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STATISTICAL REVIEW(S)

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Statistical Review and Evaluation

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This submission includes two 6-month, masked, Phase 3, randomized, sham-controlled trials and addresses the efficacy as well as safety of DEX PS DDS 700μg applicator (DEX 700) for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The primary objective was to show that DEX 700 was efficacious compared to Sham as measured by the improvement of best corrected visual acuity (BCVA). The original protocol planned primary efficacy endpoint was the proportion of patients with at least 15 letters improvement from baseline in BCVA at Day 180 post DEX 700 injection. Data from both studies failed to demonstrate statistically significant efficacy of DEX 700 compared to Sham as assessed by the original primary endpoint at Day 180. A new parameter, the time to respond (achieve at least 15 letters improvement from baseline in BCVA), was later adapted as the primary efficacy endpoint in one study and seemed to show superiority of DEX 700 over Sham in cumulative response rates. However, there was no scientific rationale provided for this post hoc change, which could introduce serious issues with interpreting the results and potential biases. Additionally, this new endpoint could not be accurately determined given the study design because neither trial was adequately designed to measure onset or duration of a treatment response.

This review finds out that DEX 700 treatment provides no sustained benefits. Although some patients had earlier achieved at least 15 letters improvement from baseline in BCVA, their improvement could not be retained at subsequent visits, i.e., relapse occurred. The sponsor's analysis of time to respond can be misleading because it did not account for the fact that relapse happened in almost half of those patients who showed improvements after DEX 700 injection. When time to achieve a sustained improvement is considered, there is no statistical difference between DEX 700 and Sham in either study. Note again that the onset or duration of a response could not be adequately determined given the study design.

The lack of sustained treatment response is supported by consistent data from the two trials. The proportion of patients with at least 15 letters improvement from baseline in BCVA was significantly higher with DEX 700 compared to Sham at Days 30, 60, and 90 but the difference disappeared by the primary time point Day 180. Although not for the exact indication of macular edema following BRVO or CRVO, the internal FDA Draft Guidance for Industry (3/1/2008) recommends minimum 6 or 12 months of efficacy data for the primary endpoint because earlier findings in macular edema are not predictive of later findings.

Therefore, this submission did not provide statistically persuasive evidence of DEX 700 on a sustained response, though an early but short term improvement was observed. Given the study design, it is difficult to measure both the onset and duration of the

treatment effect. This is important information for the patients and physicians. If the medical division accepts the change from a 6 month endpoint to a short term response, this reviewer recommends DEX 700 be investigated further in an additional study to more accurately measure the onset and duration of a response.

1.2 Brief Overview of Clinical Studies

Two studies, Study 206207-008 and Study 206207-009, have been submitted to provide support for the efficacy of DEX PS DDS applicator in the treatment of macular edema. These studies compared two doses, DEX PS DDS 700μg applicator (henceforth referred to as DEX 700) and DEX PS DDS 350μg applicator (henceforth referred to as DEX 350), to a sham needleless applicator (henceforth referred to as Sham). Both were randomized, multi-center, 3-arm comparative trials with a 6-month masked initial treatment followed by a 6-month open-label extension. Patients were administered DEX 700, or DEX 350, or Sham on Day 0 and might receive DEX 700 at Day 180. All patients were monitored under masked condition during the first 6 months and then followed for another 6 months for safety. Efficacy was evaluated at the end of first 6 months. Registration was sought for DEX 700 to be used in the treatment of macular edema following BRVO or CRVO.

In Studies 206207-008 and 206207-009, the original protocol planned primary efficacy variable was the proportion of patients who had at least 15 letters improvement from baseline in BCVA at Day 180 visit. In Study 206207-008 after trial completion, the primary endpoint was changed to the time to achieve at least 15 letters improvement from baseline in BCVA. Note that there was no requirement for sustained improvement with this definition.

1.3 Statistical Issues and Findings

The main statistical issue encountered during the review was pertinent to the primary efficacy endpoint as described below:

1. ***Post hoc change of endpoint:*** There was a late change in the primary efficacy endpoint in Study 206207-008. The original protocol planned primary endpoint was the proportion of patients with at least 15 letters of improvement from baseline in BCVA at Day 180 in both studies. However, in Study 206207-008 at 5.5 months after trial completion and 1 day before database lock, the time to respond (achieve at least 15 letters improvement from baseline in BCVA) was adapted as a new primary efficacy endpoint. The change was initiated after observing results from Study 206207-009, which failed to demonstrate superiority of DEX 700 according to the original protocol planned primary efficacy endpoint. Given the late timing of the change as well as the fact that no scientific rationale was provided and that this study was not designed to adequately assess the new endpoint (data were only collected on visit Days 30, 60, 90, and 180 post procedure), the change of the primary endpoint is concerning.

2. ***No durable treatment benefits:*** There was no statistically significant difference between DEX 700 and Sham in the proportion of patients with at least 15 letters improvement from baseline in BCVA at Day 180. Although there appeared to be an early treatment effect, the efficacy decreased after Day 60 and disappeared by Day 180. This is due to the fact that relapses occurred after improvement. Among patients who ever achieved at least 15 letters of improvement from baseline in BCVA, almost half of them experienced relapse. That means, their BCVA scores were not improved by at least 15 letters from baseline at subsequent visits.

3. ***Time frame for efficacy determination:*** Although not for the identical indication of macular edema following BRVO or CRVO, the internal FDA Draft Guidance for Industry (3/1/2008) recommends that efficacy data for the primary endpoint can be accepted at 12 months or more for macular edema secondary to inflammation, 6 months or more for macular edema secondary to surgery or vascular event. The 6-month or 12-month minimum has been suggested because past trials have demonstrated that earlier findings in macular edema are not predictive of later findings.

4. ***Design limitation in evaluating onset and duration of a treatment effect***: Neither of the two studies was adequately designed to measure onset or duration of a treatment response. There were only 4 post baseline visits to collect BCVA data for efficacy purpose and there was a large window during which a patient could be seen for a particular visit: study day 19 to 45 for Day 30 visit, study day 46 to 75 for Day 60 visit, study day 76 to 135 for Day 90 visit, and study 136 to 210 for Day 180 visit. Thus, time to respond (achieve at least 15 letters improvement) as well as duration of a response cannot be accurately determined.

5. ***Definition of responders:*** There was no clear definition of responders when the time to respond was considered as a primary efficacy endpoint. A responder could be defined as either a patient who ever improved by $\geq$15 letters from baseline in BCVA or one who reached and remained $\geq$15 letters above its baseline BCVA at subsequent visits. The sponsor's analysis reported patients who ever improved by $\geq$15 letters from baseline in BCVA as responders, regardless of whether they relapsed or not. Due to lack of information on responder specification, this reviewer performed an alternative analysis by including patients who had $\geq$15 letter improvements from baseline in BCVA without relapse as responders.

A total of 599 and 668 patients were randomized in Study 206207-008 and Study 206207-009, respectively. All were included in the intent-to-treat (ITT) population for the primary analyses of BCVA and results from the two studies were similar.

1. ***Protocol planned endpoint:*** There was no statistical difference in the proportion of patients with at least 15 letters improvement in BCVA from baseline at Day 180. Although the proportion was significantly higher with DEX 700 and DEX

350 compared to Sham at Days 30, 60, and 90 (P-values ≤ 0.022 in Study 206207-008 and P-values ≤0.039 in Study 206207-009), the difference disappeared by the primary time point Day 180. At Day 180, the difference (95% CI) between DEX 700 and Sham was 1.1% (-6.6% to 8.7%) with P-value = 0.780 and the difference (95% CI) between DEX 350 and Sham was -2.0% (-9.4% to 5.4%) with P-value = 0.600 in Study 206207-008. For Study 206207-009, the difference (95% CI) between DEX 700 and Sham was 6.5% (-0.9% to 13.9%) with P-value = 0.087 and the difference (95% CI) between DEX 350 and Sham was 5.1% (-2.3% to 12.4%) with P-value = 0.180. Neither comparison was considered to be statistically significant according to the pre-specified gate-keeping approach. The results seem to be robust with various sensitivity analyses as well as analyses by gender, race, and age group. There appears to be an early effect of DEX treatment but it is not maintained to Day 180, which was considered the most relevant time point at the planning stage of both trials.

2. ***Post hoc endpoint:*** The time to respond (achieve at least 15 letters improvement in BCVA from baseline) was reported by the sponsor to be statistically different between DEX treatment and Sham group. In the sponsor's analysis, the cumulative response rates curves were significantly higher in the DEX 700 group compared to the Sham group (P-value = 0.001) and in the DEX 350 group compared to the Sham group (P-value = 0.009) in Study 206207-008. In Study 206207-009, the cumulative response rates were significantly higher with DEX 700 and DEX 350 than with Sham group (P-values < 0.001). However, this significance is due to only short term response by patients in the DEX groups. The sponsor's analysis considered as a responder if a patient achieved short term improvement followed by relapse. The results can be misleading since it did not account for the fact that relapse occurred in almost half of those patients who showed improvement after DEX 700 or DEX 350 injection. When only patients with sustained improvement (including those who improved by Day 180 with no additional follow up) are considered as responders, the cumulative response rate curves are similar among 3 arms in both studies. Analysis of time to respond without relapse finds no significant statistical difference in the DEX 700 group compared to the Sham group in Study 206207-008 (P-value = 0.829) and Study 206207-009 (P-value = 0.085). Likewise, there is no significant statistical difference in the DEX 350 group compared to the Sham group in Study 206207-008 (P-value = 0.601) and Study 206207-009 (P-value = 0.160). There is no apparent separation of the cumulative response curves during the initial treatment period. Note that the two studies were not appropriately designed for measuring onset or duration of a treatment response. The primary efficacy data were only collected 4 times post baseline at Days 30, 60, 90, 180, and each visit had a large window during which a patient could be seen. Therefore, the time to respond cannot be accurately determined.

3. ***Other:*** For patients who ever responded (achieved at least 15 letters improvement from baseline in BCVA), the median time to a treatment response is 37 to 42 days with DEX 700 compared to 61 to 69 days with Sham (P-values ≤ 0.030). The

median duration of the improvement is 43 to 47 days with DEX 700 compared to 41 to 72 days with Sham. The median time to a treatment response is 54 to 58 days in the DEX 350 groups with a median duration of 49 to 50 days. Again, the two studies were not designed to accurately measure timing and duration of a treatment response. Hence, interpretation of this result is limited.

