CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 218158
Supplement #:	Original
Drug Name:	(b) (4) (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%)
Indication(s):	For the treatment of post-operative inflammation and pain following ocular surgery
Applicant:	Formosa Pharmaceuticals, Inc.
Date(s):	Submitted: May 4, 2023 PDUFA Goal date: March 4, 2024
Review Priority:	Standard
Biometrics Division:	DBIV
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Keywords: post-operative inflammation and pain following ocular surgery

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1 EXECUTIVE SUMMARY

This original NDA seeks the approval of [redacted] (b) (4) (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%) for the treatment of post-operative inflammation and pain following ocular surgery.

Clobetasol propionate is a corticosteroid used to treat skin conditions such as eczema, contact dermatitis, seborrheic dermatitis, and psoriasis. It was first approved by the Agency in 1994 and since then has been approved in different topical format for applying to the skin as a cream, ointment, or shampoo. According to the Applicant, clobetasol propionate has not previously been developed for ophthalmic application presumably due to its poor aqueous solubility. The Applicant assumed that their proprietary nanomilling technology enables an aqueous formulation containing clobetasol propionate particles of mean particle size distribution in the [redacted] (b) (4) nm range which are expected to efficiently penetrate into the target tissues of the eye upon ocular surface instillation.

The applicant conducted two similarly designed Phase 3 studies (Study CPN-301, referred to as Study 301; and Study CPN-302, referred to as Study 302) to evaluate efficacy and safety of [redacted] (b) (4) (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%, also known as APP13007 throughout this review). Both studies were multicenter, randomized, double-masked, placebo-controlled, parallel-group studies, evaluating the efficacy and safety of APP13007 (0.05%) 1 drop instilled twice daily (BID) in the study eye for 14 days in approximately 370 subjects per study following routine uncomplicated unilateral cataract surgery. The co-primary efficacy endpoints for both studies were:

- The proportion of subjects with Anterior Chamber Cell (ACC) Count = 0 [ACC Grade = 0] at post-operative day 8 (POD8), maintained through POD15
- The proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15

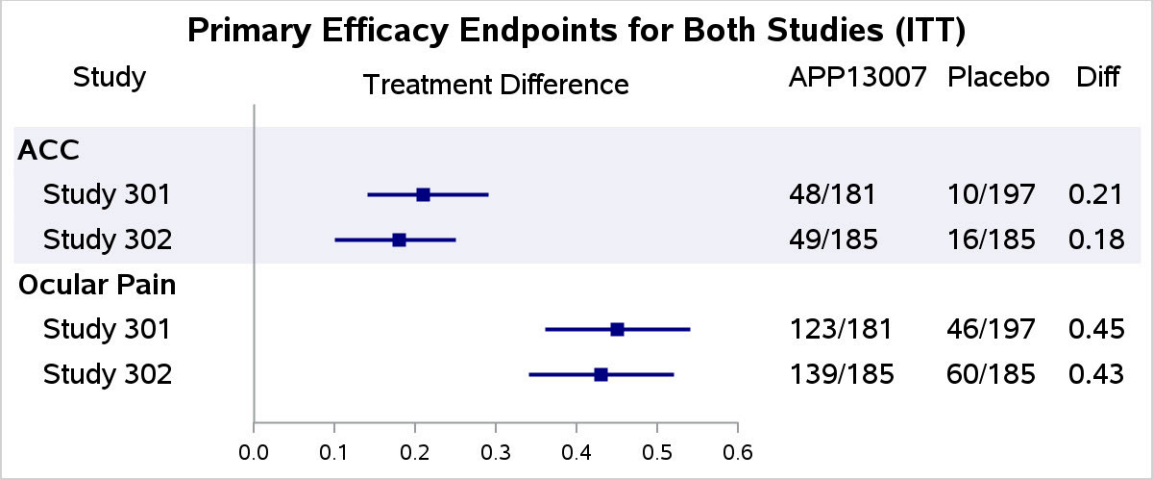
Both studies demonstrated superiority of APP13007 to the vehicle for both primary endpoints (Table 1 and Figure 1). Therefore, the statistical reviewer recommends the approval of clobetasol propionate ophthalmic nanosuspension, 0.05% for the treatment of post-operative inflammation and pain following ocular surgery.

Table 1: Summary of the Primary Efficacy Results (ITT)

		Study 301			Study 302		
		APP13007 (N=181)	**Placebo (N=197)**	**Difference (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Difference (95% CI)**
ACC	**Responders (%)**	48 (26.5%)	10 (5.1%)	21.4% (14.3%, 28.6%)	49 (26.5%)	16 (8.6%)	17.8% (10.3%, 25.4%)
	p-value			<0.001			<0.001
Ocular Pain	**Responders (%)**	123 (68.0%)	46 (23.4%)	44.6% (35.6%, 53.6%)	139 (75.1%)	60 (32.4%)	42.7% (33.5%, 51.9%)
	p-value			<0.001			<0.001

Note: ITT = Intent-to-Treat, APP13007 = Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%, V = Vehicle, CI = Confidence Interval
* p-value was from the Pearson's Chi-Square test to compare treatment groups. The estimated 95% CI was based on normal approximation.
Source: Tables 13 and 14 of Study 301 Clinical Study Report (CSR), Tables 13 and 14 of Study 302 CSR, and the reviewer's calculation.

Figure 1: Summary of the Primary Efficacy Endpoints (ITT)



Note: ITT = Intent-to-Treat, APP13007 = Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%, V = Vehicle, CI = Confidence Interval
* The estimated 95% CI was based on normal approximation.
Source: Tables 13 and 14 of Study 301 Clinical Study Report (CSR), Tables 13 and 14 of Study 302 CSR, and the reviewer's calculation

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Post-cataract surgery regimen of anti-inflammatory agents is typically prescribed because it reverses inflammation, pain and discomfort and reduces the risk of further complications. Ocular administration of corticosteroids is often the therapy of choice for the treatment of inflammation and pain after ocular surgery. Multiple marketed products are currently available that utilize corticosteroids such as dexamethasone (Maxidex®), prednisolone (PredForte®), loteprednol etabonate (Lotemax®), and difluprednate (Durezol®).

APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%) contains the active ingredient clobetasol propionate. Clobetasol propionate, an analog of prednisolone, is a potent corticosteroid that has anti-inflammatory, antipruritic, and vasoconstrictive properties and is considered to be the most potent corticosteroid compared with other corticosteroids on the market and is classified as a Class 1 - Superpotent corticosteroid in the US. It was first approved by the Agency in 1985 and since then has been approved in different topical format for applying to the skin as a cream, ointment, or shampoo.

2.1.2 History of Drug Development

The pharmacological, pharmacokinetic and toxicological profiles of clobetasol propionate have been previously established for the approved dermatological products containing clobetasol propionate, including Temovate® and Temovate® E. Temovate® ointment 0.05% was originally approved by the Food and Drug Administration (FDA) in 1985 and remained on the market until the product was discontinued or withdrawn from the US market by the innovator GlaxoSmithKline for reasons other than safety or efficacy. In this 505(b)(2) New Drug Application (NDA) for APP13007, Temovate® ointment 0.05% (NDA Nos. 019322 and 019323) will serve as the Reference Listed Drug (RLD).

There were three formal meetings between the FDA and the Sponsor during the development of APP13007 (clobetasol propionate ophthalmic nanosuspension, 0.05%).

The first meeting was a pre-IND (PIND 128133) meeting held between the FDA and the prior Sponsor for APP13007, Activus Pharma Co. Ltd. in Japan (Activus) On January 21, 2016. The Agency in general agreed with the Activus proposed overall clinical development plan and the Phase 2 study included in the meeting backgrounder. The Agency recommended that in order to identify adverse events at a rate of 1% or greater, approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing.

On September 2nd, 2020, the Applicant and the Agency had an End-of-Phase 2 (EOP2) meeting to discuss the next steps in the development of APP13007. Based on the meeting minutes, the Agency agreed the Applicant's proposal of treating "Rescued subjects" as "Non-Responders" to the study drug. (b) (4) The Agency recommended that rescued subjects should be continued in the study for follow up, including adverse events may later emerge, and evaluations for these subjects should be included in the safety results. In addition, The Applicant proposed using last observation carried forward (LOCF) to impute missing data for the primary analyses for subjects who discontinue from the study, including rescued subjects. The Agency stated this approach is acceptable, but the Applicant should also conduct additional analyses, including analyses using just observed data on study.

The third and final IND meeting between the Applicant and the Agency was on October 31st, 2022, where the Agency agreed with most of the NDA submission related ISS and ISE proposal.

2.1.3 Studies Reviewed

The Applicant has completed ophthalmological clinical Phase 1, Phase 2 and two pivotal Phase 3 safety and efficacy studies of APP13007. Table 2 summarized the two pivotal Phase 3 studies (Study CPN-301 and Study CPN-302), which are the focus of this statistical review.

Table 2: Summary of Efficacy Studies to be assessed in the Statistical Review

Study No	Design	Objective	Treatment / Sample Size	Study Population	Primary Endpoint
CPN-301 & CPN-302	Multi-center, randomized, double-blinded, parallel group, vehicle-controlled	To evaluate the efficacy and safety of APP13007 (0.05%) 1 drop instilled twice daily (BID) in the study eye for 14 days versus matching vehicle for the treatment of inflammation and pain through post-operative day (POD) 15 after routine uncomplicated cataract surgery	CPN-301: APP13007 / 181 Placebo / 197 CPN-302: APP13007 / 185 Placebo / 185	Adult patients who underwent unilateral uncomplicated cataract extraction via phacoemulsification and posterior chamber intraocular lens implantation in one eye	Primary: • The proportion of subjects with Anterior Chamber Cell (ACC) Count = 0 [ACC Grade = 0] at postoperative day 8 (POD8), maintained through POD15 • The proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15

Source: Statistical Reviewer's Summary.

