Statistical Analysis Plan for Study 1491-801-007

Evaluation of an Updated Dexamethasone Posterior Segment Drug Delivery System Applicator in Participants with Macular Edema due to Retinal Diseases

Date: 16Dec 2021

Version 1.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for updated DEX PS DDS applicator study 1491-801-007, evaluation of an updated dexamethasone posterior segment drug delivery system applicator in participants with macular edema due to retinal diseases.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under either or both the Linux and UNIX operating systems.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 14.0.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

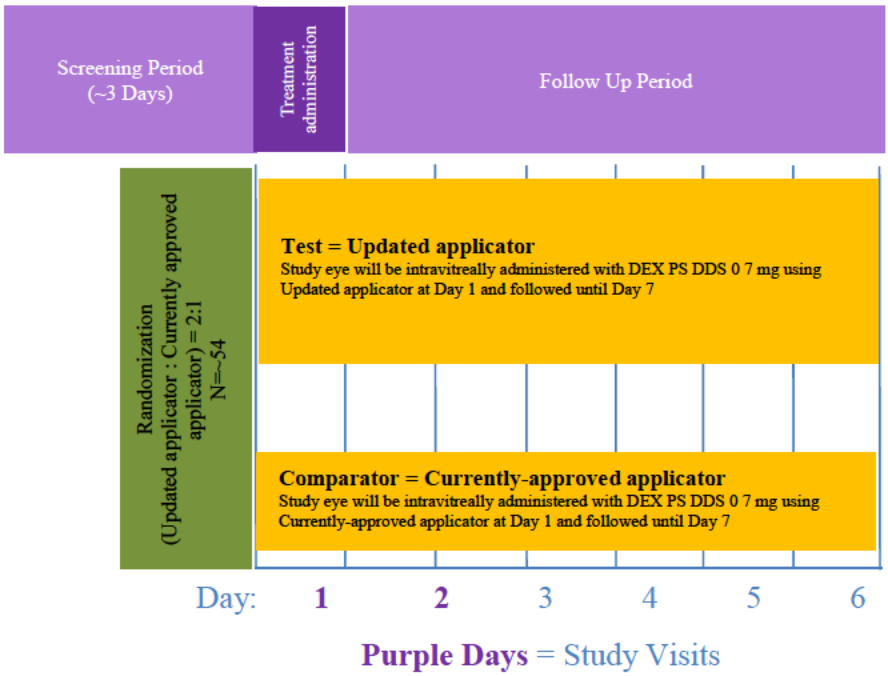
The primary objective is to demonstrate that the updated DEX PS DDS applicator (that incorporates the final, to-be-marketed design) delivers the DEX PS DDS Implant to the vitreous cavity and is suitable for commercial use in subjects with macular edema due to retinal diseases.

There is no defined clinical hypothesis or estimands for this study.

2.2 Study Design Overview

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



DEX PS DDS = Dexamethasone Posterior Segment Drug Delivery System

2.3 Treatment Assignment and Blinding

All subjects will be treated with DEX PS DDS Implant in an unmasked, open-label manner. Subjects will be randomly assigned in a 2:1 ratio to receive the DEX PS DDS implant using either the updated applicator (test) or the currently-approved applicator (comparator), respectively.

2.4 Sample Size Determination

The sample size is determined empirically based on discussions with FDA to evaluate a minimum of 30 eyes using the updated applicator and a minimum of 15 eyes using the

currently approved applicator. Assuming a dropout rate of about 15% and the need to achieve 30 and 15 subjects to use the updated applicator and currently-approved applicator, respectively, the total enrollment would require approximately 54 subjects.

3.0 Endpoints

3.1 Efficacy Endpoint(s)

The study is not designed to assess efficacy of the study drug. The DEX PS DDS Implant is an FDA-approved drug, and its efficacy is already well-established.

3.2 Safety Endpoint(s)

This study is not designed to assess safety of the study drug, but AEs will be collected. The DEX PS DDS Implant is an FDA-approved drug, and its safety is already well established.