In conclusion, data from the two studies failed to demonstrate statistically significant efficacy of DEX 700 compared to Sham as measured by the original protocol planned endpoint of proportion of patients with ≥15 letters improvement from baseline in BCVA at Day 180. Additionally, a significant effect was not seen in time to achieve a sustained treatment response of 15 or more letters improvement from baseline in BCVA. Although a short term treatment effect was observed in both studies, given the study design and its limitations, it is impossible to accurately measure the onset and duration of the treatment effect. Based on the review of study data, this submission did not provide statistically persuasive evidence for efficacy of DEX 700.

2 INTRODUCTION

2.1 Overview

Macular edema is a nonspecific response of retina to a variety of insults, and is associated with a number of diseases. Prolonged edema can cause irreversible damage resulting in permanent visual loss. Currently there are no approved pharmacologic therapies for macular edema.

DEX PS DDS Applicator System is an intraocular drug delivery system developed for treatment of macular edema and other retinal diseases. The active ingredient, dexamethasone, is combined with biodegradable polymers and extruded into a small implant suitable for delivery into the posterior segment of the eye. This implant delivers a 350μg or 700μg total dose of dexamethasone to the vitreous with gradual release over time allowing for sustained drug levels to the target areas despite lower total dose.

This New Drug Application (NDA) is for the registration of DEX PS DDS 700μg Applicator (DEX 700) in the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

2.2 Data Sources

Datasets and all modules containing clinical study reports were submitted electronically. The full electronic path according to the CDER EDR naming convention is as follows:

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3 STATISICAL EVALUATION

The use of DEX PS DDS Applicator System has been evaluated in 7 studies, out of which 3 were conducted in patients with macular edema (DC103-06, 206207-008, and 206207-009). Study DC103-06 was a Phase 2 dose-ranging study with tablet DEX PS DDS in patients with persistent macular edema. Study 206207-008 and Study 206207-009 were Phase 3 studies with DEX PS DDS 700µg and 350µg Applicator in patients with retinal vein occlusion.

This document contains a statistical review of the two Phase 3 studies 206207-008 and 206207-009. Both were randomized, 3-arm, sham-controlled, Phase 3 trials with 6-month masked initial treatment period followed by a 6-month open-label extension. Results from the 6-month initial treatment period will be evaluated in this review.

3.1 Evaluation of Efficacy

Protocol 206207-008: A six-month, phase 3, multicenter, masked, randomized, sham-controlled trial (with six-month open-label extension) to assess the safety and efficacy of 700µg and 350µg Dexamethasone posterior segment drug delivery system (DEX PS DDS) applicator system in the treatment of patients with Macular Edema following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion.

Protocol 206207-009: A six-month, phase 3, multicenter, masked, randomized, sham-controlled trial (with six-month open-label extension) to assess the safety and efficacy of 700µg and 350µg Dexamethasone posterior segment drug delivery system (DEX PS DDS) applicator system in the treatment of patients with Macular Edema following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion.

3.1.1 Objectives and Study Design

The study design for Studies 206207-008 and 206207-009 is summarized in Table 1.

Table 1 Summary of Design of Studies 206207-008 and 206207-009

Feature	206207-008	206207-009
Clinical Phase	3	3
Randomization	randomized	randomized
Blinding	Double-masked	Double-masked
Active Treatment	DEX PS DDS 700µg applicator DEX PS DDS 350µg applicator	DEX PS DDS 700µg applicator DEX PS DDS 350µg applicator
Control treatment	sham needleless applicator	sham needleless applicator
Patient Diagnosis	macular edema due to branch or central retinal vein occlusion	macular edema due to branch or central retinal vein occlusion
Primary Endpoint*	Time to response of ≥ 15 letters (3 lines) improvement in BCVA.	Proportion of patients with ≥ 15 letters (3 lines) improvement in BCVA at Day 180.
Duration	6-month masked initial treatment followed by 6-month open-label extension	6-month masked initial treatment followed by 6-month open-label extension
Study Timeline	October 22, 2004 to March 31, 2008 (end of 6 months)	November 18, 2004 to March 3, 2008 (end of 6 months)
Patients recruited	599	668
Study Centers	85	82
Countries or Regions where studies were conducted	North America, Latin America, Europe, Asia Pacific, and Israel/South Africa	North America, Latin America, Europe, and Asia Pacific

** Major difference between the two trials was highlighted in gray.*

Both Studies 206207-008 and 206207-009 were Phase 3 trials with very similar design. Their primary objective was to evaluate the safety and efficacy of DEX 700 and DEX 350 compared with Sham in patients with macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Each trial was a 6-month, multicenter, masked, randomized, sham-controlled, safety and efficacy study followed by a 6-month open-label extension. Patients were randomized in a 1:1:1 ratio to DEX 700: DEX 350: Sham for the first 6 months (initial treatment). All patients received an assigned treatment on randomization (Day 0) and might receive an open-label dose of DEX 700 at initial treatment Day 180. There were 12 scheduled visits (14 visits if retreatment occurs) consisting of qualification/baseline, randomization (Day 0), initial treatment Days 1, 7, 30, 60, 90 and 180 and open-label extension Days 1, 7, 30, 60, 90 and 180. All patients (whether they received the open-label treatment or not) were followed up for safety for an additional 6 months following the initial treatment Day 180 visit. Study 206207-008 was conducted from October 22, 2004 to March 31, 2008 and enrolled 599 patients in 85 centers in 13 countries. Study 206207-009 was conducted from November 18, 2004 to March 3, 2008 and enrolled 668 patients in 82 centers in 13 countries.

The primary efficacy assessment was the same for both studies 206207-008 and 206207-009, which was best corrected visual acuity (BCVA) measured in the study eye using the Early Treatment Diabetic Retinopathy Study method. BCVA scores were collected at qualification/baseline visit, and initial treatment and open-label extension Days 1, 7, 30, 60, 90 and 180. Data collected at initial treatment Days 1 and 7 and open-label extension Days 1 and 7 post-insertion were considered as safety measures and were not included in the efficacy analysis. Secondary efficacy measures included contrast sensitivity (CS), optical coherence tomography (OCT), fundus photography (FP), and fluorescein angiography (FA). Except for FA, all were performed in study eye only.

In Study 206207-008, the primary efficacy endpoint was the time to achieve a treatment response of 15 or more letters improvement from baseline in BCVA during the initial treatment period. The primary efficacy analysis was the comparison between DEX 700 and Sham in the ITT population. The primary efficacy analysis used a Kaplan-Meier method with a 2-sided log-rank test at $\alpha = 0.05$ level. The cumulative response rates were calculated using the Kaplan-Meier method for each group. The secondary efficacy analyses included comparisons of DEX 700 versus Sham or DEX 350 versus Sham for BCVA variables. A gate-keeping procedure with a pre-specified sequence for controlling the overall experiment-wise type I error at 5% was used. Ten pair-wise comparisons were performed, and the statistical significance was assessed sequentially.

Reviewer's comments: According to the original protocol of Study 206207-008, the primary efficacy variable was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye. This was changed to the time to a response of ≥15 letters improvement in BCVA after 5.5 months of trial completion (See Section 3.1.5.1 for details).

In Study 206207-009, the primary efficacy endpoint was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at in initial treatment Day 180. The primary efficacy analyses included the comparisons of DEX 700 versus Sham and DEX 350 versus Sham in the ITT population. The primary analysis employed the Pearson's Chi-square method and used a gate-keeping procedure to control the overall type I error rate at 5%. The comparison of DEX 700 versus Sham was tested first. If, and only if the comparison of DEX 700 versus Sham was significant (P-value < 0.05), would the comparison of DEX 350 versus Sham be performed and at $\alpha = 0.05$. Otherwise, the comparison of DEX 350 versus Sham wasn't considered statistically significant regardless of its p-value. The secondary efficacy analyses were the comparisons between DEX 700 and Sham, and between DEX 350 and Sham for the primary efficacy variable at initial treatment Day 180 in the ITT subpopulation of BRVO patients.

Reviewer's comments: According to the original protocol, the primary analysis would use the Cochran-Mantel-Haenszel (CMH) method stratified by investigator and the Hochberg's procedure to control overall type I error rate at 5% for multiple between-treatment comparisons (DEX 700 versus Sham and DEX 350 versus Sham). This was

later changed to a gate-keeping approach based on the published phase 2 data and agreements with FDA (2/26/2007, 5/16/2007, and 4/4/2007).

Three analysis groups of interest were defined for the initial treatment period:

- Intent-to-Treat (ITT) population: All randomized patients
- Per protocol (PP) population: All patients who had no major protocol violations determined prior to database lock
- Safety population: All randomized and treated patients

The ITT and PP populations were used in all efficacy analyses. The safety population was used in all safety analyses.

Initial treatment Day 0 was defined as the day when the patients received initial treatment. For patients who did not receive the initial treatment, the randomization day will be used as the initial treatment Day 0. Baseline data refer to assessments performed at the Qualification/Baseline visit. Screening or unscheduled but prior to Day 0 visits could be used for baseline in the absence of pertinent data at the Qualification/Baseline visit.

For both studies the trial population consisted of patients aged 18 years or up with macular edema involving the center of the macula due to BRVO or CRVO in at least one eye. Disease duration prior to qualification/baseline visit was 6 weeks to 9 months for CRVO patients or 6 weeks to 12 months for BRVO patients, respectively. The inclusion criteria included BCVA score between 34 and 68 letters measured by the ETDRS method and retinal thickness of $\geq$ 300μm by OCT in the central 1 mm macular subfield of the study eye at qualification/baseline visit. If both eyes were eligible, the one with shorter duration of disease were used as the study eye. The study eye was identified at the qualification/baseline visit and remained the same throughout the entire study. Only one eye was treated with study drug during the study.

Studies 206207-008 and 206207-009 were conducted to show that the DEX 700 or DEX 350 was more effective than the Sham Applicator System in the improvement of best corrected visual acuity (BCVA). The sample size calculation was based on the analysis of the proportion of patients with improvement of 15 or more letters in BCVA from baseline in the study eye comparing the DEX 700 with Sham and comparing the DEX 350 with Sham. Assuming a 9% improvement rate for Sham and a between-group absolute difference of 11% in the improvement rate, 165 patients per group were needed to achieve 81% power at $\alpha = 0.05$. A total of approximately 550 patients will be enrolled after accounting for an estimated 10% dropout rate.

Reviewer's comments: The originally planned sample size for each study was 195 patients per group, or 650 patients with adjustment for 10% dropout. The sample size was reduced to 165 patients per group, or total 550 patients by changing $\alpha = 0.025$ to $\alpha = 0.05$. There was no documentation about why the change was necessary. The final number of patients enrolled, however, was 599 in Study 206207-008 and 668 in Study 206207-009, respectively.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows disposition of patients in Studies 206207-008 and 206207-009.