2.2 Data Sources

The data sources for this review include clinical study reports, protocols, statistical analysis plan (SAP), and datasets. All data sources were electronic submitted and located at \\cdsesub1\evsprod\NDA218158\0001.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the primary and secondary efficacy endpoints can be verified by the statistical reviewer with minor data manipulation. The statistical reviewer's analyses were primarily based on the analysis datasets.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of the two Phase 3 studies together. Sections 3.2.1 and 3.2.2 summarize the study design, endpoints, and statistical methods. Section 3.2.3 summarizes subject disposition as well as demographic and baseline characteristics. Section 3.2.4 discusses the primary analysis and supporting evidence.

3.2.1 Study Design and Endpoints

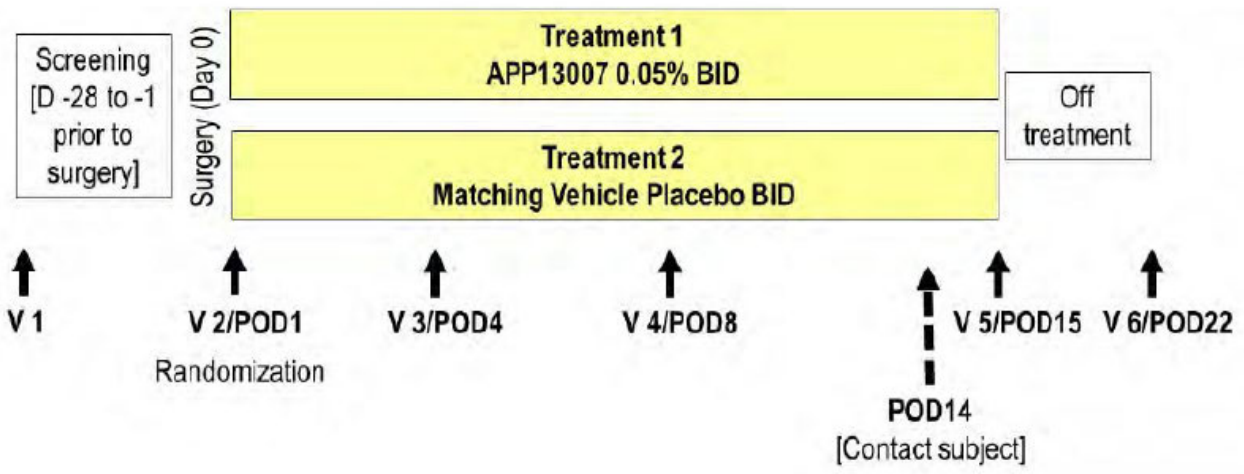
The efficacy of APP13007 was evaluated in two nearly identically designed Phase 3 pivotal clinical trials: CPN-301 (referred to as Study 301), and CPN-302 (referred to as Study 302); except that Study 302 had an additional sub-study for the evaluation of corneal endothelial cell safety parameters (for only those subjects from the Main Study meeting specific criteria for the Sub-study).

Both studies were multicenter, randomized, double-masked, placebo-controlled, parallel-group studies, evaluating the efficacy and safety of APP13007 (0.05%) 1 drop instilled twice daily (BID) in the study eye for 14 days versus matching vehicle for the treatment of inflammation and pain through post-operative day (POD) 15 after routine uncomplicated cataract surgery. Study 301 was conducted in 27 sites across US, and Study 302 was conducted in 29 sites across US.

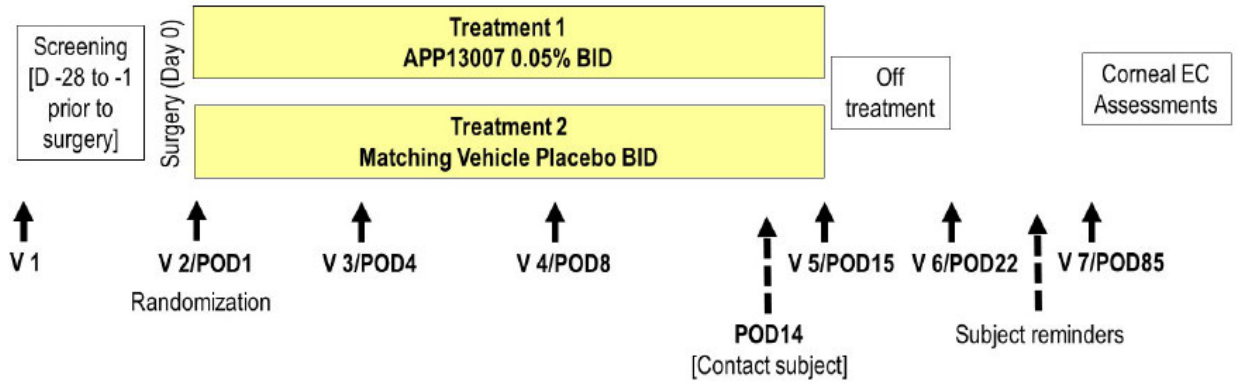
Eligible adult patients were randomized at 1:1 ratio at baseline to either APP13007 or matching vehicle. The treatment regimen was instilled to the operated study eye BID for 14 days. In both studies, subjects participated had 7 clinic visits: Visit 1 (Screening [Day -28 to Day -1 prior to cataract surgery on Day 0]); Day of Surgery (Day 0); Visit 2 (Baseline; Randomization; Post-operative Day 1 [POD1]); Visit 3 (POD4; ±1 day); Visit 4 (POD8; ±1 day); Visit 5 (POD15; +1 day); and Visit 6 (POD22; ±2 days). After randomization, the study drug was administered by the subjects into their operated study eye starting at Visit 2 (POD1) and ending on POD14. Ophthalmic assessments were performed in both eyes at Visit 1 (Screening), Visit 2 (POD1), Visit 3 (POD4), Visit 4 (POD8), Visit 5 (POD15) and Visit 6 (POD22) or Early Termination/Withdrawal. In Study 302 sub-study, subjects returned for the POD85 visit (Visit 7, ±4 days) for safety assessments, which included further measurement of corneal endothelial parameters in the study eye and recording of AEs and concomitant medications. Figure 2 presents the schematics of the two studies.

Figure 2: Study Schematics

Study 001 Schematic



Study 002 Schematic



Source: Figures 1 of Study 301 Clinical Study Report (CSR) and Figure 1 of Study 302 CSR.

The key inclusion criteria in the two studies were:

- Adult patients expected to undergo unilateral uncomplicated cataract extraction via phacoemulsification and posterior chamber intraocular lens implantation in one eye (designated the 'Study Eye').
- Had a pin-hole corrected visual acuity without other correction of ≤ 1.3 logarithm of the minimum angle of resolution (logMAR) in the study eye to be operated and contralateral eye as measured using an ETDRS chart at Visit 1 (Screening). Subjects who were unable to read the lines in an ETDRS chart because of the density of the cataract in the study eye could be enrolled if, in the opinion of the Investigator, there was no other significant ocular pathology that would account for the low visual acuity.
- At Visit 2 (Baseline):
    - No significant ocular pathology affecting visual acuity that was identified after posterior chamber intraocular lens implantation in the study eye.
    - Had ≥ 10 cells in the anterior chamber (excluding red blood and pigment cells).

- Had an IOP ≤ 30 mmHg.

The co-primary efficacy endpoints for both studies were:

- The proportion of subjects with Anterior Chamber Cell (ACC) Count = 0 [ACC Grade = 0] at post-operative day 8 (POD8), maintained through POD15
- The proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15

Where ACC count was assessed by the Investigator using a slit-lamp biomicroscope and then graded on a 5-point numeric rating scale from 0 (0 cell) to 4 (> 30 cells) as follows

Grade	0	1	2	3	4
ACC Count	0 cell	1-5 cells	6-15 cells	16-30 cells	> 30 cells

And ocular pain was graded by the subject on a 5-point scale as follows.

Grade	Description
0	None: No pain
1	Minimal: Presence of minimal throbbing or aching pain (expected following cataract surgery)
2	Mild: Presence of mild throbbing or aching pain, easily tolerated.
3	Moderate: Presence of moderate throbbing or aching pain leading to the desire to use an analgesic.
4	Severe: Presence of severe throbbing or aching pain that is not tolerable.

Any subject not responding to the study drug because of lack of efficacy at any time after randomization at Visit 2 (POD1) may be rescued and placed on an appropriate alternative therapy determined by the Investigator. According to the study protocol, in general, at any visit, a subject with worsening inflammation or showing no improvement in degree of inflammation compared with the previous visit is eligible for rescue therapy at the discretion of the Investigator. However, the following guidance is also specified in the protocol providing Investigators for consistency in the way subjects are rescued:

- Subjects who, on examination of the anterior chamber, have one or more of the following quantitative criteria should be rescued and discontinued from study drug dosing and placed on rescue mediation:
  - An increase of ACC count by > 15 cells from the Visit 2 (POD1) pre-dose baseline.
  - A ≥ 2 grade increase in Anterior Chamber Flare (ACF) grade from the Visit 2 (POD1) pre-dose baseline.
- Subjects who have the following qualitative criteria may be rescued. If the subject is rescued, the study drug should be discontinued, and rescue mediation started:
  - Subjects who have pain and/or photophobia that does not improve, even when there is an improvement in ACC count and/or ACF grade, may be rescued at the discretion of the investigator.

- Subjects who have pain and/or photophobia that worsens may be rescued at the discretion of the investigator.

3.2.2 Statistical Methodologies

For both studies, the primary analysis set was the Intent-to-Treat (ITT) population, which consisted of all subjects who were randomized to the study drug. Subjects were analyzed according to the treatment assignment at randomization.

Primary efficacy analyses were also performed using the PP population as a sensitivity analysis. The Per-Protocol (PP) population consisted of all subjects in the ITT population who (i) received at least 1 dose of study drug, (ii) did not have major protocol deviations that would impact the evaluation of efficacy, and (iii) had at least 80% overall treatment compliance. Subjects to be excluded from the PP population were identified prior to database lock and unmasking of the treatment assignment, and the reason for exclusion was documented and listed.

