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Study ID: 206207-026

Title: Dexamethasone Posterior Segment Drug Delivery System Versus Laser Photocoagulation in Patients With Diabetic Macular Edema

Statistical Analysis Plan Date: 13Jan2020

Title Page

STATISTICAL ANALYSIS PLAN

Dexamethasone Posterior Segment Drug Delivery System Versus Laser Photocoagulation in Participants with Diabetic Macular Edema

Study Number:	206207-026
Development Phase:	3
Product Name:	Dexamethasone Posterior Segment Drug Delivery System
Sponsor:	Allergan PLC 2525 Dupont Drive, Irvine, California USA 92612 [redacted]

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List of Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BCVA	Best corrected visual acuity
CFB	Change from baseline
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRT	Central retinal thickness
D	Day
DEX PS DDS	Extruded dexamethasone posterior segment drug delivery system
DME	Diabetic macular edema
ETDRS	Early treatment diabetic retinopathy study
Ecrf	Electronic case report form
FA	Fluorescein angiography
IOP	Intraocular pressure
LS	Least squares
M	Month
MedDRA	Medication Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
OCT	Optical coherence tomography
OU	Both eyes
PE	Physical examination
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SE	Study eye
SOC	System organ class
TEAE	Treatment-emergent adverse event
VA	Visual acuity
VFQ	Visual functioning questionnaire
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy, safety data and health outcomes outlined or specified in the final protocol of Study 206207-026 amendment 1. Specifications of tables, figures, and data listings are contained in a separate document.

Study 206207-026 is a Phase 3, multicenter, randomized, 12-month comparative study. This study is conducted to evaluate the safety and efficacy of the 700 µg DEX PS DDS compared with laser photocoagulation in participants with diabetic macular edema (DME). This is a regional multicenter Phase 3 registration trial and is conducted exclusively in China and The Philippines.

1.1 Primary Study Objectives and Design

The objective of the study is to evaluate the safety and efficacy of 700µg DEX PS DDS administered every 5 months.