Table 2 Distribution of Patients in Studies 206207-008 and 206207-009

	206207-008			206207-009		
	DEX 700	**DEX 350**	**Sham**	**DEX 700**	**DEX 350**	**Sham**
Enrolled/ Randomized	201	196	202	226	218	224
Treated	196	197[a]	202[b]	225	215	221
Completed Day 180	189	189	189	214	206	209
Terminated before Day 180						
Total	12	7	13	12	12	15
Adverse events	3	6	3	5	2	5
Lack of efficacy	0	0	2	0	3	2
Lost of follow up	2	0	1	0	0	2
Personal reasons	5	1	3	2	2	1
Protocol violation	2	0	2	2	1	0
Other	0	0	2	3	4	5
BCVA analyses						
ITT	201	196	202	226	218	224
Per-protocol	189	181	185	213	201	209

[a]*Subject 4398-1666 was randomized to the DEX 700 group but received DEX 350*
[b]*Subject 4447-0302 was randomized to the DEX 700 group but received Sham; Subject 8305-0578 was randomized to Sham but did not receive treatment*

A total of 599 eligible patients were randomized in Study 206207-008, all but 4 received study treatment. There were 4 patients randomized but not treated: 3 in the DEX 700 (#4347-1487, #3983-0542, #4347-1493) and 1 in the Sham group (#8305-0578). These 4 patients, together with other 28, discontinued the trial before Day 180 for the following reasons: 12 due to adverse events, 2 due to lack of efficacy, 3 due to loss of follow up, 9 due to personal reasons, 4 due to protocol violation, and 2 due to other reasons. All randomized patients were included in the intent-to-treat analysis of BCVA. In addition, 2 patients who were randomized to the DEX 700 group received a different treatment (#4398-1666 with DEX 350 and #4447-0302 with Sham) and completed Day 180.

A total of 668 eligible patients were randomized in Study 206207-009, all but 7 received study treatment. There were 7 patients randomized but not treated: 1 in the DEX 700 group (#4300-2579), 3 in the DEX 350 (#4220-2361, #4259-2242, #4336-2115) and 3 in the Sham group (#0469-2673, #4354-3468, #4614-3700). These 7 patients, together with other 32, discontinued the trial before Day 180 for the following reasons: 12 due to adverse events, 5 due to lack of efficacy, 2 due to loss of follow up, 5 due to personal reasons, 3 due to protocol violation, and 12 due to other reasons. All randomized patients were included in the intent-to-treat analysis of BCVA.

Selected demographic characteristics and baseline covariates were compared among treatment groups for both studies in Table 3. In Study 206207-008, the mean (range) age was 65.5 years (32 to 91), 54.6% (327/599) were male, and 83.8% (502/599) were Caucasian. The diagnosis was CRVO for 34.2% (205/599) and BRVO for 65.8% (394/599). In Study 206207-009, the mean (range) age was 63.6 years (31 to 96), 52.4% (350/668) were male, and 67.2% (449/668) were Caucasian. The diagnosis was CRVO for 34.7% (232/668) and BRVO for 65.3% (436/668). There were no statistically significant differences among the treatment groups in the demographic and baseline characteristics in both studies.

Table 3 Patients Demographics and Baseline Characteristics

Characteristic	206207-008			206207-009		
	DEX 700 N=201	**DEX 350 N=196**	**Sham N=202**	**DEX 700 N=226**	**DEX 350 N=218**	**Sham N=224**
Age (years) mean (range)	65.8 (36 to 90)	65.9 (37 to 88)	64.8 (32 to 91)	63.7 (33 to 89)	64.0 (31 to 96)	63.1 (31 to 89)
Sex						
male	106 (52.7%)	104 (53.1%)	117 (57.9%)	111 (49.1%)	116 (53.2%)	123 (54.9%)
female	95 (47.3%)	92 (46.9%)	85 (42.1%)	115 (50.9%)	102 (46.8%)	101 (45.1%)
Race						
Caucasian	169 (84.1%)	166 (84.7%)	167 (82.7%)	152 (67.3%)	146 (67.0%)	151 (67.4%)
Black	4 (2.0%)	3 (1.5%)	11 (5.4%)	11 (4.9%)	11 (5.0%)	9 (4.0%)
Asian	7 (3.5%)	9 (4.6%)	10 (5.0%)	31 (13.7%)	27 (12.4%)	34 (15.2%)
Japanese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	1 (0.4%)
Hispanic	17 (8.5%)	14 (7.1%)	13 (6.4%)	20 (8.8%)	15 (6.9%)	12 (5.4%)
Other	4 (2.0%)	4 (2.0%)	1 (0.5%)	12 (5.3%)	17 (7.8%)	17 (7.6%)
Iris Color						
dark	109 (54.2%)	110 (56.1%)	125 (62.5%)	132 (58.4%)	134 (61.5%)	140 (62.5%)
light	92 (45.8%)	86 (43.9%)	75 (37.5%)	94 (41.6%)	84 (38.5%)	84 (37.5%)
Diagnosis in study eye						
CRVO	61 (30.3%)	72 (36.7%)	72 (35.6%)	75 (33.2%)	82 (37.6%)	75 (33.5%)
BRVO	140 (69.7%)	124 (63.3%)	130 (64.4%)	151 (66.8%)	136 (62.4%)	149 (66.5%)
Duration of macular edema						
< 90 days	28 (13.9%)	40 (20.4%)	24 (11.9%)	42 (18.6%)	36 (16.5%)	41 (18.3%)
90 to 179 days	111 (55.2%)	95 (48.5%)	100 (49.5%)	108 (47.8%)	123 (56.4%)	120 (53.6%)
180 to 269 days	42 (20.9%)	44 (22.4%)	55 (27.2%)	51 (22.6%)	44 (20.2%)	44 (19.6%)
≥ 270 days	20 (10.0%)	17 (8.7%)	23 (11.4%)	25 (11.1%)	15 (6.9%)	19 (8.5%)

3.1.3 Applicant's Main Efficacy Results

The sponsor's efficacy assessment for both studies was based on the analyses of improvement of 15 letters or more from baseline in BCVA in ITT population. However, in Study 206207-008 the time to achieve at least 15 letters improvement was designated as primary efficacy endpoint after trial completion while in Study 206207-009 the proportion of patients with at least 15 letters of improvement remained primary endpoint as originally specified. Table 4 presents number and percentage of patients with ≥15 letters of improvement from baseline in BCVA for both studies. The analysis of time to achieve ≥15 letters of improvement from baseline in BCVA is summarized in Table 5.

Reviewer's comments: According to the original protocol of Study 206207-008, the primary efficacy variable was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye. This was changed to time to a response of ≥15 letters improvement in BCVA on September 18, 2009 which was 5.5 months after the last patient completed Day 180 visit (See Section 3.1.5.1).

In Study 206207-008, the time to respond (achieve at least 15 letters improvement from baseline in BCVA) was analyzed using a Kaplan-Meier survival analysis with the log-rank test for treatment differences (Table 5). Overall, cumulative response rate curves were significantly different in the DEX 700 group compared to the Sham group (P-value = 0.001) and in the DEX 350 group compared to the Sham group (P-value = 0.009).

Reviewer's comments: Similar results were obtained in Study 206207-009, where the log-rank test comparing the cumulative response curves across time yielded statistically differences between DEX 700 and Sham as well as between DEX 350 and Sham. However, the time to respond analysis conducted by the sponsor can be misleading since it didn't account for the fact that some patients improved earlier and then relapsed (see Sections 3.1.5.2 and 3.1.5.3 for details).

In Study 206207-009, the proportion of patients with a BCVA improvement of 15 or more letters was analyzed using Pearson's Chi-square method (Table 4). Missing data were imputed by last observation carried forward (LOCF). The proportion of patients with ≥15 letters improvement in BCVA from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment Days 30, 60, 90 (P-values ≤ 0.039). At the primary time point initial treatment Day 180, the difference (95% CI) between DEX 700 and Sham was 6.5% (-0.9% to 13.9%) with P-value = 0.087. The difference (95% CI) between DEX 350 and Sham was 5.1% (-2.3% to 12.4%) with P-value = 0.180. Using the gate-keeping approach, neither comparison was considered to be statistically significant.

Reviewer's comments: Similar results were obtained in Study 206207-008, where the proportion of patients with ≥15 letters improvement from baseline in BCVA was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment Days 30, 60, 90 but not at the primary time point Day 180. This is due to the fact that some patients experienced relapses (see Sections 3.1.5.2 and 3.1.5.3 for details).

Reviewer's comments: Although not for the exactly same indication, the internal FDA Draft Guidance for Industry (3/1/2008) on macular edema recommends that efficacy data for the primary endpoint be accepted at 12 months or more for macular edema secondary to inflammation, 6 months or more for macular edema secondary to surgery or vascular event because past trials have demonstrated that earlier findings in macular edema are not predictive of later findings (See Section 5.1).

Table 4 Number (Percent) of Patients with ≥15 Letters Improvement from Baseline in BCVA (ITT Population)

	206207-008			206207-009		
Visit (Study Days)	**DEX 700 N=201**	**DEX 350 N=196**	**Sham N=202**	**DEX 700 N=226**	**DEX 350 N=218**	**Sham N=224**
Day 30 (19 – 45)	40 (19.9%)	29 (14.8%)	15 (7.4%)	51 (22.6%)	45 (20.6%)	17 (7.6%)
Difference in Proportion (DP)	12.5%	7.4%	-	15.0%	13.1%	-
95% C.I. of DP	(5.9%, 19.1%)	(1.2%, 13.5%)	-	(8.5%, 21.4%)	(6.7%, 19.4%)	-
P-value*	<0.001	0.019	-	<0.001	<0.001	-
Day 60 (46 – 75)	58 (28.9%)	50 (25.5%)	21 (10.4%)	67 (29.6%)	68 (31.2%)	27 (12.1%)
Difference in Proportion (DP)	18.5%	15.1%	-	17.6%	19.1%	-
95% C.I. of DP	(10.9%, 26.0%)	(7.7%, 22.5%)	-	(10.3%, 24.9%)	(11.7%, 26.6%)	-
P-value*	<0.001	<0.001	-	<0.001	<0.001	-
Day 90 (76 – 135)	45 (22.4%)	41 (20.9%)	25 (12.4%)	48 (21.2%)	56 (25.7%)	31 (13.8%)
Difference in Proportion (DP)	10.0%	8.5%	-	7.4%	11.8%	-
95% C.I. of DP	(2.7%, 17.3%)	(1.3%, 15.8%)	-	(0.4%, 14.4%)	(4.5%, 19.2%)	-
P-value*	0.008	0.022	-	0.039	0.002	-
Day 180 (136 – 210)	39 (19.4%)	32 (16.3%)	37 (18.3%)	53 (23.5%)	48 (22.0%)	38 (17.0%)
Difference in Proportion (DP)	1.1%	-2.0%	-	6.5%	5.1%	-
95% C.I. of DP	(-6.6%, 8.7%)	(-9.4%, 5.4%)	-	(-0.9%, 13.9%)	(-2.3%, 12.4%)	-
P-value*	0.780	0.600	-	0.087	0.180	-

** P-values were based on the Pearson's Chi-square test.*

Missing data were imputed via LOCF. Primary analyses are highlighted in gray.