The Pearson's Chi-square test was used to test the null hypothesis that there was no difference between treatment groups for the primary efficacy endpoints. Subjects who were rescued at any time after the first dose of study drug and before the efficacy assessments at POD15 were considered as treatment failures (Non-responders, with Rescue Medication use) in the analysis of primary efficacy endpoints.

A gatekeeping hierarchical procedure was used to control the overall type I error rate at the 0.05 level. The primary analysis first compared the proportion of subjects with ACC count = 0 (ACC grade = 0) at POD8, maintained through POD15, between APP13007 and the matching vehicle placebo. If the test was statistically significant at the 2-sided $\alpha = 0.05$ level in favor of APP13007, the comparison of the proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15, between APP13007 and matching vehicle placebo was then tested at the two-sided $\alpha = 0.05$ level.

Based on the gatekeeping hierarchical procedure for testing the proportion of subjects with ACC count = 0 first then followed by testing the proportion of subjects with Ocular Pain = 0, it indicates that the ACC endpoint has a higher priority to the ocular pain endpoint in this testing order.

Sensitivity analyses were performed to confirm the robustness of the primary efficacy analysis results:

1) Analysis of the primary endpoints was performed using the PP population.
2) "Completed-Case" analysis of the primary endpoints was performed using the subgroup of Completers in the ITT population. Completers were defined as the subjects who had the data for the ACC count and ocular pain grade assessments at all visits up to POD15 regardless of rescue medication use.
3) "Observed-Case" analysis of the primary endpoints was performed using the ITT population and the observed data for subjects who missed one of the assessments to

determine the primary endpoints without taking rescue medication. The subjects with missing data were considered as treatment failures (Non-responders).

4) "Worst-Case in the Analysis Window" analysis of the primary endpoints was performed using the ITT population and using the worst response at PODs 4, 8 and 15 when multiple efficacy assessments fell within the same analysis window for each Analysis Visit.
5) If more than 5% of data were missing for determining the primary efficacy endpoints in any treatment group, a tipping point analysis was performed when the statistical significance of a treatment difference between two groups had been claimed for each of the two primary endpoints. Missing data for subjects who took a rescue medication were not considered as 'missing' since the subjects had been assigned as treatment failures (Non-responders). The tipping point analysis of the primary endpoints was to be performed using the ITT population to determine the number of subjects with imputed data in the placebo group whose response status had to be changed from Non-Responder to Responder in order to make the treatment difference between the two treatment groups no longer statistically significant.

The assumption for the sample size determination was estimated using the Package Inserts of Durezol®, Lotemax® and Inveltys® and results from the APP13007 Phase 2 study (CPN-201). The sample size for the ACC count/grade primary efficacy endpoint was based upon the following assumptions:

- 26% of subjects randomized to APP13007 would have an ACC count/grade = 0 at POD8 and maintained through POD15 as compared to 12% of subjects randomized to the matching vehicle placebo
- The 2-group Pearson's Chi-square test, with a 2-sided significance level of 5%
- 92% power

Which yielded 175 subjects per treatment group to detect the difference between APP13007 and matching vehicle placebo.

The same sample size for ocular pain score would be based on the assumptions:

- 57% of subjects randomized to APP13007 having Ocular Pain Grade = 0 at POD4 and maintained through POD15
- 38% of subjects randomized to matching vehicle placebo
- 95% power
- Pearson's Chi-square test, with a 2-sided significance level of 5%

With an estimated 5% dropout rate, this study was planned to randomize approximately 185 subjects per treatment group for a total of approximately 370 subjects.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Studies 301, and 302 each randomized 378, and 370 subjects, respectively. Table 3 is a summary of number of subjects in each analysis population by study and by treatment:

- In Study 301, a total of 181 subjects were randomized to the APP13007 group and 197 were randomized to the placebo group; these subjects comprised the ITT and Safety Populations.
- In Study 302, a total of 185 subjects were randomized to the APP13007 group and 185 were randomized to the placebo group; these subjects comprised the ITT Population. One subject was randomized to the APP13007 group but was not dosed because no investigational product was available to dispense at the time of randomization. Therefore, the Safety Population comprised 184 subjects randomized and dosed with APP13007, and 185 subjects randomized to and dosed with placebo.

Table 3: Summary of Analysis Population (All Randomized)

	Study 301		Study 302	
	APP13007 (N=181)	**Placebo (N=197)**	**APP13007 (N=185)**	**Placebo (N=185)**
ITT	181 (100%)	197 (100%)	185 (100%)	185 (100%)
Safety	181 (100%)	197 (100%)	184 (99.5%)	185 (100%)
PP	175 (96.7%)	195 (99.0%)	180 (97.3%)	178 (96.2%)

Source: Table 6 of Study 301 CSR and Table 6 of Study 302 CSR.

Table 4 shows the subject disposition. Most subjects completed the studies, only a small percentage (< 3%) of randomized subjects in the two studies discontinued early from the study (the main study of Study 302). Among subjects who discontinued study treatments early, majority of the placebo subjects (> 44%) in both studies discontinued due to rescue use. For the primary analysis, subjects who were rescued at any time after the first dose of study drug and before the efficacy assessments at POD15 were considered as treatment failures.

Table 4: Subject Disposition (ITT)

	Study 301		Study 302	
	APP13007 (N=181)	**Placebo (N=197)**	**APP13007 (N=185)**	**Placebo (N=185)**
Completed the Study	180 (99.4%)	197 (100%)	183 (98.9%)	180 (97.3%)
Discontinued the Study Early	1 (0.6%)	0	2 (1.1%)	5 (2.7%)
Reasons				
Withdrew Consent	0	0	0	3 (1.6%)
AE	0	0	0	1 (0.5%)
Investigator/Sponsor Discretion	1 (0.6%)	0	1 (0.5%)	0
Lost to Follow-up	0	0	0	0
Other			1 (0.5%)	1 (0.5%)
Subjects Who Completed ≥14 Days of Study Drug	171 (94.5%)	97 (49.2%)	167 (90.8%)	104 (56.2%)
Subjects Who Discontinued Study Drug Early	10 (5.5%)	100 (50.8%)	17 (9.2%)	81 (43.8%)
Reasons				
Withdrew Consent				2 (1.1%)
AE	3 (1.7%)	0		2 (1.1%)

Rescue	7 (3.9%)	100 (50.8%)	13 (7.1%)	72 (38.9%)
Other			4 (2.2%)	5 (2.7%)

Source: Table 6 of Study 301 CSR; and Table 6 of Study 302 CSR.

3.2.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics were generally balanced between treatment groups in the two studies (Table 5). Most study subjects were non-Hispanic (over 70%), white (over 70%), and had brown eyes (over 55%). The mean age in the two studies was approximately 68 years old (range: 30 to 91). The study eyes were relatively balanced between the left and the right eye.

Table 5: Demographic and Baseline Characteristics (ITT)

	Study 301		**Study 302**	
	APP13007 (N=181)	**Placebo (N=197)**	**APP13007 (N=185)**	**Placebo (N=185)**
Age				
Mean (SD)	68.7 (8.9)	67.8 (8.6)	67.2 (9.7)	68.0 (8.4)
Median	69.0	69.0	68.0	68.0
Min, Max	30, 91	33, 87	30, 89	30, 87
< 65	39 (21.5%)	56 (28.4%)	61 (33.0%)	48 (25.9%)
≥ 65	142 (78.5%)	141 (71.6%)	179 (39%)	167 (36.6%)
Female	106 (58.6%)	119 (60.4%)	98 (53.0%)	97 (52.4%)
Male	75 (41.4%)	78 (39.6%)	87 (47.0%)	88 (47.6%)
Race				
American Indian or Alaska Native	1 (0.6%)	1 (0.5%)	0	0
Asian	11 (6.1%)	16 (8.1%)	97(21.1%)	95 (20.8%)
Black or African American	18 (9.9%)	27 (3.7%)	15 (8.1%)	17 (9.2%)
Native Hawaiian or Pacific Islander	0	0	20 (10.8%)	22 (11.9%)
White	150 (82.9%)	151 (76.6%)	150 (81.1%)	145 (78.4%)
Multiple	1 (0.6%)	2 (1.0%)	0	0
Ethnicity				
Hispanic or Latino	35 (19.3%)	52 (26.4%)	38 (20.5%)	35 (18.9%)
Not Hispanic/Latino	146 (80.7%)	145 (73.6%)	147 (79.5%)	150 (81.1%)
Iris Color				
Blue	49 (27.1%)	42 (21.3%)	41 (22.2%)	50 (27.0%)
Brown	101 (55.8%)	123 (62.4%)	115 (62.2%)	112 (60.5%)
Other	31 (17.1%)	32 (16.2%)	29 (15.7%)	23 (12.4%)
Study Eye				
OD (right)	97 (53.6%)	92 (46.7%)	93 (50.3%)	98 (53.0%)
OS (left)	84 (46.4%)	105 (53.3%)	92 (49.7%)	87 (47.0%)

Source: Table 11 of Study 301 CSR, and Table 11 of Study 302 CSR.

3.2.4 Results and Conclusions

3.2.4.1 ACC Grade

The applicant analyzed the proportion (%) of subjects with ACC Count = 0 (ACC Grade = 0) on each individual visit at PODs 4, 8 and 15. As demonstrated in the table below, starting from POD 8, the APP13007 group had more subjects with ACC grade = 0 comparing with the placebo group.

Table 6: Proportion (%) of Subjects with ACC Count = 0 (ACC Grade = 0) at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
4	9 (5.0%)	13 (6.6%)	-1.6% (-6.3%, 3.1%)	18 (9.7%)	11 (5.9%)	3.8% (-1.7%, 9.3%)
8	59 (32.6%)	23 (11.7%)	20.9% (12.8%, 29.1%)	55 (29.7%)	24 (13.0%)	16.8% (8.6%, 24.9%)
15	106 (58.6%)	31 (15.7%)	42.8% (34.0%, 51.6%)	107 (57.8%)	35 (18.9%)	38.9% (29.8%, 48.0%)

* The estimated 95% CI was based on normal approximation.
Source: Table 14.2.3 of Study 301 CSR, and Table 14.2.3 of Study 302 CSR.