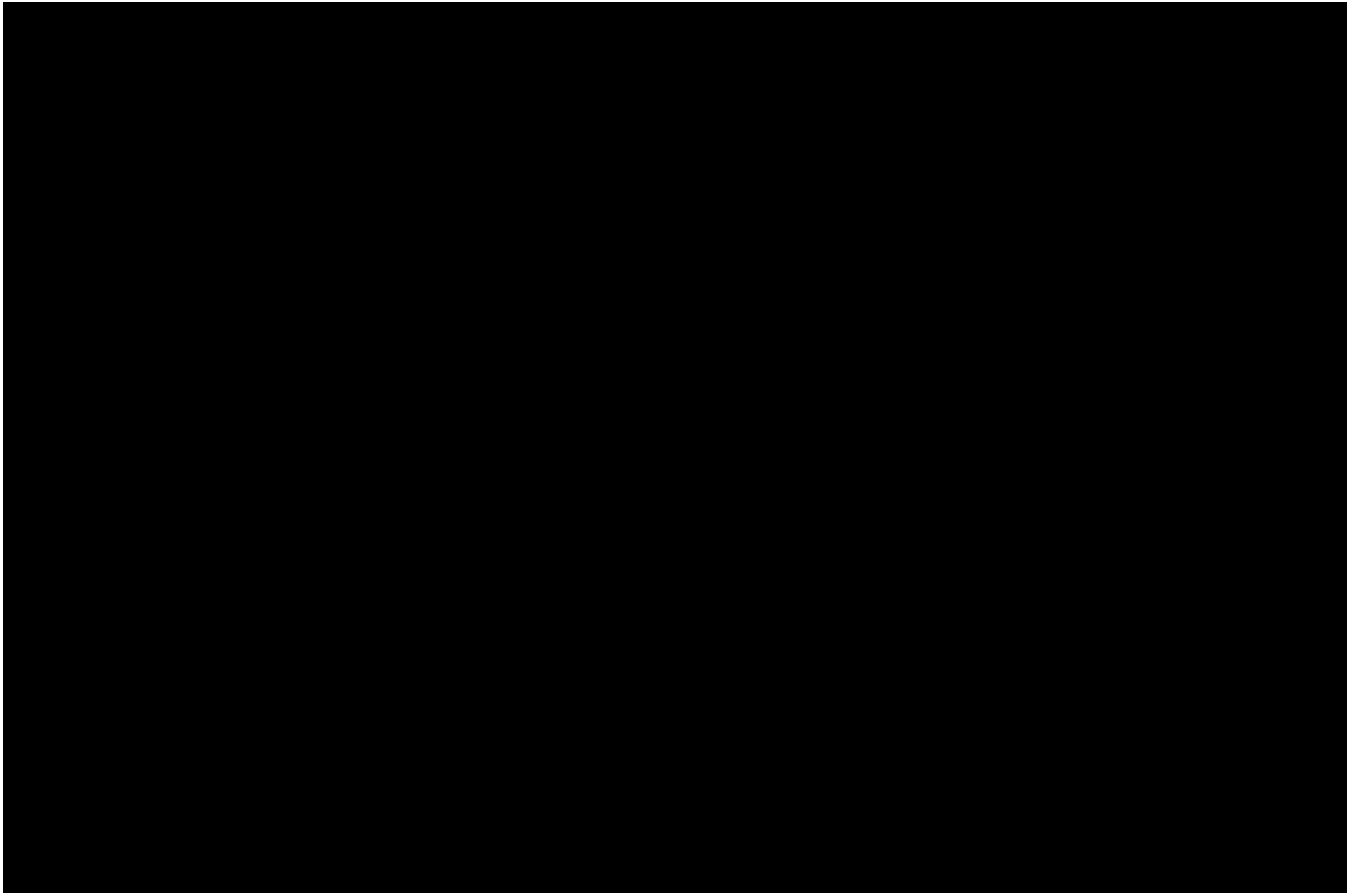
Consenting participants will participate in a screening period lasting 2 to 14 days to evaluate participant eligibility. After eligibility has been determined by the investigator, participants will be randomized in a 1:1 ratio to receive:

- 700 µg DEX PS DDS every 5 months

or

- laser photocoagulation according to the modified ETDRS protocol

The randomization will be stratified by BCVA categories at baseline (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70) within each investigator site. The primary efficacy variable is average change of BCVA over a period of 12 months. The total duration of study participation for each participant is approximately 12.5 months including screening and randomization/retreatment period. Participants will attend the following 11 visits: screening visit, randomization visit, 8 assessment/retreatment visits, and study exit visit, as listed in Table 1-1.



2. Analysis Populations and Data Conventions

2.1 Analysis Populations

Approximately 356 participants will be enrolled at approximately 20 sites to ensure that at least 151 participants in each treatment group complete the study. Of those, approximately 10 participants assigned to DEX PS DDS at selected sites will participate in therapeutic drug monitoring.

The following 3 populations will be used for statistical analyses: modified intent-to-treat (mITT), per protocol (PP), and safety populations.

The mITT population consists of randomized and treated participants with at least one postbaseline BCVA measurement. The mITT population will be used for all analyses except per-protocol and safety analyses. Analysis for mITT will be based on the randomized treatment regardless of the actual treatment that the participant received.

The PP population is a subset of mITT population. [redacted]

The safety population consists of all participants who received the study medication or had the study procedure performed on the study eye. All safety analyses will be based on the safety population using the actual treatment that the participant received.

2.2 Analysis Visit Windows

Visit windows are defined according to study days.