Table 5 Applicant's Analysis of Time to Achieve ≥15 Letters Improvement from Baseline in BCVA (ITT Population)

Study Days	206207-008						206207-009					
	DEX 700 N=201		DEX 350 N=196		Sham N=202		DEX 700 N=226		DEX 350 N=218		Sham N=224	
	#Patient at risk [a]	Cum. Prob. [b]	#Patient at risk [a]	Cum. Prob. [b]	#Patient at risk [a]	Cum. Prob. [b]	#Patient at risk [a]	Cum. Prob. [b]	#Patient at risk [a]	Cum. Prob. [b]	#Patient at risk [a]	Cum. Prob. [b]
Day 0	201	0%	196	0%	202	0%	226	0%	218	0%	224	0%
Day 30	182	10.1%	179	9.2%	193	4.5%	199	13.8%	195	11.7%	212	3.2%
Day 60	150	25.8%	159	20.4%	180	10.0%	159	29.0%	156	26.6%	194	11.5%
Day 90	126	35.0%	137	29.2%	165	16.5%	138	37.5%	134	37.0%	180	15.7%
Day 180	73	39.7%	65	34.9%	80	22.5%	76	43.0%	72	44.8%	88	22.5%
P-value*	<0.001		0.009		-			<0.001		<0.001		-

[a] Number of patients who have not responded or been censored and are still "at risk" prior to this tabulated time point.

[b] Cumulative probability of response at this tabulated time point estimated by Kaplan-Meier method.

** P-values were based on the log-rank test comparing the cumulative response rate curves across time during the initial treatment period using Kaplan-Meier method. Primary analysis is highlighted in gray.*

3.1.4 Applicant's Other Efficacy Results

In Study 206207-008, analyses of a 10 or more letters, and 11 to 14 or more letters, change in BCVA from baseline showed significantly greater improvements with DEX 700 and DEX 350 than with Sham at Days 30, 60, 90 with one exception. The difference between the DEX 350 group and the Sham group was not statistically significant for the 14 or more letters improvement at Day 30. The mean increase in the number of letters read correctly was significantly greater with DEX 700 compared to Sham at Days 30, 60, and 90 (P-values ≤ 0.003) and with DEX 350 compared to Sham at Days 30 and 60 (P-values ≤ 0.002). Likewise, the categorical change from baseline BCVA showed significantly improved visual acuity for DEX 700 and DEX 350 compared to Sham at Days 30, 60, and 90 (P-values < 0.001). The percentage of patients with > 3-line vision loss from baseline (equivalent to > 15 letters worsening) in the study eye was statistically significantly lower in the DEX 700 group compared to Sham at initial treatment Day 60 (P-value= 0.037). However, at the primary time point Day 180, none of the above measures was significantly different between either of the DEX groups and Sham.

In Study 206207-009, there was no statistical difference between DEX 700 versus Sham and DEX 350 versus Sham at Day 180 in the BRVO diagnostic subgroup. Analyses of a 10 or more letters and 11 to 14 or more letters treatment response showed significantly greater improvements with DEX 700 than with Sham at Days 30, 60, 90 and 180 (except for the 11 or more letters treatment response at Day 180). Significant improvements were also seen with DEX 350 compared to Sham for at Days 30, 60, 90, but not Day 180. The mean increase in the number of letters read correctly was significantly greater with DEX 700 and DEX 350 compared to Sham at Days 30, 60, 90 and 180 (P-values ≤ 0.016). Likewise, the categorical change from baseline BCVA showed significantly improved visual acuity for DEX 700 and DEX 350 compared to Sham at all follow up visits (P-values ≤ 0.009). The percentage of patients with $\geq$ 3-line vision loss from baseline (equivalent to $\geq$ 15 letters worsening) in the study eye was statistically significantly lower in the DEX 700 group compared to Sham at initial treatment Days 90 and 180 (P-values < 0.048), and in the DEX 350 group compared to Sham at each follow-up visit (P-values < 0.030).

Reviewer's comments: The above is just a summary of the secondary and other efficacy results presented by the applicant in the study reports. The results are consistent with the primary efficacy results in that only early treatment effect was observed in both studies.

3.1.5 Additional Analyses by FDA

The following analyses are performed by the FDA statistical reviewer.

3.1.5.1 Assessment of Primary Endpoint Change in Study 206207-008

The original protocols for Study 206207-008 and Study 206207-009 were finalized on 09 August, 2004. According to the original protocol, the primary efficacy variable would be the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye. The primary efficacy analyses include the comparisons between the DEX 700 and Sham groups and between the DEX 350 and Sham groups on the primary efficacy variable at initial treatment Day 180. The ITT population will be used for the analysis. In Study 206207-008, the first patient was enrolled on 22 October 2004, the last patient completed initial treatment Day 180 Visit on 31 March 2008, and the database lock was locked on 19 September 2008. In Study 206207-009, the first patient was enrolled on 18 November 2004, the last patient completed initial treatment Day 180 visit on 03 March 2008, and the database lock was locked on 28 May 2009, unlocked, and then finally locked on 01 August 2008.

Studies 206207-008 and 206207-009 were amended 3 times during the trial with the following statistical relevant changes:

- Amendment #1 (June 2006): Changed the statistical analysis sections to include a modified intent-to-treat population. Clarified that investigators will be grouped in the statistical analysis.
- Amendment #2 (June 2007): Modified the description of statistical analysis: A gate-keeping procedure will be used to control the overall type I error rate at 5% for the multiple between-group comparisons in the primary efficacy analysis.
- Amendment #3 (July 2007): Reduced the study's sample size: Sample size is reduced from 195 patients to 165 patients per arm to provide 81% power in the power and sample size calculation.

A 4th amendment was applied to Study 206207-008 only on 18 September 2009. Statistical relevant changes are listed below:

1. The reference to the proportion of patients has been deleted from the Clinical Hypothesis.
2. The modified intent-to-treat (mITT) population has been replaced by the retreated population which will be used for the analyses of data from the open-label extension.
3. The comparison between the 700 µg DEX PS DDS Applicator System and the Sham DEX PS DDS Applicator System groups for the time to achieve a treatment response of BCVA improvement of 15 or more letters from baseline in the study eye during the initial treatment period is designated as the primary efficacy analysis.

4. Ten pairwise comparisons for the secondary analyses will be performed using a gate-keeping procedure. Other efficacy analyses will be performed on additional BCVA variables, contrast sensitivity, FA, FP and retinal thickness by OCT.
5. For the European Medicines Agency (EMEA) submission, *omitted here.*
6. Pearson's chi-square test will be employed in all analyses for proportion of patients with 15 (10) letters or more of improvement in BCVA in replace of the original method using a stratified Cochran-Mantel-Haenszel test.
7. An analysis of the proportion of patients with a BCVA improvement of at least 15 letters from baseline, excluding patients with less than 90 days duration of disease was added. Analyses of the BRVO and CRVO subgroups were designated as "exploratory analysis for subpopulations".

No scientific rationale has been provided for the change of primary efficacy endpoint from the proportion of patients with ≥ 15 letters improvement in BCVA from baseline to the time to respond (achieve ≥ 15 letters improvement in BCVA from baseline). This reviewer attempted to locate documents regarding FDA's acceptance of this change but could not get any information. The internal FDA Draft Guidance for Industry (3/1/2008) on macular edema, though not for the exact indication of macular edema following BRVO or CRVO, recommends the following endpoints, which do not include time to respond:

> "1. A statistically significant difference between groups in the percentage of patients with a doubling of the visual angle (15 letters or more on an Early Treatment Diabetic Retinopathy visual acuity chart measured at 4 meters).
>
> 2. A statistically significant difference between groups in the percentage of patients with a halving of the visual angle (15 letters or more on an Early Treatment Diabetic Retinopathy visual acuity chart measured at 4 meters).
>
> 3. A statistically significant difference between groups in the percentage of patients with a quadrupling of the visual angle (30 letters or more on an Early Treatment Diabetic Retinopathy visual acuity chart measured at 4 meters).
>
> 4. A statistically significant difference between groups in mean visual acuity of 15 or more letters on a Early Treatment Diabetic Retinopathy visual acuity chart measured at 4 meters."

It is worth noting that the change of primary endpoint occurred on 18 September 2009 which was 5.5 months after trial completion and 1 day before database lock. It was also about 1.5 months post database lock and unblinding of Study 206207-009. The current submission contains major interactions and agreements between the sponsor and FDA from 08 September 2003 to 23 April 2008. But there is no documentation from either the sponsor or FDA regarding the late change in primary efficacy endpoint. If not properly planned and pre-specified, any change in design parameters can potentially introduce serious biases. Any late change to a statistical analysis plan, much less changes to the

primary end point, should be viewed with skepticism when they arise after the data has been collected, but – unverifiably – before unblinded.

3.1.5.2 Patients Status after having ≥15 Letters Improvement

While proportion of patients with at least 15 letters of improvement from baseline is significantly higher in either DEX 700 or DEX 350 treated group compared to the Sham group at Days 30, 60, and 90, the difference is not statistical significant at the pre-specified efficacy assessment time point which is Day 180. The trend is similar for both Studies 206207-008 and 206207-009. A further data examination finds out that improvement of 15 letters or more from baseline in BCVA didn't sustain in all patients. For instance, 40 patients treated with DEX 700 in Study 206207-008 had a BCVA score improved of at least 15 letters by Day 30. This improvement was maintained in 32 (80%) patients by Day 60, 27 (67.5%) patients by Day 90, and 21 (52.5%) patients by Day 180. Table 6 presents patient status after achieving ≥15 letter improvement at Day 30, 60, or 90. Not all patients who achieved ≥15 letter improvement earlier still had BCVA scores ≥15 letter improvement from baseline at later visits.