In addition, the Applicant also analyzed the change from baseline of the ACC grade on each individual day at PODs 4, 8 and 15. At each of the PODs 4, 8, and 15 in both studies, the mean change from baseline of the ACC grade for the APP13007 group was greater than the placebo group (Table 7).

Table 7: Analysis of ACC Grade Change from Baseline at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Baseline	2.6 (0.6)	2.8 (0.7)	N/A	2.7 (0.8)	2.8 (0.8)	N/A
4	-0.9 (0.8)	-0.3 (1.2)	-0.5 (-0.7, -0.3)	-1.1 (1.1)	-0.7 (1.1)	-0.5 (-0.7, -0.3)
8	-1.7 (1.0)	-0.5 (1.3)	-0.9 (-1.1, -0.7)	-1.7 (1.1)	-0.9 (1.2)	-0.9 (-1.1, -0.7)
15	-2.1 (1.0)	-0.6 (1.5)	-1.2 (-1.4, -1.0)	-2.1 (1.1)	-1.0 (1.3)	-1.2 (-1.4, -1.0)

* Difference and 95% CI is estimated from an analysis of covariance model that included treatment as a fixed effect and baseline as a covariate.
Source: Table 14.2.7 of Study 301 CSR, and Table 14.2.7 of Study 302 CSR.

For the primary efficacy endpoint of the proportion (%) of subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15, the APP13007 group demonstrated statistically significant comparing with placebo in both Study 301 and Study 302 (Table 8):

- In Study 301, the proportion of subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15 in the APP13007 group was 26.5% (48/181) vs. 5.1% (10/197) in the placebo group. The treatment difference was 21.4% with the 95% CI of (14.3%, 28.6%), p-value < 0.001.
- In Study 302, the proportion of subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15 in the APP13007 group was 26.5% (49/185) vs. 8.6% (16/185)

in the placebo group. The treatment difference was 17.8% with the 95% CI of (10.3%, 25.4%), p-value < 0.001.

- The treatment effect in both studies is relatively consistent.

Table 8: Primary Efficacy Endpoint – Proportion (%) of Subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15 (ITT Population)

	Study 301			Study 302		
	APP13007 (N=181)	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Responders (%)	48 (26.5%)	10 (5.1%)	21.4% (14.3%, 28.6%)	49 (26.5%)	16 (8.6%)	17.8% (10.3%, 25.4%)
p-value			<0.001			<0.001

* The estimated 95% CI was based on normal approximation.
Source: Table 13 of Study 301 CSR, and Table 13 of Study 302 CSR.

3.2.4.2 Ocular Pain Grade

The applicant analyzed the proportion (%) of subjects with Ocular Pain Grade = 0 at each individual visit on PODs 4, 8 and 15. As demonstrated in the table below, starting from POD4, the APP13007 group had more subjects with Ocular Pain Grade = 0 comparing with the placebo group, and the treatment difference appeared to be increasing over time.

Table 9: Proportion (%) of Subjects with Ocular Pain Grade = 0 at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
4	140 (77.3%)	86 (43.7%)	33.7% (24.6%, 42.9%)	158 (85.4%)	95 (51.4%)	34.1% (25.2%, 42.9%)
8	149 (82.3%)	84 (42.6%)	39.7% (30.8%, 48.6%)	161 (87.0%)	86 (46.5%)	40.5% (31.9%, 49.2%)
15	164 (90.6%)	83 (42.1%)	48.5% (40.4%, 56.6%)	160 (86.5%)	92 (49.7%)	36.8% (28.0%, 45.5%)

* The estimated 95% CI was based on normal approximation.
Source: Table 14.2.3 of Study 301 CSR, and Table 14.2.3 of Study 302 CSR, and the statistical reviewer's calculation.

In addition, the Applicant also analyzed the change from baseline of the ocular pain grade on each individual day at PODs 4, 8 and 15. At each of the PODs 4, 8, and 15 in both studies, the mean change from baseline of the ocular pain grade for the APP13007 group was greater than the placebo group at all the PODs (Table 10).

Table 10: Analysis of Ocular Pain Grade Change from Baseline at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Baseline	1.2 (1.0)	1.2 (1.0)	N/A	2.7 (0.8)	2.8 (0.8)	N/A

4	-0.9 (0.9)	-0.2 (1.1)	-0.6 (-0.8, -0.5)	-0.5 (0.8)	-0.2 (1.0)	-0.5 (-0.6, -0.4)
8	-1.0 (1.0)	-0.3 (1.3)	-0.7 (-0.8, -0.5)	-0.5 (1.0)	-0.1 (1.3)	-0.6 (-0.7, -0.4)
15	-1.1 (1.1)	-0.3 (1.3)	-0.7 (-0.9, -0.6)	-0.6 (1.0)	-0.2 (1.3)	-0.5 (-0.7, -0.3)

* Difference and 95% CI is estimated from an analysis of covariance model that included treatment as a fixed effect and baseline as a covariate.
Source: Table 14.2.7 of Study 301 CSR, and Table 14.2.7 of Study 302 CSR.

For the primary efficacy endpoint of the proportion (%) of subjects with ocular pain grade = 0 at POD4 maintained through POD15, the APP13007 group demonstrated statistically significant comparing with placebo in both Study 301 and Study 302 (Table 11):

- In Study 301, the proportion of subjects with ocular pain grade = 0 at POD4 maintained through POD15 in the APP13007 group was 68.0% (123/181) vs. 23.4% (46/197) in the placebo group. The treatment difference was 44.6% with the 95% CI of (35.6%, 53.6%), p-value < 0.001.
- In Study 302, the proportion of subjects with ocular pain grade = 0 at POD4 maintained through POD15 in the APP13007 group was 75.1% (139/185) vs. 32.4% (60/185) in the placebo group. The treatment difference was 42.7% with the 95% CI of (33.5%, 51.9%), p-value < 0.001.
- The treatment effect in both studies is consistent.

Table 11: Primary Efficacy Endpoint – Proportion (%) of Subjects of subjects with Ocular Pain Grade = 0 at POD4 maintained through POD15 (ITT Population)

	Study 301			**Study 302**		
	APP13007 (N=181)	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Responders (%)	123 (68.0%)	46 (23.4%)	44.6% (35.6%, 53.6%)	139 (75.1%)	60 (32.4%)	42.7% (33.5%, 51.9%)
p-value			<0.001			<0.001

* The estimated 95% CI was based on normal approximation.
Source: Table 14 of Study 301 CSR, Table 14 of Study 302 CSR, and the statistical reviewer's calculation.

3.2.4.3 Sensitivity Analyses of the Primary Efficacy Endpoints

The Applicant's analyses of the primary endpoints (ACC Grade = 0 at POD8 and Maintained through POD15, and Ocular Pain Grade = 0 at POD4 and Maintained through POD15) in the different analysis sets and/or using different methods for missing data yielded similar results (Table 12 and Table 13).

Table 12: Sensitivity Analyses of the Proportion (%) of Subjects with ACC Count=0 (ACC Grade=0) at POD8 and Maintained through POD15

	Study 301			**Study 302**		
	APP13007 (N=181)	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Per-Protocol Population, n/N (%)	46/175 (26.3%)	10/195 (5.1%)	21.2% (13.9%, 28.4%)	49/180 (27.2%)	16/178 (9.0%)	18.2% (10.5%, 26.0%)
Completed-Case (ITT Population, Completers), n/N (%)	47/177 (26.6%)	10/196 (5.1%)	21.5% (14.3%, 28.7%)	49/179 (27.4%)	15/178 (8.4%)	19.0% (11.3%, 26.7%)

Observed-Case (ITT Population), n/N (%)	47/181 (26.0%)	10/197 (5.1%)	20.9% (13.8%, 28.0%)	49/185 (26.5%)	16/185 (8.6%)	17.8% (10.3%, 25.4%)
Worst-Case-In-Analysis Window (ITT Population), n/N (%)	48/181 (26.5%)	10/197 (5.1%)	21.4% (14.3%, 28.6%)	49/185 (26.5%)	15/185 (8.1%)	18.4% (10.9%, 25.9%)

* The estimated 95% CI for the treatment difference was based on normal approximation.
Source: Table 15 of Study 301 CSR, Table 15 of Study 302 CSR, and the statistical reviewer's calculation.

Table 13: Sensitivity Analyses of the Proportion (%) of Subjects with Ocular Pain Grade=0 at POD4 and Maintained through POD15

	Study 301			**Study 302**		
	APP13007 (N=181)	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Per-Protocol Population, n/N (%)	119/175 (68.0%)	46/195 (23.6%)	44.4% (35.3%, 53.5%)	137180 (76.1%)	58/178 (32.6%)	43.5% (34.2%, 52.8%)
Completed-Case (ITT Population, Completers), n/N (%)	119/177 (67.6%)	45/196 (23.1%)	44.3% (35.2%, 53.4%)	138/179 (77.1%)	60/178 (33.7%)	43.4% (34.1%, 52.7%)
Observed-Case (ITT Population), n/N (%)	119/181 (65.7%)	45/197 (22.8%)	42.9% (33.8%, 52.0%)	138/185 (74.6%)	60/185 (32.4%)	42.2% (33.0%, 51.4%)
Worst-Case-In-Analysis Window (ITT Population), n/N (%)	123/181 (68.0%)	46/197 (23.4%)	44.6% (35.6%, 53.6%)	139/185 (75.1%)	60/185 (32.4%)	42.7% (33.5%, 51.9%)

* The estimated 95% CI for the treatment difference was based on normal approximation.
Source: Table 16 of Study 301 CSR, Table 16 of Study 302 CSR, and the statistical reviewer's calculation.

Additionally, the Applicant analyzed the primary efficacy endpoints where rescued subjects were not considered as treatment failures and all primary endpoint data collected were included. The results were consistent with the primary analysis results as well (see Table 14 below).