Safety variables that will be evaluated in the study include vital signs, AEs, and ocular parameters as determined through assessments of BCVA, biomicroscopic slit-lamp examination, ophthalmoscopy, and IOP.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Safety Analysis Set (SAS) consists of all subjects who received DEX PS DDS Implant. Subjects will be included in the analysis according to the updated applicator or currently-approved applicator that was used to deliver the DEX PS DDS Implant.

5.0 Subject Disposition

The total number of subjects who were screened, enrolled (randomized), and treated will be summarized. Reasons for exclusion, including screen failure, will be summarized. A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group:

- Subjects enrolled (randomized) in the study;
- Subjects who took the dose of study drug;
- Subjects who prematurely discontinued study drug (all reasons and primary reason).

For end of study participation, the number and percentage of subjects who completed the protocol defined follow-up period (or did not with associated reasons) will be summarized overall and by treatment group.

6.0 Study Drug Duration and Compliance

Not applicable.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the SAS overall and by treatment group. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age. Categorical demographic variables include sex, ethnicity and race.

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.3 Ophthalmic Medical History

Ophthalmic medical history is defined as indicated on the medical history eCRF form marked 'OD','OS' or 'OU' to the question of the location of the medical history. Ophthalmic medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each ophthalmic medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the study drug.

A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Not applicable.

9.0 Efficacy Analyses

Not applicable.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the SAS. Safety summaries will be presented by treatment group. For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

Study eye is defined as the eye that received DEX PS DDS Implant.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs

multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. Each treatment-emergent AE will be determined as ocular or non-ocular AE. The ocular treatment-emergent AE is defined as indicated on the AE form of eCRF marked "OD" or "OS" to the question of "what was the location of the adverse event All treatment-emergent AEs, ocular treatment-emergent AEs in either the study eye or fellow eye, and non-ocular AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to death
- Any ocular treatment-emergent AE
- Any AEs of Special Interest
- All deaths

- TEAEs related to COVID-19 infection.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent AEs, ocular treatment-emergent AEs in either the study eye or fellow eye, and non-ocular AEs will be summarized by SOC and PT; by maximum relationship to study procedure as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

Not applicable.

10.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Discontinuation

SAEs (including deaths) and AEs leading to study discontinuation will be summarized by SOC and PT and in listing format.

10.2.6 Adverse Events of Special Interest

There are no protocol-specific AEs of special interest.

However, AEs possibly related to DEX PS DDS implant position and administration will be tabulated by PT. These AEs include, but not limit to, conjunctival hemorrhage, conjunctival tear cataract, lens or lenticular abnormality or change from baseline, vitreous

haze, vitreous hemorrhage, vitreous leak, retinal hemorrhage, retinal tear, retinal hole, retinal detachment, other retinal abnormality or change, intraocular inflammation, blindness, visual acuity or vision decrease. Also, abnormality or change of best corrected visual acuity (BCVA) (≥2 lines or more worse than baseline) and IOP change by 10 mmHg from baseline will be reported as AE, and will be included.

10.3 Analysis of Laboratory Data

Not applicable.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure and heart rate will be summarized.

Each vital sign variable will be summarized for all visits (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean.

10.5 Other Safety Analyses

10.5.1 Best Corrected Visual Acuity (BCVA)

BCVA will be performed for both eyes at each follow-up visit.

BCVA for the study eye and fellow eye will be summarized by a categorical tabulation of the number of line change from baseline at each follow-up visit for the following categories:

- 3 lines or better than baseline (“Much Better”)
- 2 lines better than baseline (“Better”)

- Between 1 line worse and 1 line better than baseline ("No change")
- 2 lines worse than baseline ("Worse")
- 3 lines or worse than baseline ("Much Worse")

10.5.2 Intraocular Pressure (IOP)

Intraocular pressure (IOP) is measured at each follow-up visit prior to pupil dilation for both eyes.

IOP of the study eye and fellow eye will be summarized for the raw IOP values and change from baseline at each visit with descriptive statistics by treatment group.

The IOP of the study eye will be summarized by three cut-off values at each follow-up visit:

- ≥ 35 mmHg,
- ≥ 30 mmHg, and
- ≥ 25 mmHg

In addition, the change from baseline IOP in the study eye of ≥ 10 mmHg increase will be analyzed.