Table 6 Patient Status after achieving ≥15 Letters Improvement from Baseline in BCVA (ITT Population)

Patients and Visit*	206207-008			206207-009		
	DEX 700 N=201	DEX 350 N=196	Sham N=202	DEX 700 N=226	DEX 350 N=218	Sham N=224
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Number of patients with ≥15 Letter Improvement by Day 30	40/201 (19.9)	29/196 (14.8)	15/202 (7.4)	51/226 (22.6)	45/218 (20.6)	17/224 (7.6)
Still with ≥15 Letter Improvement by Day 60	32/40 (80.0)	26/29 (89.7)	10/15 (66.7)	39/51 (76.5)	39/45 (86.7)	13/17 (76.5)
Day 90	27/40 (67.5)	21/29 (72.4)	8/15 (53.3)	32/51 (62.7)	30/45 (66.7)	14/17 (82.4)
Day 180	21/40 (52.5)	13/29 (44.8)	10/15 (66.7)	27/51 (52.9)	25/45 (55.6)	13/17 (76.6)
Number of patients with ≥15 Letter Improvement by Day 60	58/201 (28.9)	50/196 (25.5)	21/202 (10.4)	67/226 (29.6)	68/218 (31.2)	27/224 (12.1)
Still with ≥15 Letter Improvement by Day 90	35/58 (60.3)	31/50 (62.0)	12/21 (57.1)	34/67 (50.7)	44/68 (64.7)	19/27 (70.4)
Day 180	28/58 (48.3)	21/50 (42.0)	13/21 (61.9)	32/67 (47.8)	33/68 (48.5)	21/27 (77.8)
Number of patients with ≥15 Letter Improvement by Day 90	45/201 (22.4)	41/196 (20.9)	25/202 (12.4)	48/226 (21.2)	56/218 (25.7)	31/224 (13.8)
Still with ≥15 Letter Improvement by Day180	25/45 (55.6)	18/41 (43.9)	18/25 (72.0)	31/48 (64.6)	33/56 (58.9)	26/31 (83.9)
Number of patients with ≥15 Letter Improvement by Day 180 (no follow up)	39/201 (19.4)	32/196 (16.3)	37/202 (18.3)	53/226 (23.5)	48/218 (22.0)	38/224 (17.0)

** Visit refers to Initial Treatment Phase 1 Day 30 (19-45), Day 60 (46-75), Day 90 (76-135), and Day 180 (136-210). Missing data were imputed via LOCF.*

3.1.5.3 Examination of Relapse

The existence of improvement relapse measured by BCVA score is graphically illustrated in Figure 1. A relapse means that a patient's BCVA scores fall below the ≥15 letter improvement mark after achieving a ≥15 letter improvement from baseline. Patients are grouped into 4 exclusive categories according to whether ≥15 letter improvement in BCVA was achieved during the 6-month initial treatment period as follows:

1 - BCVA score never improved by ≥15 letter from baseline
2 - BCVA score improved by ≥15 letter earlier but not by ≥15 letter at later visits
3 - BCVA score improved by ≥15 letter earlier and still by ≥15 letter at later visits
4 - BCVA score fluctuated earlier and improved by ≥15 letter on Day 180

The horizontal line refers to a BCVA value that is 15 letters improvement over individual subject's baseline score.

Figure 1 BCVA Score over Time for Selected Patients in Study 206207-008
(Horizontal reference indicates 15 letters improvement from baseline)

Category	Examples from Study 206207-008
1 Never improved	
2 Improved then went down	
3 Sustained improvement	
4 Improved on Day 180	

b(4)

Table 7 presents the number and percentage of patients in each category summarized by treatment group for both studies. In the DEX 700 group, 40 (50.6%) out of the 79 patients who ever had ≥15 letter improvement in Study 206207-008 relapsed and their BCVA scores at Day 180 were not above baseline by at least 15 letters. Out of the 101 patients considered responders by the sponsor in Study 206207-009, 48 (47.5%) relapsed. Relapse rates were similar for patients receiving DEX 350 treatment, i.e., 54.3% (38 of 70) in Study 206207-008 and 50.0% (48 of 96) in Study 206207-009. Relapse rates in the Sham group were lower and occurred in 14 (27.5%) of 51 patients in Study 206207-008 and 12 (24.0%) of 50 patients in Study 206207-009. Overall, relapse rates are about 50% in DEX group and 26% in the Sham group (P-values < 0.05).

The sponsor's analysis of time to respond (achieve at least 15 letters improvement from baseline in BCVA) treated patients who ever had ≥15 letter improvements from baseline in BCVA as responders, regardless whether the improvement was maintained at subsequent visits or not. Thus patients in Category 2, 3, and 4 were all included as responders and the first occurrence of reaching ≥15 letter improvement was used to estimate response time. The number of responders was over counted for an analysis of durable response because patients in Category 2 only experienced transient improvement and should be evaluated more carefully.

Alternatively, the FDA's analysis as reported in Table 7 counts patients who had ≥15 letter improvements from baseline in BCVA without relapse as responders (Category 3 and 4). Patients who improved on Day 180 are also included as responders although they had no additional follow up. The results are depicted in Figures 2 and 3 for Study 206207-008 and 206207-009, respectively. The cumulative response rate curves are similar among 3 arms in both studies. There is no significantly statistical difference in the DEX 700 group compared to the Sham group in Study 206207-008 (P-value = 0.829) and Study 206207-009 (P-value = 0.085). There is no difference between DEX 350 and Sham in Study 206207-008 (P-value = 0.601) and Study 206207-009 (P-value = 0.160) either. When improvement without relapse is considered as a treatment response, DEX treatment is not statistically different from Sham.

Note that neither Study 206207-008 nor Study 206207-009 was adequately designed to measure the newly adapted endpoint of time to respond. There were only 4 post baseline visits to collect BCVA data for efficacy purpose and there was a large window during which a patient could be seen for a particular visit: study day 19 to 45 for Day 30 visit, study day 46 to 75 for Day 60 visit, study day 76 to 135 for Day 90 visit, and study 136 to 210 for Day 180 visit. Therefore, the calculation of time to respond can be very inaccurate. For instance, if a patient had a response from day 2 to 30 and was seen on day 38 (for Day 30 visit), s/he would be classified as no improvement compared to the fact that s/he had an early short tem response. Similarly, if a patient achieved ≥15 letter improvements on day 28, had no relapse, and was seen on day 26 (for Day 30 visit) and day 72 (for Day 60 visit), the calculated time to respond would be 72 days compared to the actual 28 days.

Table 7 Classification of Patients by ≥15 Letters Improvement (ITT Population)

Feature	206207-008			206207-009		
	DEX 700 N=201	DEX 350 N=196	Sham N=202	DEX 700 N=226	DEX 350 N=218	Sham N=224
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Category*						
Patients who never improved (1)	122 (60.7)	126 (64.3)[a]	151(74.8)	125 (55.3)	122 (56.0)[b]	174 (77.7)
Patients who improved but relapsed (2)	40 (20.0)	38 (19.4)	14 (7.0)	48 (21.2)	48 (22.0)	12 (5.4)
Patients with improvement and no Relapse (3,4)	39 (19.4)	32 (16.4)	37 (18.3)	53 (23.5)	48 (22.0)	38 (17.0)
Improved on Day 30 No Relapse	17 (8.5)	10 (5.1)	5 (2.5)	22 (9.7)	22 (10.1)	12 (5.4)
Improved on Day 60 No Relapse	4 (2.0)	6 (3.1)	5 (2.5)	3 (1.3)	8 (3.7)	6 (2.7)
Improved on Day 90 No Relapse	4 (2.0)	2 (1.0)	8 (4.0)	6 (2.7)	3 (1.4)	8 (3.6)
Improved on Day 180 (no follow up)	14 (7.0)	14 (7.1)	19 (9.4)	22 (9.7)	15 (6.9)	12 (5.4)
For Analysis of Time to Respond						
Sponsor's Analysis						
Responders	79 (39.3)	72 (36.7)[a]	51 (25.3)	101 (44.7)	97 (44.5)[b]	50 (22.3)
Non Responders	122 (60.7)	124 (63.3)	151 (74.7)	125 (55.3)	121 (55.5)	174 (77.7)
FDA's Analysis						
Responders	39 (19.4)	32 (16.3)	37 (18.3)	53 (23.5)	48 (22.0)	38 (17.0)
Non Responders	162 (80.6)	164 (83.7)[a]	165 (81.7)	173 (76.5)	170 (78.0)[b]	186 (83.0)

** Number in parenthesis indicates category defined in Section 3.1.5.3. Visit refers to Initial Treatment Phase 1 Day 30 (19-45), Day 60 (46-75), Day 90 (76-135), and Day180 (136-210). Missing data were imputed via LOCF.*

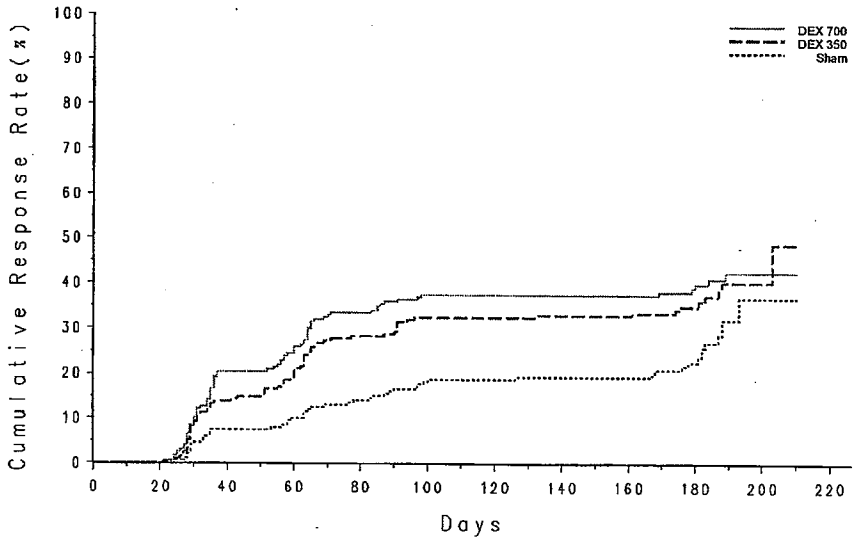
[a] Two subjects (5100-0158 and 7871-1892) are included in "Patients who never improved" according to their scheduled visits. They are included as "Responders" by the sponsor according to their unscheduled visit in survival analysis. The FDA analysis included them as "Non Responders" because of relapse.