Table 14: Sensitivity Analyses of Proportion (%) of Subjects with ACC Count=0 (ACC Grade=0) at POD8 and Maintained through POD15 and Proportion (%) of Subjects with Ocular Pain Grade=0 at POD4 and Maintained through POD15 (Rescued Subjects Included without being Considered as Treatment Failures) (ITT Population)

	Study 301			**Study 302**		
	APP13007 (N=181)	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
ACC Grade = 0						
Responders (%)	48 (26.5%)	18 (9.1%)	17.4% (9.8%, 25.0%)	51 (27.6%)	20 (10.8%)	16.8% (8.9%, 24.6%)
Ocular Pain Grade = 0						
Responders (%)	122 (67.4%)	75 (38.1%)	29.3% (19.7%, 39.0%)	147 (79.5%)	80 (43.2%)	36.2% (27.0%, 45.4%)

* The estimated 95% CI was based on normal approximation.
Source: Table 16 of Study 301 CSR, and Table 16 of Study 302 CSR.

The Applicant reported the analysis of overall proportion of subjects rescued during the treatment period and the cumulative proportion of subjects rescued at PODs 4, 8, and 15 (Table 15):

- In Study 301, the cumulative proportion of subjects rescued was statistically significantly greater in the placebo group than in the APP13007 group at POD4 (31.5% vs 2.8%), POD8 (50.3% vs 5.5%) and POD15 (58.9% vs 8.8%).
- In Study 302, the cumulative proportion of subjects rescued was greater in the placebo group than in the APP13007 group at POD4 (25.4% vs 3.2%), POD8 (38.4% vs 7.0%) and POD15 (51.9% vs 14.6%), respectively.
- Based on the reviewer's summary, it is noted that more subjects were rescued due to pain and/or photophobia reasons alone:
    - In Study 301:
        - During the 14-day treatment period, 47 (47%, 47/100) placebo subjects took rescue due to pain and/or photophobia reasons; 31 (31%, 31/100) placebo subjects were rescued due to meet ACC or ACF rescue criteria; and 22 (22%, 22/100) placebo subjects due to both ACC/ACF and pain and/or photophobia reasons. Six (60%, 6/10) APP13007 subjects took rescue due to pain and/or photophobia reasons; two (2) (20%, 2/10) APP13007 subjects were rescued due to meet ACC or ACF rescue criteria; and two (2) (20%, 2/10) APP13007 subjects recued due to meeting both ACC/ACF and pain and/or photophobia reasons.
        - By POD15, 61 (53%, 61/116) placebo subjects took rescue due to pain and/or photophobia reasons; 33 (28%, 33/116) placebo subjects were rescued due to meet ACC or ACF rescue criteria; and 22 (19%, 22/116) placebo subjects due to both ACC/ACF and pain and/or photophobia reasons. While 11 (69%, 11/16) APP13007 subjects took rescue due to pain and/or photophobia reasons; three (3) (19%, 3/16) APP13007 subjects were rescued due to meet ACC or ACF rescue criteria; and two (2) (13%, 2/16) APP13007 subjects recued due to meeting both ACC/ACF and pain and/or photophobia reasons.
    - In Study 302:
        - During the 14-day treatment period, 60 (85%, 60/71) placebo subjects took rescue due to pain and/or photophobia reasons; 5 (7%, 5/71) placebo subjects were rescued due to meet ACC or ACF rescue criteria; and 6 (8%, 6/100) placebo subjects due to both ACC/ACF and pain and/or photophobia reasons. 12 (92%, 12/13) APP13007 subjects took rescue due to pain and/or photophobia reasons; one (1) (8%, 1/13) APP13007 subjects were rescued due to meet ACC or ACF rescue criteria; and no subjects were rescued due to meeting both ACC/ACF and pain and/or photophobia reasons.
        - By POD15, 83 (86%, 83/96) placebo subjects took rescue due to pain and/or photophobia reasons; six (6) (6%, 6/96) placebo subjects were rescued due to meet ACC or ACF rescue criteria; and seven (7) (7%, 7/96) placebo subjects due to both ACC/ACF and pain and/or photophobia reasons. While 26 (96%, 26/27) APP13007 subjects took rescue due to pain and/or photophobia reasons; one (1) (4%, 1/27) APP13007 subjects were rescued due to meet ACC or ACF rescue criteria; and no subjects were rescued due to meeting both ACC/ACF and pain and/or photophobia reasons.

Table 15: Analysis of the Overall Proportion (%) of Subjects Rescued During the Treatment Period and the Cumulative Proportion of Subjects Rescued at PODs 4, 8, and 15 (ITT Population)

	Study 301		Study 302	
	APP13007 (N=181)	**Placebo (N=197)**	**APP13007 (N=185)**	**Placebo (N=185)**
Overall rescued during the 14-day Treatment Period, n (%)	10 (5.5%)	100 (50.8%)	13 (7.0%)	71 (38.4%)
Reason for rescue				
Reasons				
>15 cells increase from baseline	3 (1.7%)	52 (26.4%)	1 (0.5%)	10 (5.4%)
≥2 grade of increase ACF from baseline	2 (1.1%)	8 (4.1%)	0	1 (0.5%)
Investigator discretion	8 (4.4%)	69 (35.0%)	12 (6.5%)	65 (35.1%)
Pain and/or photophobia not improved even ACC and/or ACF improved	3 (1.7%)	32 (16.2%)	7 (3.8%)	34 (18.4%)
Pain and/or photophobia increased	4 (2.2%)	51 (25.9%)	3 (1.6%)	29 (15.7%)
Other	4 (2.2%)	14 (7.1%)	6 (3.2%)	18 (9.7%)
Rescued by POD4[*], n (%)	5 (2.8%)	62 (31.5%)	6 (3.2%)	47 (25.4%)
Reason for rescue				
Reasons				
>15 cells increase from baseline	3 (1.7%)	37 (18.8%)	0	8 (4.3%)
≥2 grade of increase ACF from baseline	1 (0.6%)	8 (4.1%)	0	0
Investigator discretion	3 (1.7%)	39 (19.8%)	6 (3.2%)	43 (23.2%)
Pain and/or photophobia not improved even ACC and/or ACF improved	3 (1.7%)	17 (8.6%)	2 (1.1%)	19 (10.3%)
Pain and/or photophobia increased	3 (1.7%)	28 (14.2%)	1 (0.5%)	19 (10.3%)
Other	0	8 (4.1%)	4 (2.2%)	15 (8.1%)
Rescued by POD8[*], n (%)	10 (5.5%)	99 (50.3%)	13 (7.0%)	71 (38.4%)
Reason for rescue				
Reasons				
>15 cells increase from baseline	3 (1.7%)	51 (25.9%)	1 (0.5%)	10 (5.4%)
≥2 grade of increase ACF from baseline	2 (1.1%)	8 (4.1%)	0	1 (0.5%)
Investigator discretion	8 (4.4%)	68 (34.5%)	12 (6.5%)	65 (35.1%)
Pain and/or photophobia not improved even ACC and/or ACF improved	3 (1.7%)	32 (16.2%)	7 (3.8%)	34 (18.4%)
Pain and/or photophobia increased	4 (2.2%)	50 (25.4%)	3 (1.6%)	29 (15.7%)
Other	4 (2.2%)	14 (7.1%)	6 (3.2%)	18 (9.7%)
Rescued by POD15[*], n (%)	16 (8.8%)	116 (58.9%)	27 (14.6%)	96 (51.9%)
Reason for rescue				
Reasons				
>15 cells increase from baseline	4 (2.2%)	54 (27.4%)	1 (0.5%)	12 (6.5%)
≥2 grade of increase ACF from baseline	2 (1.1%)	8 (4.1%)	0	1 (0.5%)
Investigator discretion	13 (7.2%)	83 (42.1%)	26 (14.1%)	89 (48.1%)
Pain and/or photophobia not improved even ACC and/or ACF improved	4 (2.2%)	38 (19.3%)	17 (9.2%)	48 (25.9%)
Pain and/or photophobia increased	7 (3.9%)	54 (27.4%)	5 (2.7%)	35 (18.9%)
Other	6 (3.3%)	21 (10.7%)	10 (5.4%)	23 (12.4%)

[*] Included all rescue medications used prior to or at this analysis visit.
Source: Table 28 of Study 301 CSR and Table 28 of Study 302 CSR.

The reviewer further investigated the treatment effect based on treatment policy strategy for rescue subjects, where subjects with rescue were analyzed as observed. As demonstrated in the following two tables, based on observed outcomes regardless rescue use, for ACC scores:

- From POD8 to POD15, the APP13007 group had more subjects with ACC grade = 0 comparing with the placebo group.
- By POD22, the percentage of subjects achieved ACC grade = 0 were similar between the two treatment groups (about 60%). In total, there were about 85% of subjects had ACC = 0 or 1 by POD22 in both APP13007 and placebo group, comparing with 0% at baseline (due to inclusion criteria for ACC ≥ 2). These results indicate the self-limiting nature of the indication.
- It should be noted that much more placebo subjects received rescue medications. In Study 301, ten (10) (5.5%) subjects in APP13007 group received rescue before Day 15, while 100 (50.8%) in placebo group received rescue; and in Study 302, 13 (7.1%) in the APP13007 group received rescue vs. 72 (38.9%) in the placebo group.