The analysis visit windows for efficacy and safety endpoints except total leakage area are defined as follows:

Table 2-1 Analysis Visit Definitions for Safety and Efficacy (BCVA, OCT and IOP)

Study Visit (eCRF)	Analysis Visit (Derived)	Target Day (Number of Days from Day 1)	Window (Study Days)
Day 1(Baseline)	Baseline	1	≤ 1
Month 1	Month 1	30	[2, 45]
Month 2	Month 2	60	[46, 75]
Month 3	Month 3	90	[76, 120]
Month 5	Month 5	150	[121, 165]
Month 6	Month 6	180	[166, 195]
Month 7	Month 7	210	[196, 240]
Month 9	Month 9	270	[241, 285]
Month 10	Month 10	300	[286, 330]
Month 12/Exit	Month 12	360	[331, 450]

Month is defined as 30 days.

The analysis visit windows for total leakage area are defined as follows:

Table 2-2 Efficacy Analysis Visit Definitions for Total Leakage Area

Study Visit (eCRF)	Analysis Visit (Derived)	Target Day (Number of Days from Day 1)	Window (Study Days)
Day 1(Baseline)	Baseline	1	≤ 1
Month 3	Month 3	90	[2, 135]
Month 6	Month 6	180	[136, 225]
Month 9	Month 9	270	[226, 315]
Month 12/Exit	Month 12	360	[316, 450]

Month is defined as 30 days.

In cases where multiple visits occurred within a single visit window, the last visit with non-missing data will be used.

2.3 Data Conventions

- Unless stated otherwise in specific subsequent sections, data conventions and definitions listed below will be applied to all analyses. Study duration will be calculated for each participant as:
  Study duration = date of the last visit – date of the 1st study treatment + 1

- In general, study day of a visit/assessment/treatment/event/procedure (i.e., BCVA assessment, escape therapy) will be calculated as below.

  If the visit date is on or after the 1st study treatment, study day will be calculated as:

  Study Day = visit date – date of the 1st study treatment + 1
  Day 1 is the day of the 1st study treatment

  If visit date is before the 1st study treatment, study day will be calculated as:

  Study Day = visit date – date of the 1st study treatment
  Day -1 is the day before the 1st study treatment

- Unless otherwise specified, baseline data refer to assessments performed at the Baseline (Day 1) visit prior to the first treatment. Screening or unscheduled but prior to Day 1 visits can be used for baseline in the absence of pertinent data at the baseline visit.

- For continuous variables, descriptive statistics will include mean, median, standard deviation, 25-percentile, 75-percentile, minimum and maximum. Descriptive summary for the categorical data will be count and percentage for each category.

- The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events, biomicroscopy, and ophthalmoscopy findings.

- The Anatomical-Therapeutic-Chemical classification text from World Health Organization (WHO) Drug Dictionary will be used to code all medications for drug class and for drug name.

- All data will be listed.

- Data after the escape therapy will be excluded from efficacy analyses and will be included in safety analyses. Since assessments (e.g., BCVA, CRT) are usually performed before any treatments (e.g., study treatment, escape therapy), data collected on the same day but prior to the escape therapy will be included in analysis.

- Due to IP recall during the study, a small number of participants have delayed Ozurdex treatment at Month 12. It is recommended that these participants can come back 2 months after the last treatment for a follow-up visit. Therefore, data collected up to day 450 will be used in efficacy analysis. However, all data during the study will be included in safety analysis.

3. Disposition and Exit Status

Disposition and exit status of enrolled participants will be summarized.

3.1 Disposition and Exit Status

Participant disposition will be summarized as a frequency distribution by treatment groups. Participant disposition encompasses the distribution of participants who screened, randomized, complete, and discontinue, along with eCRF-reported discontinuation reasons.

3.2 Protocol Deviation

Protocol deviations will be captured and classified by categories in a separate document. Significant protocol deviations will be summarized for the mITT Population by treatment group.

3.3 Analysis Population

Number of participants included for mITT, PP and Safety population will be summarized for all participants in total and by treatment group. Listing of participants excluded from PP population will be provided with reasons for exclusions.