[b] One patient (4618-3644) is included in "Patients who never improved" according to its scheduled visits. It is included as "Responders" by the sponsor according to its unscheduled visit in survival analysis. The FDA analysis included it as "Non Responders" because of relapse.

Figure 2 Time to Achieve ≥15 Letters Improvement in Study 206207-008 (ITT Population)

Sponsor's analysis

Log-Rank Test P-value
DEX 700 vs. Sham: 0.001
DEX 350 vs. Sham: 0.009



FDA analysis

Log-Rank Test P-value
DEX 700 vs. Sham: 0.829
DEX 350 vs. Sham: 0.601

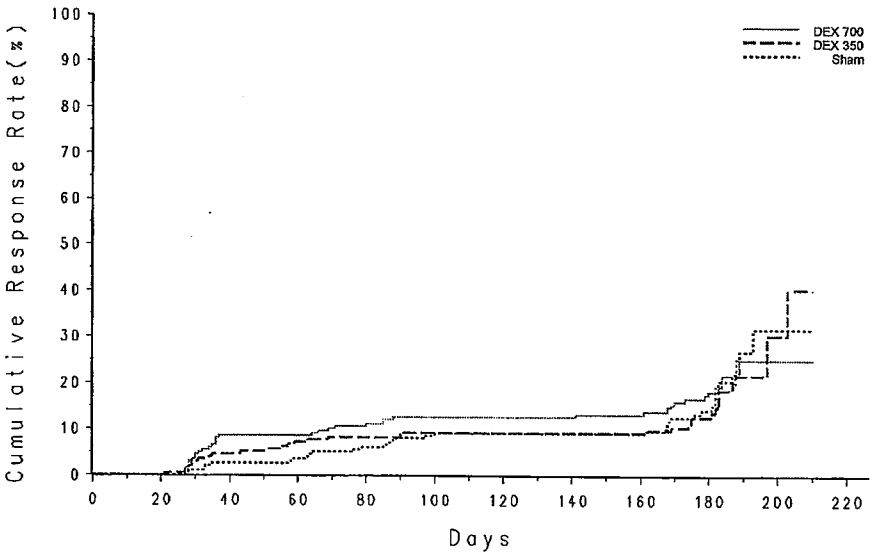
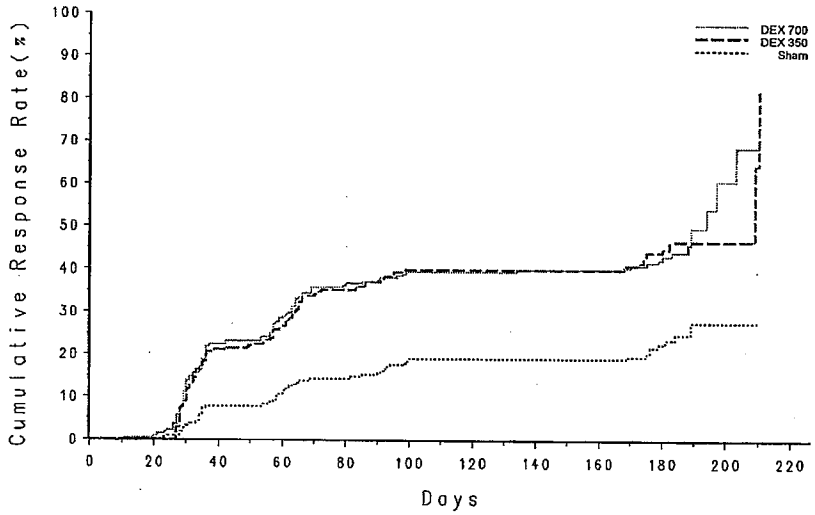


Figure 3 Time to Achieve ≥15 Letters Improvement in Study 206207-009 (ITT Population)

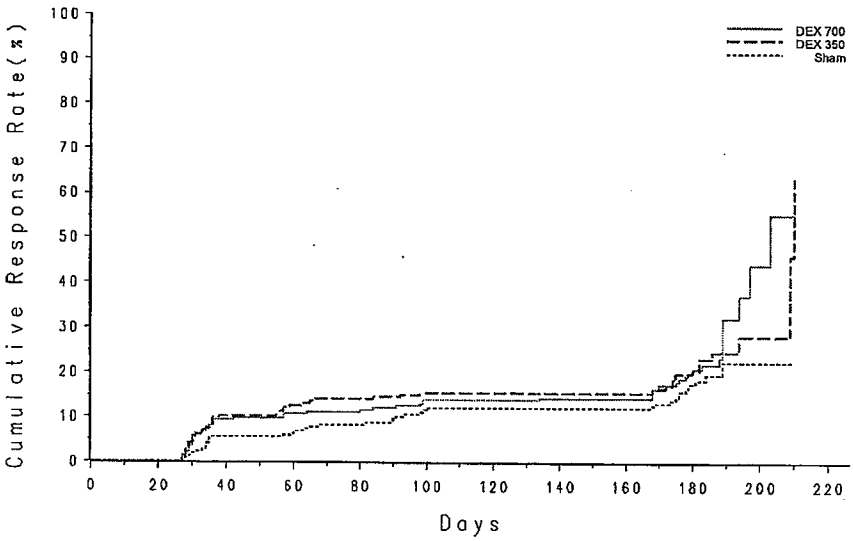
Sponsor's analysis

Log-Rank Test P-value
DEX 700 vs. Sham: < 0.001
DEX 350 vs. Sham: <0.001



FDA analysis

Log-Rank Test P-value
DEX 700 vs. Sham: 0.085
DEX 350 vs. Sham: 0.160



3.1.5.4 Further Evaluation of Early Improvement

Further analysis is conducted to evaluate onset and duration of a treatment response. A treatment response is defined as 15 letters or more improvement from baseline in BCVA in the study eye. Patients who never had at least 15 letters improvement are excluded from this analysis. Time to a response is calculated based on the earliest time a patient achieving a ≥15 letters improvement from baseline in BCVA (time to first response). For patients whose BCVA scores remained ≥15 letters above baseline following first response, their duration of a response is the first response time to last visit. For patients who relapsed (BCVA score fell below the ≥15 letters improvement mark) after first response, their duration of a response is the first response time to the middle point between first relapse and previous visit. For example, if a patient had a ≥15 letters improvement on day 34 (for Day 30 visit) and day 50 (for Day 60 visit), but his BCVA score was not ≥15 letters from baseline on day 82 (for Day 90 visit), the time to a response is 34 days. Assuming relapse occurred middle way between day 50 and 82, i.e., day 66, the duration of a response is from day 34 to 66 which is 32 days.
Table 8 summarizes time to the first treatment response and duration of this first response. The median time to a treatment response is 37 to 42 days with DEX 700 compared to 61 to 69 days with Sham. The median duration is 43 to 47 days with DEX 700 compared to 49 to 72 days with Sham. The median time to a treatment response is 54 to 58 days with DEX 350 and the effect may last for a median time of 49 to 50 days.

As discussed in Section 3.1.5.3, neither of the two studies was designed to accurately measure onset or duration of a treatment response. Because BCVA data were only collected 4 times after treatment on Days 30, 60, 90, 180, and there was a large window during which a patient could be seen for a particular visit, the calculation of time to a response and length of a response is very inaccurate. For example, if a patient had a response from day 17 to day 22 and was seen on day 20 (for Day 30 visit) and day 75 (for Day 60 visit), the calculated time to a response is 20 days compared to the actual 17 days whereas the calculated duration is 27.5 days compared to the actual 5 days. Likewise, if a patient had a response from day 2 to day 67 and was seen on day 34 (for Day 30 visit), day 50 (for Day 60 visit), and day 82 (for Day 90 visit), the calculated time to a response is 34 days compared to the actual 2 days whereas the calculated duration is 32 days compared to the actual 65 days. Due to the inadequacy of study design to evaluate timing and duration, interpretation of the results is very limited.

Table 8 Time to Achieve ≥ 15 Letters Improvement and Response Duration (ITT Population)

	206207-008			206207-009		
	DEX 700 N=201	**DEX 350 N=196**	**Sham N=202**	**DEX 700 N=226**	**DEX 350 N=218**	**Sham N=224**
Patients without a response (%)	122 (60.7)	124 (63.3)	151 (74.7)	125 (55.3)	121 (55.5)	174 (77.7)
Patients with a response (%)	79 (39.3)	72 (36.7)	51 (25.3)	101 (44.7)	97 (44.5)	50 (22.3)
Time in Days to 1st response						
median	37	58	69	42	54	61
(25th, 75th Percentile)	(30, 65)	(31, 74)	(35, 167)	(30, 66)	(30, 70)	(35, 94)
P-value*	0.002	0.027	-	0.030	ns	-
Duration in Days of 1st response						
Median	47	49	41	43	50	72
(25th, 75th Percentile)	(17, 109)	(17, 104)	(0, 99)	(15, 112)	(14, 123)	(14, 136)
P-value*	ns	ns	-	ns	ns	-

** P-values were calculated using the Wilcoxon 2-sample test (ns: P-value>0.05).*

3.1.5.5 Missing Data Impact

Table 9 shows the number of patients whose BCVA values were missing and imputed by the sponsor using the last observation carried forward (LOCF) method. This accounts for approximately 3% to 6% of all patients and appears to be randomly distributed across treatment groups.

Table 9 Number of Patients with BCVA Missing and Imputed by LOCF

	206207-008			206207-009		
	DEX 700 N=201	DEX 350 N=196	Sham N=202	DEX 700 N=226	DEX 350 N=218	Sham N=224
Visit*	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Day 30	9 (4.5)	3 (1.5)	5 (2.5)	3 (1.3)	4 (1.8)	6 (2.7)
Day 60	12 (6.0)	14 (7.1)	6 (3.0)	6 (2.7)	8 (3.7)	19 (8.5)
Day 90	7 (3.5)	5 (2.6)	7 (3.5)	6 (2.7)	7 (3.2)	15 (6.7)
Day 180	12 (6.0)	10 (5.1)	17 (8.4)	13 (5.8)	12 (5.5)	15 (6.7)
Overall	40 (5.0)	32 (4.1)	35 (4.3)	28 (3.1)	31 (3.6)	55 (6.1)

**Visit refers to Initial Treatment Phase 1 Day 30 (19-45), Day 60 (46-75), Day 90 (76-135), and Day180 (136-210)*

Various sensitivity analyses are performed to evaluate the impact of missing data, including missing counted as no improvement, missing counted as improvement, and missing data excluded. The number and proportion of patients with ≥ 15 letters improvement from baseline in BCVA at Day 180 are summarized in Table 10 for the ITT population and Table 11 for patients who completed Study Day 180. The results from sensitivity analyses are similar to the one when missing data were imputed by LOCF method. There is no statistical difference in the number of patients achieving at least 15 letter improvements in BCVA between DEX 700 and Sham as well as between DEX 350 and Sham at Day 180 for both studies.