Table 16: Study 301 Sensitivity Analyses of Proportion (%) of Subjects with ACC Count at Each Study Visit (observed outcomes regardless rescue use, ITT)

		ACC Scores				
Study Day	**Treatment**	**0**	**1**	**2**	**3**	**4**
Baseline	APP13007 (N=181)	0	0	81 (44.8%)	83 (45.9%)	17 (9.4%)
	Placebo (N=197)	0	0	77 (39.3%)	86 (43.9%)	34 (17.3%)
4	APP13007 (N=181)	9 (5.0%)	55 (30.4%)	86 (47.5%)	26 (14.4%)	5 (2.8%)
	Placebo (N=196)	14 (7.1%)	26 (13.3%)	54 (27.6%)	58 (29.6%)	44 (22.5%)
8	APP13007 (N=181)	59 (32.6%)	86 (47.5%)	30 (16.6%)	6 (3.3%)	0
	Placebo (N=197)	30 (15.2%)	45 (22.8%)	67 (34.0%)	36 (18.3%)	19 (9.6%)
15	APP13007 (N=181)	112 (61.9%)	54 (29.8%)	10 (5.5%)	3 (1.7%)	2 (1.1%)
	Placebo (N=197)	71 (36.0%)	61 (31.0%)	51 (25.9%)	10 (5.1%)	4 (2.0%)
22	APP13007 (N=181)	118 (65.2%)	37 (20.4%)	22 (12.2%)	3 (1.7%)	1 (0.6%)
	Placebo (N=197)	115 (58.4%)	50 (25.4%)	29 (14.7%)	3 (1.5%)	0

Source: Statistical reviewer's analysis based on raw dataset OE.xpt, analysis datasets adoeqs.xpt and adsl.xpt of Study 301.

Table 17: Study 302 Sensitivity Analyses of Proportion (%) of Subjects with ACC Count at Each Study Visit (observed outcomes regardless rescue use, ITT)

		ACC Scores				
Study Day	**Treatment**	**0**	**1**	**2**	**3**	**4**
Baseline	APP13007 (N=185)	0	0	85 (46.2%)	66 (35.7%)	34 (18.4%)
	Placebo (N=185)	0	0	82 (44.3%)	61 (33.0%)	42 (22.7%)
4	APP13007 (N=181)	18 (9.9%)	68 (37.6%)	71 (39.2%)	16 (8.8%)	8 (4.4%)
	Placebo (N=181)	12 (6.6%)	41 (22.7%)	72 (39.8%)	36 (19.9%)	20 (11.1%)
8	APP13007 (N=182)	57 (31.3%)	87 (47.8%)	35 (19.2%)	1 (0.6%)	2 (1.1%)
	Placebo (N=181)	30 (16.6%)	61 (33.7%)	69 (38.1%)	12 (6.6%)	9 (5.0%)
15	APP13007 (N=182)	111 (61.0%)	56 (30.8%)	12 (6.6%)	2 (1.1%)	1 (0.6%)
	Placebo (N=179)	64 (35.8%)	58 (32.4%)	46 (25.7%)	7 (3.9%)	4 (2.2%)
22	APP13007 (N=183)	115 (62.8%)	44 (24.0%)	21 (11.5%)	2 (1.1%)	1 (0.6%)
	Placebo (N=184)	113 (61.4%)	48 (26.1%)	18 (9.8%)	3 (1.6%)	2 (1.1)

Source: Statistical reviewer's analysis based on raw dataset oe.xpt, analysis datasets adoeqs.xpt and adsl.xpt of Study 302.

For pain measurement, as demonstrated in the following table, based on observed outcomes regardless rescue use in both treatment groups:

- In Study 301, about 32% subjects had no pain on POD1 (baseline); and in Study 302, about 50% of subjects had no pain on POD1 (baseline).
- From POD4 to POD15, the APP13007 group had more subjects with Ocular Pain grade = 0 comparing with the placebo group. The treatment difference was the largest on POD4 (32.5% in Study 301 and 34.4% in Study 302), started to get smaller on POD8 (16.5% in Study 301 and 34.4% in Study 302), and almost diminished by POD15 (9.8% in Study 301 and 5.1% in Study 302).
- By POD22, the percentage of pain free placebo subjects (with rescue) was similar to those in the APP13007 group in both studies. These results indicate the self-limiting nature of the indication.

Table 18: Study 301 and Study 302 Sensitivity Analyses of Proportion (%) of Subjects with No Pain at Each Study Visit (observed outcomes regardless rescue use, ITT)

		Study 301			Study 302	
Study Day	**Treatment**	**No Pain**	**Pain Exists**	**Treatment**	**No Pain**	**Pain Exists**
Baseline	APP13007 (N=181)	58 (32.0%)	123 (68.0%)	APP13007 (N=184)	106 (57.6%)	78 (42.4%)
	Placebo (N=196)	63 (32.1%)	133 (67.9%)	Placebo (N=185)	90 (48.7%)	95 (51.4%)
4	APP13007 (N=181)	140 (77.4%)	31 (17.1%)	APP13007 (N=181)	159 (87.9%)	22 (12.2%)
	Placebo (N=196)	88 (44.9%)	108 (55.1%)	Placebo (N=181)	97 (53.6%)	84 (46.4%)
8	APP13007 (N=181)	152 (84.0%)	29 (16.0%)	APP13007 (N=182)	167 (91.8%)	15 (8.2%)
	Placebo (N=197)	133 (67.5%)	64 (32.5%)	Placebo (N=181)	126 (69.6%)	55 (30.4%)
15	APP13007 (N=176)	168 (95.5%)	8 (4.6%)	APP13007 (N=182)	170 (93.4%)	12 (6.6%)
	Placebo (N=196)	168 (85.7%)	28 (14.3%)	Placebo (N=179)	158 (88.3%)	21 (11.7%)
22	APP13007 (N=180)	167 (92.8%)	13 (7.2%)	APP13007 (N=183)	168 (91.8%)	15 (8.2%)
	Placebo (N=196)	183 (93.4%)	13 (6.6%)	Placebo (N=184)	175 (95.1%)	9 (4.9%)

Source: Statistical reviewer's analysis based on raw dataset qs.xpt, analysis datasets adoeqs.xpt and adsl.xpt of Study 301 and Study 302.

These sensitivity analyses based on observed observations regardless of rescue medication support the treatment effect of APP13007 for timely reducing post-operative inflammation and pain; while indicating the self-limiting nature of the indication – majority of study subjects had either no (ACC = 0) or mild (ACC = 1) inflammation and have no pain about 3 weeks post cataract surgery.

3.2.4.4 Conclusion

Both Study 301 and Study 302 demonstrated statistical superiority of APP13007 to the placebo for both primary efficacy endpoints: the proportion of subjects with ACC count = 0 (ACC Grade=0) at POD8 and maintained through POD15 and the proportion of subjects with ocular pain grade = 0 at POD4 and maintained through POD15; with p-values < 0.001 for both endpoints in both studies. Additional sensitivity analyses by the Applicant and the reviewer also support the primary efficacy results. Therefore, the statistical reviewer concludes that there is substantial evidence to support the treatment effect of APP13007.

3.3 Evaluation of Safety

As presented in the following table, based on the pooled safety analysis, the APP13007 group had similar incidents of all AEs, ocular AEs, severe AEs, treatment-related AEs, AEs leading to discontinuation of study treatment, SAEs. There was no death reported in both clinical studies.

Table 19: Summary of Number of Subjects Experiencing Adverse Events (Safety Population)

	Study 301		Study 302	
Category	**APP13007 (N=181)**	**Vehicle (N=197)**	**APP13007 (N=185)**	**Vehicle (N=185)**
Any AEs	38 (21.0%)	39 (19.8%)	47 (25.5%)	48 (25.9%)
Ocular AEs	30 (16.6%)	35 (17.8%)	43 (23.4%)	45 (24.3%)
Severe AEs	0	1 (0.5%)	1 (0.5%)	2 (1.1%)
Serious AEs	0	0	1 (0.5%)	4 (2.2%)
AEs Related to Treatment	4 (2.2%)	8 (4.1%)	9 (4.9%)	7 (3.8%)
AEs Leading to Discontinuation of Study Treatment	2 (1.1%)	0	0	2 (1.1%)

Source: Table 32 of Study 301 CSR, and Table 32 of Study 302 CSR.

Table 20 below presented the treatment-emergent ocular adverse events associated with ≥ 1.0% in the study eye in either treatment group for each of the two studies.

Table 20: Safety Analysis: Treatment-emergent ocular adverse events associated with ≥ 1.0% in the study eye (Safety Population)

	Study 301		Study 302	
System Organ Class **Preferred Term**	**APP13007 (N=181)**	**Vehicle (N=197)**	**APP13007 (N=185)**	**Vehicle (N=185)**
Subjects with ≥ 1 Ocular TEAE	29 (16.0%)	34 (17.3%)	38 (20.7%)	42 (22.7%)
Eye Disorders	21 (11.6%)	29 (14.7%)	22 (12.0%)	31 (16.8%)
Anterior chamber inflammation	7 (3.9%)	3 (1.5%)	0	0
Corneal oedema	3 (1.7%)	10 (5.1%)	5 (2.7%)	5 (2.7%)
Cystoid macular oedema	3 (1.7%)	1 (0.5%)	4 (2.2%)	5 (2.7%)
Vitreous detachment	3 (1.7%)	2 (1.0%)	0	0
Vitreous floaters	3 (1.7%)	2 (1.0%)	1 (0.5%)	2 (1.1%)
Conjunctival hemorrhage	2 (1.1.%)	1 (0.5%)	0	0
Anterior chamber cell	1 (0.6%)	2 (1.0%)	0	0
Eye inflammation	1 (0.6%)	2 (1.0%)	6 (3.3%)	14 (7.6%)
Photophobia	1 (0.6%)	3 (1.5%)	2 (1.1%)	2 (1.1%)
Anterior chamber fibrin	0	2 (1.0%)	0	0
Eye pain	0	4 (2.0%)	2 (1.1%)	2 (1.1%)

Foreign body sensation in eyes	0	2 (1.0%)	1 (0.5%)	2 (1.1%)
Retinal haemorrhage	0	2 (1.0%)	0	0
Iritis	0	0	3 (1.6%)	1 (0.5%)
Dry Eye	0	0	1 (0.5%)	2 (1.1%)
Iridocyclitis	0	0	1 (0.5%)	3 (1.6%)
Investigations	2 (1.1%)	0	6 (3.3%)	1 (0.5%)
Intraocular pressure increased	2 (1.1%)	0	6 (3.3%)	1 (0.5%)

Source: Table 33 of Study 301 CSR, and Table 33 of Study 302 CSR.