4. Demographics and Other Baseline Characteristics

4.1 Demographics

Demographic data including age, age group (<45, 45-65, >65), sex, and race will be summarized with descriptive statistics and frequency distribution in total and by treatment group.

4.2 Baseline Characteristics

The following baseline characteristics will be summarized in total and by treatment group.

- Height (meters) and Weight (kilograms)
- Iris color (Blue, Green, Hazel, Brown, Other)
- Iris color groups, defined as Dark (brown, black, other which contains black in comments), Light (blue, green, hazel, other which doesn't contain black in comments)
- Duration of diabetic macular edema (DME) (months) in the study eye, calculated as (randomization date - DME onset date)/30.4
- BCVA score as a continuous variable and BCVA by randomization strata
- Central retinal thickness (CRT) (microns)
- Total area of macular leakage (mm^2)
- lens status assessment: Phakic, Pseudophakic or Ahakic

4.3 Prior Medications

Prior medications include medications taken prior to the first study treatment. A medication or ophthalmic medication will be considered as a prior medication if it satisfies at least one of the following:

- The start date is prior to day 1, regardless of the stop date;
- The start date is unknown but marked as > 1 year; or
- The stop date is prior to or on day 1, regardless of the start date

For medications with a partial start or stop date where "> 1 year" is not marked for the start date or "ongoing" is not marked for the stop date and the day and/or the month is unknown, comparison to the study treatment date (Day 1) will start with the year followed by the month, if applicable, for determination of prior medications. In cases where a full determination cannot be made based on the partial information, the start date will be assigned to the 1st day of the month if the day of the month is missing or to January if the month of the year is missing; conversely, the stop date will be assigned to the last day of the month if the day of the month is missing or to December if the month is missing. This missing data imputation will be done for tabulation purposes. All partial dates will be listed as recorded in the medication listing.

Number and percentage of participants who reported prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT in total and by treatment group. ATC4 classes will be sorted alphabetically; PTs will be sorted in descending frequency in the

highest dose group. A separate analysis for prior ophthalmic medications used in the study eye will be performed.

4.4 Concomitant Medications

Concomitant medications include medications taken after the first study treatment. A medication will be considered as a concomitant medication or concurrent procedure if it satisfies at least one of the following:

- The start date is on or after the Day 1 treatment date regardless of the stop date;
- The stop date is after the Day 1 treatment date, regardless of the start date; or
- The stop date is unknown but marked as ongoing

For medications with a partial start or stop date, the same conventions and algorithms as described for prior medications will be used for determination of concomitant medications

Medications and procedures will be coded the same way as prior medications. Concomitant medications will be summarized in the same way as that for prior medications. A separate summary for concomitant ophthalmic medications used in the study eye will be done. Further, concurrent procedures will be summarized for each treatment group. Similarly, concurrent ocular procedures used for the study eye will be summarized for each treatment group.

4.5 Medical and Surgical History

Medical history including those ocular and non-ocular history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1 or newer.

Number and percentage of participants who reported medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) in total and by treatment group for the mITT Population. SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group. The similar summaries or listings will be done for the following events as appropriate:

- Medical history
- Medical conditions at the trial initiation
- Ophthalmic history in the study eye
- Ophthalmic condition in the study eye at trial initiation
- Surgical history

- Ophthalmic surgical history in the study eye

5. Efficacy Analyses

Unless stated otherwise, analyses for efficacy will be performed using the mITT population for the study eye based on the 2-sided hypothesis test with a nominal significance level of 0.05.

5.1 Primary Efficacy Analyses

5.1.1 Collection of Primary Efficacy Measurements and Derivation of Primary Efficacy Variable

BCVA is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) method. The number of letters read correctly will be recorded.

The primary endpoint is the average change from baseline in BCVA in study eye over the 12-month study period for each participant. The average BCVA will be calculated as the area under the BCVA curve divided by the study days at the last BCVA measurement of the study eye over the 12-month study period.

Change from baseline = average BCVA – Baseline BCVA.