Table 10 Sensitivity Analyses of Proportion of patients with ≥ 15 letters Improvement at Day 180 (ITT population)

	206207-008			206207-009		
	DEX 700 N=201	**DEX 350 N=196**	**Sham N=202**	**DEX 700 N=226**	**DEX 350 N=218**	**Sham N=224**
Missing data imputed via LOCF						
Number of Patients w/ ≥15 Letter Improvement	39 (19.4%)	32 (16.3%)	37 (18.3%)	53 (23.5%)	48 (22.0%)	38 (17.0%)
Difference in Proportion (DP)	1.1%	-2.0%	-	6.5%	5.1%	-
95% C.I. of DP	(-6.6%, 8.7%)	(-9.4%, 5.4%)	-	(-0.9%, 13.9%)	(-2.3%, 12.4%)	-
P-value	0.780	0.600	-	0.087	0.180	-
Missing data counted as having no improvement						
Number of Patients w/ ≥15 Letter Improvement	37 (18.4%)	31 (15.8%)	36 (17.8%)	51 (22.6%)	46 (21.1%)	38 (17.0%)
Difference in Proportion (DP)	0.6%	-2.0%	-	5.6%	4.1%	-
95% C.I. of DP	(-6.9%, 8.1%)	(-9.4%, 5.3%)	-	(-1.7%, 12.9%)	(-3.2%, 11.5%)	-
P-value	0.879	0.593	-	0.136	0.268	-
Missing data counted as having improvement						
Number of Patients w/ ≥15 Letter Improvement	49 (24.4%)	41 (20.9%)	53 (26.2%)	64 (28.3%)	58 (26.6%)	53 (23.7%)
Difference in Proportion (DP)	-1.9%	-5.3%	-	4.7%	2.9%	-
95% C.I. of DP	(-10.4%, 6.6%)	(-13.6%, 3.0%)	-	(-3.4%, 12.8%)	(-5.1%, 11.0%)	-
P-value	0.668	0.212	-	0.260	0.475	-
Missing data excluded						
Number of Patients w/ ≥15 Letter Improvement	37 (19.6%)	31 (16.7%)	36 (19.5%)	51 (23.9%)	46 (22.3%)	38 (18.2%)
Difference in Proportion (DP)	0.1%	-2.8%	-	5.8%	4.2%	-
95% C.I. of DP	(-7.9%, 8.2%)	(-10.6%, 5.0%)	-	(-2.0%, 13.5%)	(-3.6%, 11.9%)	-
P-value	0.977	0.484	-	0.147	0.293	-

Table 11 Sensitivity Analyses of Proportion of patients with ≥ 15 letters Improvement at Day 180 (Patients who completed Day 180)

	206207-008			206207-009		
	DEX 700 N=189	**DEX 350 N=189**	**Sham N=189**	**DEX 700 N=214**	**DEX 350 N=206**	**Sham N=209**
Missing data imputed via LOCF						
Number of Patients w/ ≥15 Letter Improvement	37 (19.6%)	32 (16.9%)	36 (19.0%)	52 (24.3%)	46 (22.3%)	38 (18.2%)
Difference in Proportion (DP)	0.5%	-2.1%	-	6.1%	4.2%	-
95% C.I. of DP	(-7.4%, 8.5%)	(-9.8%, 5.6%)	-	(-1.7%, 13.9%)	(-3.6%, 11.9%)	-
P-value	0.896	0.592	-	0.124	0.293	-
Missing data counted as having no improvement						
Number of Patients w/ ≥15 Letter Improvement	37 (19.6%)	31 (16.4%)	36 (19.0%)	51 (23.8%)	45 (21.8%)	38 (18.2%)
Difference in Proportion (DP)	0.5%	-2.7%	-	5.7%	3.7%	-
95% C.I. of DP	(-7.4%, 8.5%)	(-10.3%, 5.1%)	-	(-2.1%, 13.4%)	(-4.0%, 11.4%)	-
P-value	0.896	0.501	-	0.154	0.351	-
Missing data counted as having improvement						
Number of Patients w/ ≥15 Letter Improvement	39 (20.6%)	35 (18.5%)	44 (23.3%)	53 (24.8%)	48 (23.3%)	40 (19.1%)
Difference in Proportion (DP)	-2.7%	-4.8%	-	5.6%	4.2%	-
95% C.I. of DP	(-11.0%, 5.7%)	(-13.0%, 3.4%)	-	(-2.2%, 13.5%)	(-3.7%, 12.0%)	-
P-value	0.534	0.255	-	0.162	0.300	-
Missing data excluded						
Number of Patients w/ ≥15 Letter Improvement	37 (19.8%)	31 (16.8%)	36 (19.9%)	51 (24.1%)	45 (22.2%)	38 (18.4)
Difference in Proportion (DP)	-0.1%	-3.1%	-	5.7%	3.8%	-
95% C.I. of DP	(-8.3%, 8.1%)	(-11.1%, 4.8%)	-	(-2.1%, 13.5%)	(-4.0%, 11.6%)	-
P-value	0.980	0.438	-	0.154	0.337	-

3.2 Evaluation of Safety

In Study 206207-008, the incidence of adverse events overall was significantly higher in the DEX 700 group (71.4%) and DEX 350 group (71.6%) compared to Sham (51.0%). There was no significant difference between the 700 and 350 doses of DEX. Ocular adverse events were likewise more commonly reported with DEX 700 (59.7%) and DEX 350 (63.5%) than with Sham (40.1%). The rate of non-ocular events was similar among the 3 treatment groups. The same patterns were observed for treatment-related events. The most frequently reported adverse event was intraocular pressure increased, which was significantly higher in the study eye with DEX 700 (23.5%) and DEX 350 (23.4%) compared to Sham (3.0%). There were no significant differences among the 3 treatment groups in the other common adverse events conjunctival haemorrhage, conjunctival hyperaemia, and eye pain. The adverse event profile for BRVO patients was similar to that observed for CRVO patients, and to the overall population.

In Study 206207-009, the incidence of adverse events overall was significantly higher in the DEX 700 group (73.3%) and DEX 350 group (72.1%) compared to Sham (62.9%). There was no significant difference between the 700 and 350 doses of DEX. Ocular adverse events were likewise more commonly reported with DEX 700 (68.0%) and DEX 350 (65.6%) than with Sham (51.1%). The rate of non-ocular events was similar among the 3 treatment groups. The same patterns were observed for treatment-related events. The most frequently reported adverse event was intraocular pressure increased, which was significantly higher in the study eye with DEX 700 (26.7%) and DEX 350 (26.0%) compared to Sham (2.3%). There were no significant differences among the 3 treatment groups in the other common adverse events conjunctival haemorrhage, conjunctival hyperaemia, and eye pain.

Reviewer's comments: The above is just a summary of the safety results presented by the applicant in the study reports. For details, please see the medical officer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Studies 206207-008 and 206207-009 were conducted in over 80 centers in a wide geographic region including North America, Latin America, Europe, Asia Pacific, and Israel/South Africa. The number and percentage of patients who achieved at least 15 letters of improvement from baseline in BCVA are summarized according to gender (Table 12), race (Table 13), and age categories (Table 14). In general, the conclusions for the proportion of patients with ≥15 letters improvement by gender, race, and age were the same as the study population as a whole; there is no statistically significant difference between DEX 700 and Sham and between DEX 350 and Sham at the primary time point Day 180.

Table 12 Patients with ≥15 Letters Improvement from Baseline in BCVA by Gender (ITT Population)

Gender	Visit*	206207-008			206207-009		
		DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Male		N=106	N=104	N=117	N=111	N=116	N=123
	Day 30	25 (23.6%)	21 (20.2%)	11 (9.4%)	29 (26.1%)	24 (20.7%)	9 (7.3%)
	Day 60	34 (32.1%)	27 (26.0%)	15 (12.8%)	34 (30.6%)	35 (30.2%)	16 (13.0%)
	Day 90	31 (29.2%)	25 (24.0%)	17 (14.5%)	27 (24.3%)	30 (25.9%)	15 (12.2%)
	Day 180	22 (20.8%)	20 (19.2%)	24 (20.5%)	30 (27.0%)	25 (21.6%)	21 (17.1%)
Female		N=95	N=92	N=85	N=115	N=102	N=101
	Day 30	15 (15.8%)	8 (8.7%)	4 (4.7%)	22 (19.1%)	21 (20.6%)	8 (7.9%)
	Day 60	24 (25.3%)	23 (25.0%)	6 (7.1%)	33 (28.7%)	33 (32.4%)	11 (10.9%)
	Day 90	14 (14.7%)	16 (17.4%)	8 (9.4%)	21 (18.3%)	26 (25.5%)	16 (15.8%)
	Day 180	17 (17.9%)	12 (13.0%)	13 (15.3%)	23 (20.0%)	23 (22.5%)	17 (16.8%)

** Visit refers to Initial Treatment Phase 1 Day 30 (19-45), Day 60 (46-75), Day 90 (76-135), and Day 180 (136-210). Missing data were imputed via LOCF.*

Table 13 Patients with ≥15 Letters Improvement from Baseline in BCVA by Race (ITT Population)

Race	Visit*	206207-008			206207-009		
		DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Caucasian		N=169	N=166	N=167	N=152	N=146	N=151
	Day 30	32 (18.9%)	26 (15.7%)	12 (7.2%)	41 (27.0%)	34 (23.3%)	10 (6.6%)
	Day 60	50 (29.6%)	43 (25.9%)	17 (10.2%)	50 (32.9%)	44 (30.1%)	18 (11.9%)
	Day 90	38 (22.5%)	35 (21.1%)	18 (10.8%)	32 (21.1%)	34 (23.3%)	19 (12.6%)
	Day 180	32 (18.9%)	27 (16.3%)	31 (18.6%)	37 (24.3%)	27 (18.5%)	25 (16.6%)
Non-Caucasian		N=32	N=30	N=35	N=74	N=72	N=73
	Day 30	8 (25.0%	3 (10.0%)	3 (8.6%)	10 (13.5%)	11 (15.3%)	7 (9.6%)
	Day 60	8 (25.0%)	7 (23.3%)	4 (11.4%)	17 (23.0%)	24 (33.3%)	9 (12.3%)
	Day 90	7 (21.9%)	6 (20.0%)	7 (20.0%)	16 (21.6%)	22 (30.6%)	12 (16.4%)
	Day 180	7 (21.9%)	5 (16.7%)	6 (17.1%)	16 (21.6%)	21 (29.2%)	13 (17.8%)