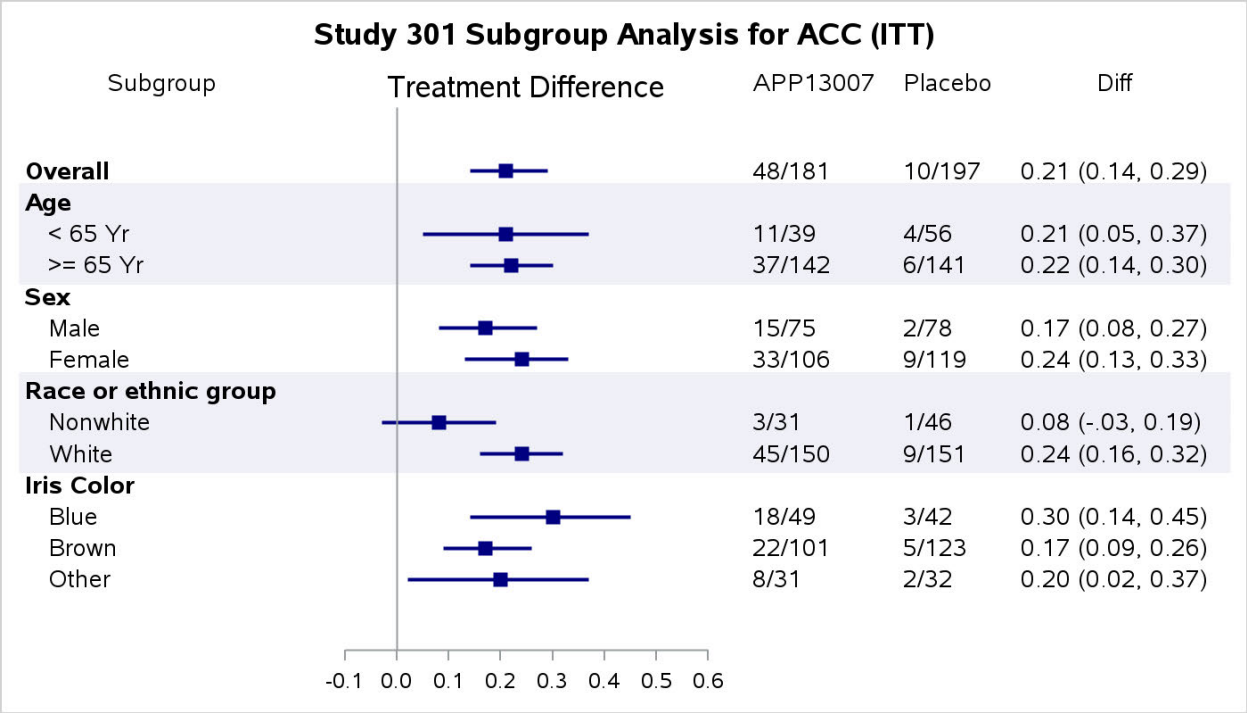
For a comprehensive review of safety, please refer to Dr. Sonal Wadhwa's clinical review.

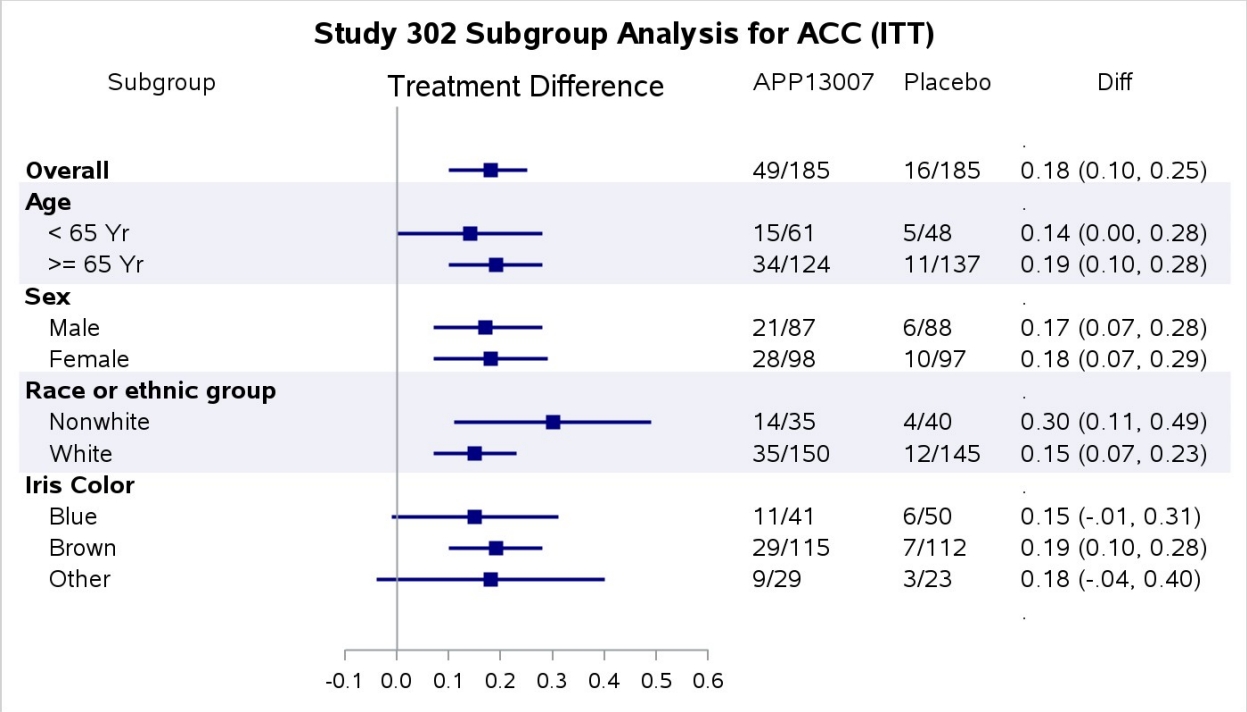
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 [redacted] Race, and Age

Subgroup analyses based on [redacted] race, age, iris color for each study were performed (see results in below) by the applicant. In both studies, the subgroup analyses results were similar to those seen for the overall population for each demographic subgroup.

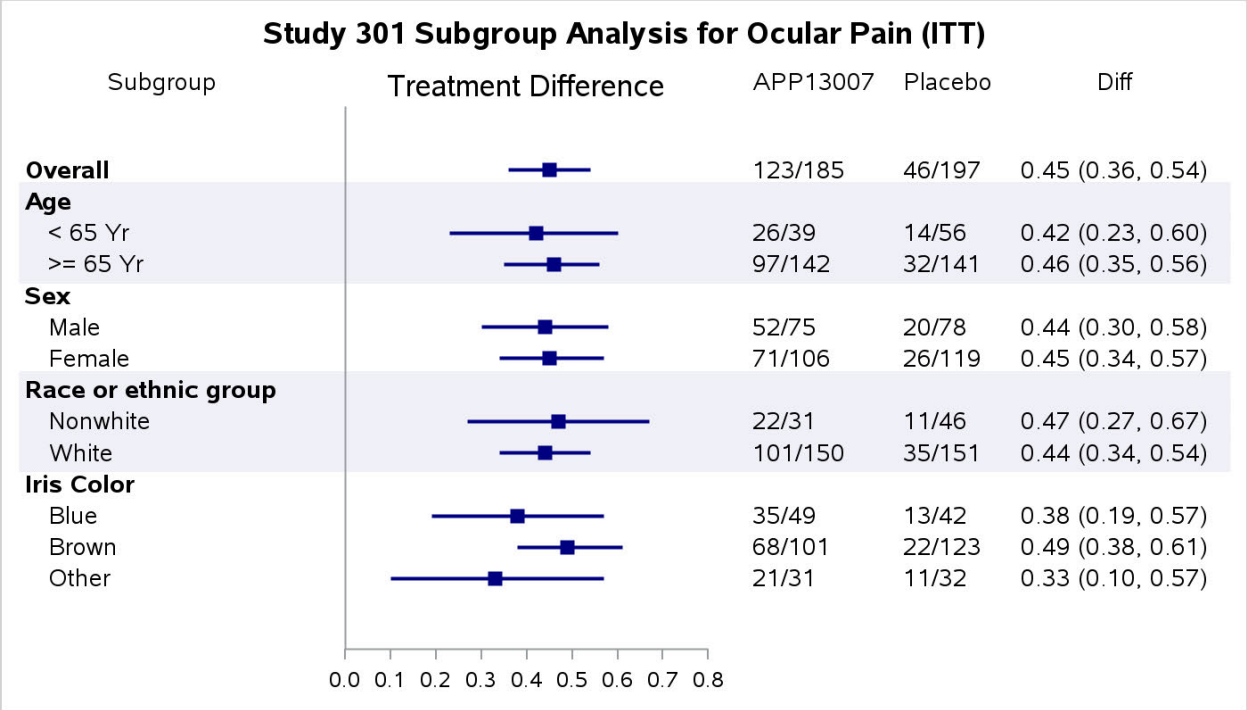
Figure 3: Subgroup Analyses for ACC (Studies 301 and 302, ITT)