The area under the BCVA curve will be calculated using the trapezoidal method and will include all BCVA data, regardless of scheduled or unscheduled visits, from day 1 to the last BCVA assessment prior to escape therapy or at exit visit. The total area under the BCVA curve can be partitioned into sub-areas divided by consecutive visits that each participant had with BCVA measurements. For a particular participant, assume that BCVA is obtained at L time points (visits) including the baseline visit. Let $t_{i,}$ and $BCVA_i$ represent the study day and BCVA value at Visit i (e.g., baseline/day 1, month 1, etc.), respectively, and

$t_i = t_{1,}\ t_{2,} \ldots t_{L,}$ where t_1 = day 1 (baseline) and,

$t_L = T$ (month 12 or time at the last BCVA if early term inated or at the 1st escape therapy)

The total area under the BCVA curve over [1, T] study days:

$$AUC_{[1,T]} = \sum_{i=1}^{L-1} AUC_i(t_i, t_{i+1}), \text{where } AUC_i = (BCVA_{i+1} + BCVA_i) * (t_{i+1} - t_i)/2$$

The average BCVA for the participant = $\frac{1}{T-1} AUC_{[1,T]}$, and

The average BCVA change for the participant= $\frac{1}{T-1} AUC_{[1,T]} - BCVA_{baseline}$

5.1.2 Primary Efficacy Analysis

The primary analysis will be an analysis of covariance (ANCOVA) comparing the treatment difference in the mean average BCVA change from baseline over a 12-month study period. The ANCOVA model will include the treatment group as the main effect and baseline BCVA score as the covariate.

The null hypothesis is that there is no difference between 700-µg DEX PS DDS and laser in the average BCVA change from baseline in a 12-month period. The alternative hypothesis is that there exists a difference between the 2 treatment groups. The hypothesis test will be based on a 2-sided test at 0.05 significance level. In addition, a 2-sided 95% confidence interval (CI) will be constructed for the difference between the treatment groups in least-square means using the same ANCOVA model.

5.1.3 Other Analyses of Primary Efficacy Variable

As a supportive analysis, the above analyses will be done using PP population.

5.2 Secondary Efficacy Analyses

Data after the 1st escape therapy will be set to missing. For participants who receive escape therapy or terminate early prior to month 12, month 12 data will be imputed using LOCF (Last Observation Carry Forward). The last observation prior to the 1st escape therapy or at early exit will be used for month 12. In the event of mis-randomization with an incorrect stratum, the actual stratum that the participant belongs will be used for statistical analysis.

5.2.1 BCVA Improvement of ≥ 15 Letters from Baseline at month 12

Analysis for proportion of participants with 15 or more letters improvement from baseline in BCVA of study eye at month 12 will be done using a Cochran–Mantel-Haenszel (CMH) test stratified by baseline BCVA categories (≥ 34 to ≤ 49 and ≥ 50 to ≤ 70). The 95% confidence intervals for the between-group difference in the proportion will be calculated using normal approximations.

5.2.2 Change from Baseline in Central Retinal Thickness at Month 12

Analysis for change from baseline in central retinal thickness measured by OCT at month 12 will be performed using an ANCOVA model with treatment and baseline BCVA category as the main effects and baseline retinal thickness as the covariate. The between-group difference and the corresponding 2-sided 95% CI in least-square means will be computed using the ANCOVA model.

5.2.3 Change from Baseline in Total Leakage Area at Month 12

The total area of macular leakage measured by FA is defined as the sum of focal and diffuse leakage area. Analysis for change from baseline in total leakage area at month 12 will be performed using an ANCOVA model with treatment and baseline BCVA categories as the main effects and baseline total leakage area as the covariate. The between-group difference and the corresponding 2-sided 95% CI in least-square means will be computed using the ANCOVA model.

6. Safety Analyses

The safety analysis will be based on safety population using observed data.

