relating to clinical performance, efficacy and safety (i.e. residual risks) of the study medication when used in accordance with its approved labelling.

1: **Primary Objective**

The primary objective of this study is to evaluate improvements in the signs and/or symptoms of DED following the use of CEQ in subjects whose DED is inadequately controlled by cyclosporine 0.05% ophthalmic emulsion.

2: **Secondary Objective**

The secondary objective of this study is to evaluate changes in additional signs and/or symptoms over the 12-week course of CEQ therapy.

The primary endpoint is as follows:

-the mean CFB in total CFS and the mean CFB in modified SAnDE score at Week 12 for all patients

The secondary endpoints are as follows:

- Mean CFB in total conjunctival staining score at Week 12
- Mean CFB in central corneal staining score at Week 12
- Mean CFB in tear osmolarity at Week 12
- Mean CFB in frequency of ATP use at Week 12
- Mean CFB in unanaesthetized Schirmer's score at Week 12
- Percentage (%) of subjects who prefer study treatment over prior treatment at Week 12

Overall Study Design

This is an open-label, multisite, single-arm, phase IV clinical study that will evaluate the efficacy of Cequa™ cyclosporine 0.09% ophthalmic emulsion in patients with DED that is not well controlled by cyclosporine 0.05% ophthalmic emulsion. Subjects will be enrolled in up to 10 clinical sites throughout the United States. Informed consent will be obtained prior to any study specific procedure is performed.

Subjects who withdraw or are withdrawn/discontinued from the study after they have signed the informed consent and received the study treatment will not be replaced. This is an Electronic Data Capture (EDC) study utilizing web-based electronic case report forms. The study is designed using Celes web-based EDC system. KCT Data Management, Inc. will manage the EDC system according to their standard operating procedures throughout the study.

Analysis Populations:

Two analysis populations will be defined for this study: Safety (SAF) and Intent-to-Treat (ITT). The determination of which subjects will be included in each population will be made prior to locking the final database. All efficacy variables will be analyzed using the ITT set of subjects, and all safety variables will be analyzed using the SAF set of subjects.

Safety Analysis Population:

All patients who receive at least 1 dose of the study medication will be included in the SAF population. No subjects (or data) will be excluded because of protocol deviations that occur during the study.

Intent-to-Treat Population:

The Intent-to-Treat (ITT) population will be comprised of all subjects who receive at least 1 dose of the study medication and have at least 1 post-baseline assessment. Following the ITT principle, subjects will be analyzed irrespective of dosing compliance or any deviations in the study medication received.

Efficacy Analyses:

The efficacy analysis will be performed after all subjects have completed Week 12 or discontinued prior to Week 12, and after the study database has been cleaned, verified, and locked. All efficacy analyses will be performed using the ITT population. All analyses will be implemented using SAS® version 9.4 or later (SAS Institute,Inc., Cary, NC).

Statistical Methodology:

Summary statistics will be presented for continuous variables with descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables including binary variables, frequency counts and percentages will be presented. P-values will be computed for each analysis group separately. In addition, 95% 2-sided confidence intervals (CIs) will be presented, where relevant. In case of percentages, the CI will be computed using the Clopper-Pearson method. The CI will be computed for continuous variables using t-test analysis. Summary statistics will be displayed by baseline groups.

Demographics and Baseline Characteristics:

Demographics will be presented in a summary table and in a by-subject listing, including age, gender, race, iris color, and ethnicity. Baseline characteristics, presented in a summary table and in a by-subject listing.

Prior Medical, Ocular and Treatment History:

All medical and ophthalmic histories reported at the screening and baseline visits will have their verbatim term mapped to their corresponding thesaurus terms using version 25.1 of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Efficacy Analysis:

Primary Efficacy Analysis

The primary efficacy endpoint parameters for the study are the mean CFB in total CFS and the mean CFB in modified SAnDE score at Week 12. Significance will be set at $p<0.05$ for the analysis of all groups and endpoints.

Secondary Efficacy Analysis:

Same as primary

Safety Analyses:

All safety analyses will be performed using the SAF population. No imputation of missing data will be performed. Safety analyses will be presented in summary tables and in by-subject listings.

Compliance:

Drug accountability data was assessed at each visit and used for further patient counselling but was not collected for analysis.

Adverse Events:

Adverse events will be coded according the MedDRA version that will be available at the time of the data cut-off. A treatment emergent AE (TEAE) is defined as an AE starting on or after the day of treatment. A serious AE (SAE) that is ongoing at the time of completion or discontinuation from the study will be followed until stabilization or resolution of the event.