10.5.3 Biomicroscopy

The biomicroscopy examinations are performed for both eyes at every follow-up visit. The following assessments are performed:

- Findings from conjunctiva (edema, hyperemia and subconjunctival hemorrhage), cornea (edema and superficial punctuate keratopathy), and iris/pupil (rubeosis iridis) using a 5-point scale (0=none, 0.5=trace, 1=mild, 2=moderate, 3=severe)

- Anterior chamber (flare) using a 5-point scale (0 = None, 1 = Faint, 2 = Moderate, 3 = Marked, 4 = Intense).
- Cells of anterior chamber using a 6-point scale (0 = 0 cells, 0.5 = 1-5 cells, 1 = 6-15 cells, 2 = 16-25 cells, 3 = 26-50 cells, 4 = >50 cells)
- Iris/Pipil using a on a 5-scale in cells (0=no visible rubeosis iridis, +0.5= trace visible rubeosis iridis, +1=obvious vessels in 1 quadrant, +2= obvious vessels in 2-3 quadrants, +3= obvious vessels in 4 quadrants).
- Hypopyon of anterior chamber (not evaluable, present or not and the level estimated in millimeters)
- Lens status as phakic, pseudophakic, or aphakic
- Presence and severity of nuclear, cortical, and posterior subcapsular cataract lens opacities using a 3-point scale for each type of opacity (1 = opacity is absent, 2 = opacity is present, but less than standard photo #2, and 3 = opacity is present and as severe as or worse than standard photo #2)
- Posterior capsule assessment for aphakic or pseudophakic eyes as not evaluable, intact or not

The number and percent of patients with clinically significant biomicroscopy findings at one or more visits will be tabulated for study eye and fellow eye. A clinically significant finding is defined as at least two severity grade increase (worsening) from baseline, or a status change from absent to present or non-evaluable to evaluable at follow-up visits. If a

pathology is recorded at a follow-up visit but not at baseline, the baseline will be imputed with the same pathology, with a grade of zero (none).

10.5.4 Ophthalmoscopy

The ophthalmoscopy examinations are performed for both eyes at each follow-up visit. The following assessments are performed:

- Vitreous cells and vitreous haze using a 6-point rating scale plus not evaluable (0, 0.5, 1, 2, 3, 4 and not evaluable)
- Vitreous hemorrhage using a 6-point rating scale (0, 0.5, 1, 2, 3, and 4)
- Posterior vitreous detachment evaluated as no, yes and not evaluable
- Disc hemorrhage and other disc pathology as not evaluable, no finding or present
- Fundus as no finding or present
- Intraretinal fluid, subretinal fluid, intraretinal hemorrhage, rhegmatogenous detachment, tractional detachment, pigment epithelial detachment as no finding or present
- Retinal hemorrhage, retinal tear, rhegmatogenous retinal detachment, tractional retinal detachment, exudative retinal, other retinal detachment, round (astrophic) retinal holes, and lattice degeneration as no finding or present
- Cup to disc ratio value

Similar to biomicroscopy data, the number and percent of patients with clinically significant ophthalmoscopy findings at one or more visits will be tabulated for study eye and fellow eye. A clinically significant finding is defined as at least two severity grade increase (worsening) from baseline, or a status change from absent to present or non-evaluable to evaluable at follow-up visits.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

Not applicable.

12.1 Data Monitoring Committee

Not applicable.

13.0 Overall Type-I Error Control

Not applicable.

14.0 Version History

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	16 Dec 2021	Original version

15.0 Reference

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified using the following search criteria:

Area of Safety Interest	Search Criteria
AEs related to Implant position and administration	Conjunctival hemorrhage, conjunctival tear cataract, lens or lenticular abnormality or change from baseline, vitreous haze, vitreous hemorrhage, vitreous leak, retinal hemorrhage, retinal tear, retinal hole, retinal detachment, other retinal abnormality or change, intraocular inflammation, blindness, visual acuity or vision decrease, abnormality or change of BCVA (≥2 lines or more worst then baseline), IOP change by 10 mmHg from baseline. Adjudicated terms will be further identified using CECAT and CETERM from the CE SDTM dataset.