6.1 Exposure to Study Treatment(s)

Exposure to study treatment will be summarized by the number and percentage of participants receiving 0, 1, 2, or 3 injections for the DEX PS DDS treated group, or 0, 1, 2, 3, or 4 treatments for the laser photocoagulation treated group. The mean number of study treatments and the numbers of total study days will be calculated for each treatment group.

6.2 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is an adverse event that occurs after the initiation of the study treatment (ie, the onset date is the same as or after the study treatment date), or an adverse event with onset prior to the study treatment that worsened in severity or became serious after the initiation of the study treatment.

The incidence of TEAEs will be calculated by treatment groups and presented as the number and percent of participants experiencing the TEAE during the study period. Summaries for TEAE data will be organized into the following: all TEAEs regardless of causality; treatment-related TEAEs; ocular TEAEs; and treatment-related ocular TEAEs. The number and percent of participants with TEAEs will be presented as follows:

- By primary system organ class in alphabetical order, and preferred term
- By primary system organ class in alphabetical order and by the severity (maximum severity)

Within each system organ class name, TEAEs will be tabulated by preferred term and sorted in descending order of frequency in the DEX PS DDS treated group and then by the laser photocoagulation treated group. A participant with multiple occurrences of the same preferred term within the reporting period will be counted only once for that preferred term.

In addition, TEAEs leading to discontinuation will be tabulated similarly.

Analysis for adverse events of special interest will be done for cataract and elevated IOP. Summary for cataract will be based on participants with phakic lens at baseline. MedDRA terms for AE of cataract and elevated IOP are listed in Table 6-1. Additional terms may be added before database lock when applicable.

Table 6-1 AE of Special Interest Terms

System Organ Class	Preferred Terms	Group
Eye Disorders	Cataract	Cataract AEs
	Cataract cortical	Cataract AEs
	Cataract diabetic	Cataract AEs
	Cataract nuclear	Cataract AEs
	Cataract subcapsular	Cataract AEs
	Lenticular opacities	Cataract AEs
	Ocular hypertension	Elevated IOP AE
	Angle closure glaucoma	Elevated IOP AE
	Borderline glaucoma	Elevated IOP AE
	Diabetic glaucoma	Elevated IOP AE
	Glaucoma	Elevated IOP AE
	Glaucoma Traumatic	Elevated IOP AE
	Gaucomatous optic disc atrophy	Elevated IOP AE
	Open angle glaucoma	Elevated IOP AE
	Pigmentary glaucoma	Elevated IOP AE
	Normal tension glaucoma	Elevated IOP AE
Investigations	Intraocular pressure increased	Elevated IOP AE
	Intraocular pressure fluctuation	Elevated IOP AE

Cataract AEs are limited to eyes classified as phakic at baseline.

The AE start/end day referring to initial treatment date will be presented in listings. The calculation is the same as study day described in section 2.2.

For each TEAE of a subject, the most recent treatment is defined as the most recent treatment prior to TEAE start. Most recent treatment date/day and TEAE start/end day referring to the most recent treatment will be presented in listings.

- Most recent treatment day = most recent treatment date – initial treatment date + 1.
- TEAE start/end day referring to the most recent treatment = TEAE start/end date - most recent treatment date +1.

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing). The imputation is done in order to determine TEAE. The data collected on CRF (ie, partly missing) will be presented in listings.

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:

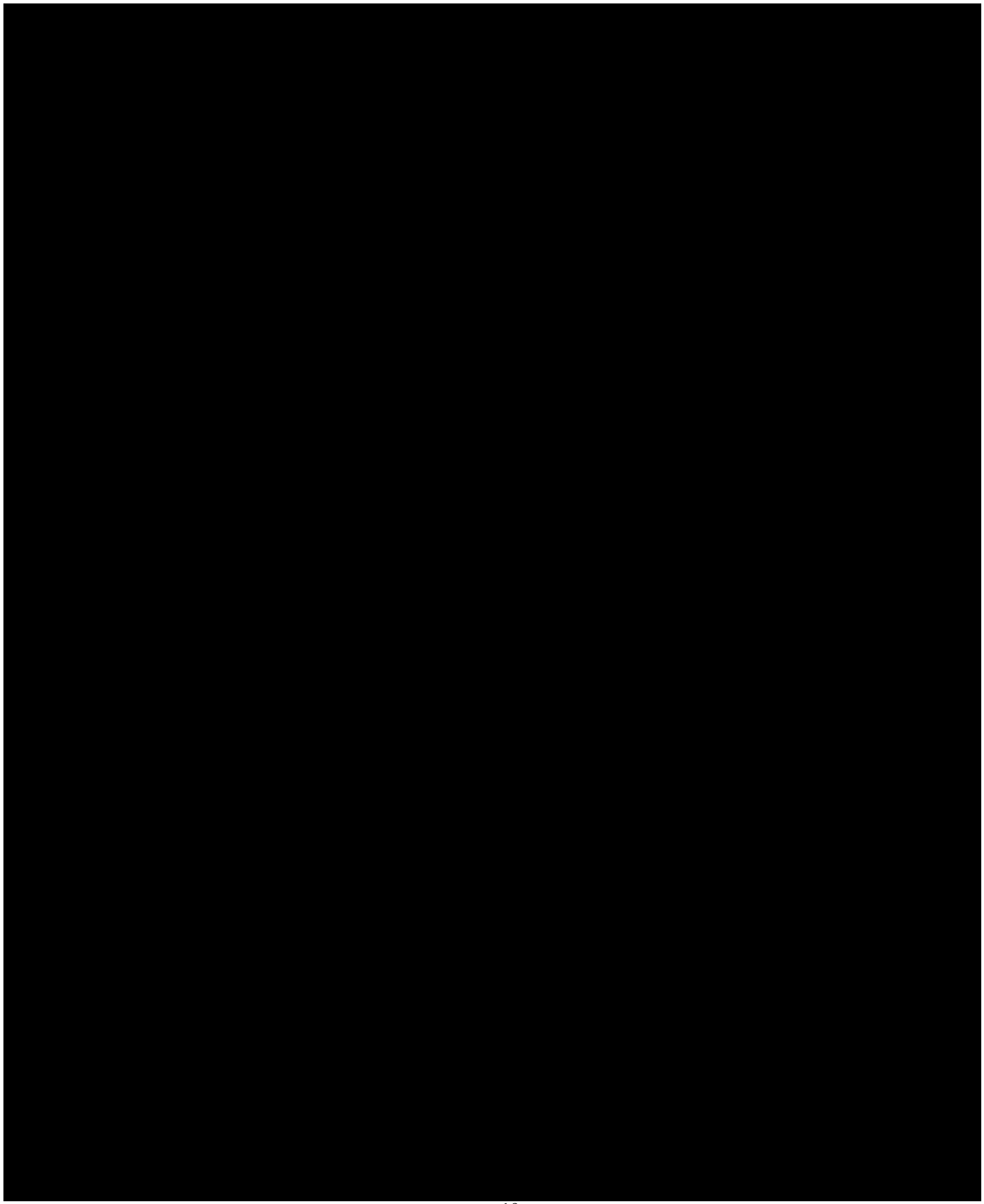
- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date.