** Visit refers to Initial Treatment Phase 1 Day 30 (19-45), Day 60 (46-75), Day 90 (76-135), and Day 180 (136-210). Missing data were imputed via LOCF.*

Table 14 Patients with ≥15 Letters of Improvement from Baseline in BCVA by Age (ITT Population)

Age	Visit*	Study 206207-008			Study 206207-009		
		DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
<65 years		N=88	N=82	N=93	N=121	N=113	N=120
	Day 30	25 (28.4%)	15 (18.3%)	9 (9.7%)	34 (28.1%)	27 (23.9%)	13 (10.8%)
	Day 60	33 (37.5%)	20 (24.4%)	8 (8.6%)	43 (35.5%)	43 (38.1%)	18 (15.0%)
	Day 90	27 (30.7%)	20 (24.4%)	16 (17.2%)	37 (30.6%)	37 (32.7%)	20 (16.7%)
	Day 180	23 (26.1%)	17 (20.7%)	27 (29.0%)	36 (29.8%)	33 (29.2%)	27 (22.5%)
65-75 years		N=63	N=68	N=76	N=52	N=63	N=55
	Day 30	7 (11.1%)	10 (14.7%)	4 (5.3%)	7 (13.5%)	5 (7.9%)	3 (5.5%)
	Day 60	17(27.0%)	21 (30.9%)	11 (14.5%)	10 (19.2%)	13 (20.6%)	6 (10.9%)
	Day 90	11 (17.5%)	13 (19.1%)	8 (10.5%)	5 (9.6%)	13 (20.6%)	9 (16.4%)
	Day 180	10 (15.9%)	12 (17.6%)	8 (10.5%)	7 (13.5%)	9 (14.3%)	8 (14.5%)
>75 years		N=50	N=46	N=33	N=53	N=42	N=49
	Day 30	8 (16.0%)	4 (8.7%)	2 (6.1%)	10 (18.9%)	13 (31.0%)	1 (2.0%)
	Day 60	8 (16.0%)	9 (19.6%)	2 (6.1%)	14 (26.4%)	12 (28.6%)	3 (6.1%)
	Day 90	7 (14.0%)	8 (17.4%)	1 (3.0%)	6 (11.3%)	6 (14.3%)	2 (4.1%)
	Day 180	6 (12.0%)	3 (6.5%)	2 (6.1%)	10 (18.9%)	6 (14.3%)	3 (6.1%)

** Visit refers to Initial Treatment Phase 1 Day 30 (19-45), Day 60 (46-75), Day 90 (76-135), and Day 180 (136-210). Missing data were imputed via LOCF.*

4.2 Other Special/Subgroup Population

Analysis of other special/subgroup population is not applicable according to the medical officer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Data from Studies 206207-008 and 206207-009 to support the use of DEX 700 for the treatment of macular edema failed to demonstrate the its superiority compared to Sham in the protocol planned primary endpoint which was proportion of patients with at least 15 letters improvement in BCVA at initial treatment Day 180.

Although the proportion of patients with ≥15 letters improvement in BCVA from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at Days 30, 60, 90, there is no statistical difference between DEX 700 and Sham or between DEX 350 and Sham at the primary time point Day 180 (P-values > 0.087). Early favorable outcome did not last till 6 months post procedure. The results seem to be robust with various sensitivity analyses as well as analyses by gender, race, and age group. The existence of only short term efficacy reflects issues addressed in the internal FDA Draft Guidance for Industry (3/1/2008) on macular edema.

> For macular edema secondary to inflammation, "Efficacy data for the primary endpoint can be accepted at 12 months or more. The 12-month minimum has been suggested because past trials have demonstrated that earlier findings in macular edema are not predictive of later findings (i.e., a drug product has shown different results at 3 or 6 months versus 12 months and longer)."
>
> For macular edema secondary to surgery or vascular event, "Efficacy data for the primary endpoint can be accepted at six months or more. The six month minimum has been suggested because past trials have demonstrated that earlier findings in macular edema are not predictive of later findings (i.e., a drug product has shown different results at three or four months versus six months and longer)."

Although the current indication is not identical to those referenced above, at least Day 180 (6 months) was considered important when both Studies 206207-008 and 206207-009 were planned.

In Study 206207-008, at 5.5 months after trial completion and 1 day before database lock, the primary efficacy endpoint was changed from the proportion of patients with ≥ 15 letters improvement from baseline in BCVA to the time to respond (achieve ≥ 15 letters improvement from baseline in BCVA). Note that although not for the exactly same indication, the internal FDA Draft Guidance for Industry (3/1/2008) on macular edema secondary to inflammation, surgery, or vascular event recommends the following endpoints which include percentage of patients with a doubling of the visual angle, percentage of patients with a halving of the visual angle, percentage of patients with a quadrupling of the visual angle, and mean visual acuity of 15 or more letters; but do not include time to respond.

Even with time to respond as a primary efficacy endpoint, the results vary depending on definition of responders. The sponsor's analysis of time to respond showed that the cumulative response rates were significantly higher with DEX 700 and DEX 350 than with Sham. However, this analysis may be misleading since it did not account for the fact that relapse occurred in almost half of those patients who showed improvement after DEX 700 or DEX 350 implantation. Thus responders included patients with short term improvement followed by relapse. When only patients with sustained improvement (including those who improved by Day 180 with no more follow up) are considered as responders, the cumulative response rate curves are similar among 3 arms in both studies. In terms of time to respond without relapse, there is no significantly statistical difference in the DEX 700 group compared to the Sham group in Study 206207-008 (P-value = 0.829) and Study 206207-009 (P-value = 0.085). Likewise, there is no significant statistical difference in the DEX 350 group compared to the Sham group in Study 206207-008 (P-value = 0.601) and Study 206207-009 (P-value = 0.160).

For patients who ever responded (achieved at least 15 letters improvement from baseline in BCVA), the median time to a response was 37 days with DEX 700 compared to 69 days with Sham in Study 206207-008 (P-value = 0.002) and 42 days with DEX 700

compared to 61 days with Sham in Study 206207-009 (P-value = 0.030). The median duration of the improvement is 43 to 47 days with DEX 700 compared to 41 to 72 days with Sham (P-values $\geq$ 0.075). The median time to a treatment response is 54 to 58 days with DEX 350 and the effect may last for a median time of 49 to 50 days.

Note that neither of the two studies was adequately designed to accurately measure timing and duration of a treatment response. BCVA data were only collected 4 times post procedure for efficacy purpose and there was a large window during which patients could be seen for a particular visit: study day 19 to 45 for Day 30 visit, study day 46 to 75 for Day 60 visit, study day 76 to 135 for Day 90 visit, and study 136 to 210 for Day 180 visit. Because of the design limitation, the time to respond (achieve at least 15 letters improvement) as well as the duration of a response cannot be accurately calculated. Therefore, interpretation of the above results is very limited.

From a strict statistical perspective, at most only one study met its primary efficacy endpoint: one if the late change in primary efficacy endpoint is accepted, neither if the change is unacceptable. Again this late change adapted a new endpoint that cannot be adequately measured given the study design. However, the two studies are similar in their results that an early but not sustained effect is associated with DEX 700 treatment.

In conclusion, the results failed to demonstrate statistically significant efficacy of DEX 700 compared to Sham as measured by the original protocol planned endpoint of proportion of patients with $\geq$15 letters improvement from baseline in BCVA at Day 180. Additionally, a significant effect was not seen in time to achieve a durable treatment response of 15 or more letters improvement from baseline in BCVA. An early yet not sustained effect was observed with both studies.

5.2 Conclusions and Recommendations

This submission includes two 6-month, masked, Phase 3, randomized, sham-controlled trials and addresses the efficacy as well as safety of DEX PS DDS 700µg applicator (DEX 700) for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The primary objective was to show that DEX 700 was efficacious compared to Sham as measured by the improvement of best corrected visual acuity (BCVA). The original protocol planned primary efficacy endpoint was the proportion of patients with at least 15 letters improvement from baseline in BCVA at Day 180 post DEX 700 injection. Data from both studies failed to demonstrate statistically significant efficacy of DEX 700 compared to Sham as assessed by the original primary endpoint at Day 180. A new parameter, the time to respond (achieve at least 15 letters improvement from baseline in BCVA), was later adapted as the primary efficacy endpoint in one study and seemed to show superiority of DEX 700 over Sham in cumulative response rates. However, there was no scientific rationale provided for this post hoc change, which could introduce serious issues with interpreting the results and potential biases. Additionally, this new endpoint could not be accurately determined given the study design because neither trial was adequately designed to measure onset or duration of a treatment response.

This review finds out that DEX 700 treatment provides no sustained benefits. Although some patients had earlier achieved at least 15 letters improvement from baseline in BCVA, their improvement could not be retained at subsequent visits, i.e., relapse occurred. The sponsor's analysis of time to respond can be misleading because it did not account for the fact that relapse happened in almost half of those patients who showed improvements after DEX 700 injection. When time to achieve a sustained improvement is considered, there is no statistical difference between DEX 700 and Sham in either study. Note again that the onset or duration of a response could not be adequately determined given the study design.

The lack of sustained treatment response is supported by consistent data from the two trials. The proportion of patients with at least 15 letters improvement from baseline in BCVA was significantly higher with DEX 700 compared to Sham at Days 30, 60, and 90 but the difference disappeared by the primary time point Day 180. Although not for the exact indication of macular edema following BRVO or CRVO, the internal FDA Draft Guidance for Industry (3/1/2008) recommends minimum 6 or 12 months of efficacy data for the primary endpoint because earlier findings in macular edema are not predictive of later findings.

Therefore, this submission did not provide statistically persuasive evidence of DEX 700 on a sustained response, though an early but short term improvement was observed. Given the study design, it is difficult to measure both the onset and duration of the treatment effect. This is important information for the patients and physicians. If the medical division accepts the change from a 6 month endpoint to a short term response, this reviewer recommends DEX 700 be investigated further in an additional study to more accurately measure the onset and duration of a response.

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