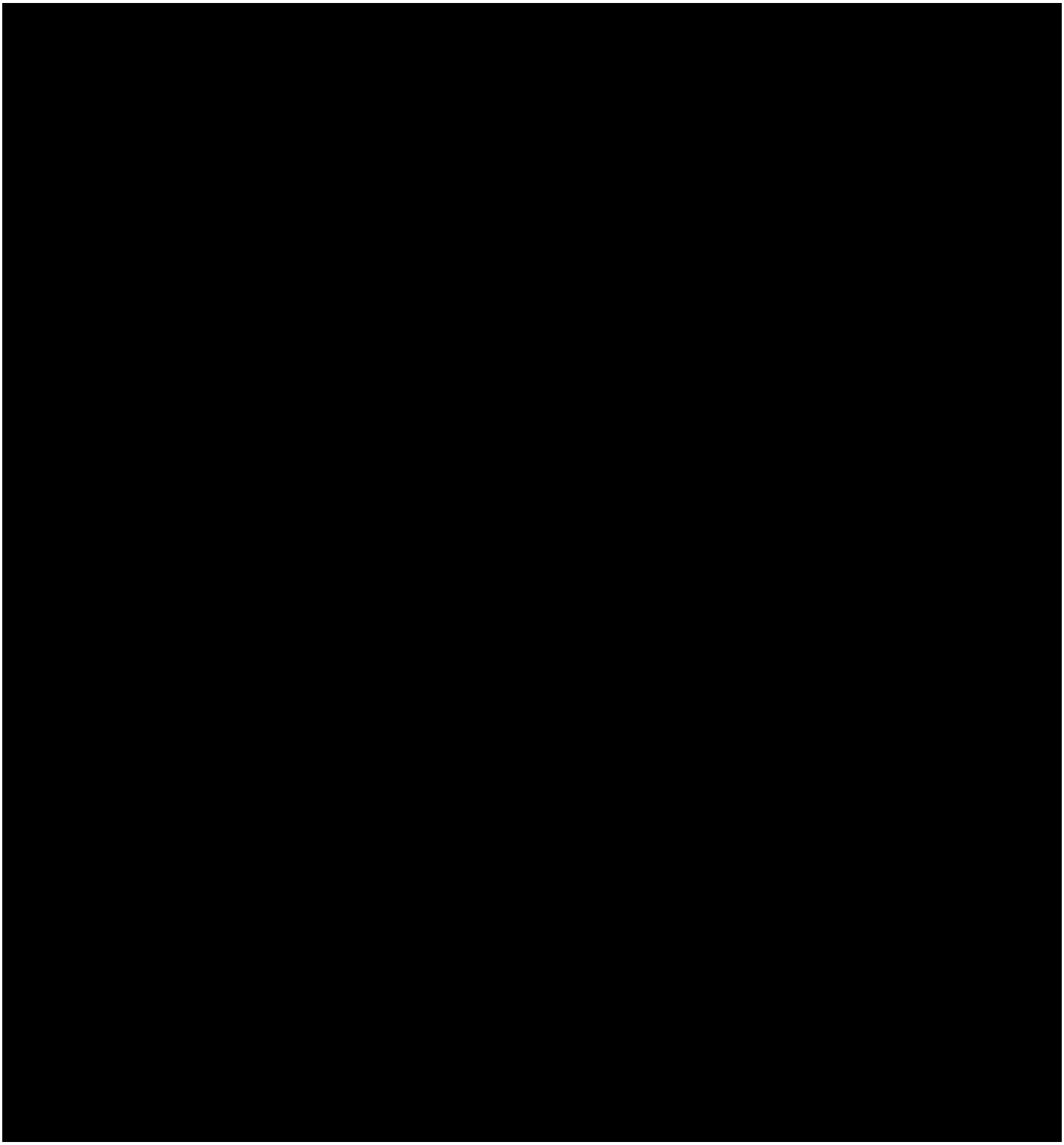
- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date.

6.3 Serious Adverse Events

The number and percent of participants reporting TESAEs will be summarized by type of event (ocular or non-ocular) and relationship to treatment.

[redacted]





8. Other Analyses

8.1 Subgroup Analyses

China subgroup is defined as all China participants. All analyses will be performed for China subgroup.

8.2 Interim Analyses

No interim analysis will be performed for this study.

[redacted]

10. References

Kenward, M.G., Roger, J.H. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53:983-97.

11. Amendments

To be added when occurred.

ALLERGAN

Ozurdex China 206207-026 SAP

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