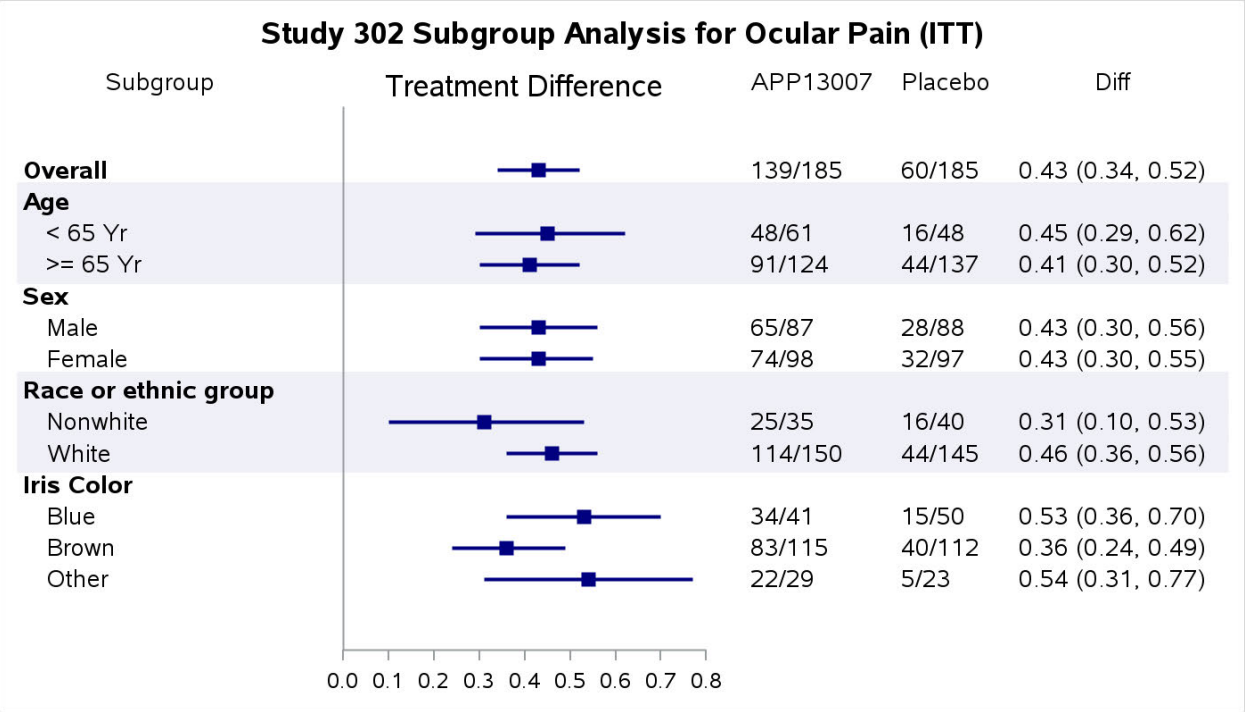




Note: ITT = Intent-to-Treat, Diff = Difference.
* The estimated 95% CI was based on normal approximation.
Source: Table 11 of Study 006 CSR, and Table 11 of Study 011 CSR, and the statistical reviewer's analysis.

Figure 4: Subgroup Analyses for ACC (Studies 301 and 302, ITT)





Note: ITT = Intent-to-Treat, Diff = Difference, CI = Confidence Interval.
* The estimated 95% CI was based on normal approximation.
Source: Table 11 of Study 006 CSR, and Table 11 of Study 011 CSR, and the statistical reviewer's analysis.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for this NDA submission.

5.2 Collective Evidence

Both Study 301 and Study 302 demonstrated superiority of the APP13007 to the placebo for the two pre-defined primary efficacy endpoints: the proportion of subjects with ACC Grade = 0 at post-operative day 8 (POD8) and maintained through POD15, and the proportion of subjects with Ocular Pain Grade = 0 at POD4 and maintained through POD15.

Sensitivity analyses demonstrated the robustness of the primary analysis results. Subgroup analyses showed a consistent treatment effect of the APP13007 across subgroups of sex, age, race, and iris color.

5.3 Conclusions and Recommendations

In conclusion, the two Phase 3 studies provided statistically substantial evidence that APP13007 (clobetasol propionate ophthalmic nanosuspension, 0.05%) is superior to placebo in treating post-operative inflammation and pain following cataract surgery. Therefore, the statistical reviewer recommends the approval of APP13007.

5.4 Labeling Recommendations

The Applicant's proposed label had the following text for the clinical studies section.

(b) (4)

(b) (4)

The statistical reviewer recommends that (b) (4)

- Report the two primary efficacy endpoints for the two studies separately (b) (4) .
- (b) (4)

Appendix 1: Summary of Study Procedure and Accessments

Table 21: Study 301 Schedule of Events

PROCEDURE/ASSESSMENTS [1]	Visit 1 Screening (Day -28 to -1)	Surgery [2] Day 0	Visit 2 POD1 [3]	Visit 3 POD4 (±1 Day)	Visit 4 POD8 (±1 Day)	Contact POD14	Visit 5 POD15 (+1 Day) [4]	Visit 6 POD22 (±2 Days) [5]
ICF, Demography, Medical History	X							
Determine Eligibility, Review Inclusion/Exclusion Criteria	X		X					
Urine pregnancy test only for WOCBP			X				X	
Ocular Symptoms Assessment [6]	X		X	X	X		X	X
ETDRS Visual Acuity	X		X	X	X		X	X
Slit-lamp Biomicroscopy [7]	X		X	X	X		X	X
Indirect Ophthalmoscopy (dilated)	X							X
IOP (Goldmann applanation tonometry) [8]	X		X	X	X		X	X
Randomization			X					
Dispense Study Drug			X					
Study Drug Dosing BID for 14 days (POD1 to POD14) [9]			X	X	X	X		
Dispense Diary Card (with instructions for completion)			X	X	X			
Contact Subject [10]						X		
Collect Study Drug							X	
Collect and Check Diary Cards for Accuracy and Compliance				X	X		X	
AEs [7] and Concomitant Medications [11]	X	X [12]	X	X	X	X [13]	X	X

[1] Ophthalmic assessments were performed in the study eye only at Visits 2-5 and were performed on both eyes at Visit 1 (Screening) and at Visit 6 (POD22), or at subject Early Termination/Withdrawal.
[2] Surgery occurred between 1 to 28 days after Visit 1 (Screening), preferably in the morning. If, due to unexpected events, surgery was postponed and would occur > 28 days past the Screening visit, the Study Medical Monitor was contacted to discuss which, if any, of the screening procedures should be repeated. Subjects were determined to be a suitable candidate for surgery during a pre-surgery medical assessment, where the routine medication list prescribed by the cataract surgeon was reviewed to rule out prohibited medications.
[3] Visit 2 (POD1) was scheduled between 18 to 34 hours following conclusion of surgery on Day 0. All assessments done on POD1 were done prior to Randomization to ensure eligibility. Note: Women-of-childbearing-potential (WOCBP) were eligible for enrollment if they had a negative urine pregnancy test on POD1 prior to Randomization and they agreed to abstinence from sexual activity or use of highly effective method of contraception.
[4] Visit 5 (POD15) occurred on the day after the subject completed the study drug administration for 14 days. Women-of-childbearing-potential had a urine pregnancy test.
[5] Visit 6 (POD22) was the last visit for subjects who completed the study. Subjects who were withdrawn early had the Visit 6 assessments and a urine pregnancy test performed prior to their release from the study.
[6] Included assessments of ocular pain and irritation.
[7] Ocular inflammation assessment using ACC count, anterior chamber flare grade, bulbar conjunctival injection, sclera - ciliary flush and corneal edema.
[8] IOP was assessed at each visit, when possible, within ± 2 hours of the IOP assessment time at Visit 1.
[9] The first dose of study drug was instilled into the study eye at the clinic visit under supervision of clinic staff. The second dose on POD1 could be administered at home. Subjects who were rescued did not continue to instill study drug or receive further diary cards but remained in the study to complete the procedures/assessments through Visit 6 (POD22).
[10] The site contacted the subject via the subject's preferred method on POD14 to remind him/her not to instill study drug on POD15 and to bring the bottle of study drug and the dosing diary back to the site at the POD15 visit.
[11] Concomitant medications used for rescue were reported in the eCRF.
[12] AEs and Concomitant Medications were only recorded on Day 0 if they resulted in disqualification (i.e., screen failure) of the subject; otherwise, the AEs and Concomitant Medications applicable to Day 0 were recorded when the subject returned for Visit 2 (POD1).
[13] Any AEs reported to the site during the POD14 contact were recorded in the source documents. Further assessment of any reported AEs could require an Unscheduled Visit on POD14 if medically significant or they could be assessed, as appropriate, during Visit 5 (POD15).

Source: Table 4 of Study 301 CSR.

Table 22: Study 302 Schedule of Events

PROCEDURE/ASSESSMENTS [1]	Visit 1 Screening (Day -28 to -1)	Surgery[2] Day 0	Visit 2 POD1[3]	Visit 3 POD4 (±1 Day)	Visit 4 POD8 (±1 Day)	Contact POD14	Visit 5 POD15 (+1 Day)[4]	Visit 6 POD22 (±2 Days)[5]	Reminders (~POD50 & ~POD78)	Visit 7 POD85 (±4 Days)[6]
ICF, Demography, Medical History	X									
Determine Eligibility, Review Inclusion/Exclusion Criteria	X		X							
Urine pregnancy test only for women of child-bearing potential			X				X			
Ocular Symptoms Assessment [7]	X		X	X	X		X	X		
ETDRS Visual Acuity	X		X	X	X		X	X		
Slit-lamp Biomicroscopy [8]	X		X	X	X		X	X		
Indirect Ophthalmoscopy (dilated)	X							X		
IOP (Goldmann applanation tonometry) [9]	X		X	X	X		X	X		
Corneal Endothelial Cell Parameters [10]	X							X		X
Randomization			X							
Dispense Study Drug			X							
Study Drug Dosing BID for 14 days (POD1 to POD14) [11]			X	X	X	X				
Dispense Diary Card (with instructions for completion)			X	X	X					
Contact Subject [12]						X			X	
Collect Study Drug							X			
Collect and Check Diary Cards for Accuracy and Compliance				X	X		X			
AEs [7] and Concomitant Medications [13]	X	X [14]	X	X	X	X [15]	X	X		X [15]

Abbreviations: POD=post-operative day; ICF=Informed Consent; EDTRS= Early Treatment Diabetic Retinopathy Study; IOP=Intra-Ocular Pressure; BID=twice daily; AEs=Adverse Events

[1] Ophthalmic assessments were performed in the study eye only at Visits 2-5 and Visit 7, and on both eyes at Visit 1 (Screening) and at Visit 6 (POD22) or at subject Early Termination/Withdrawal. In the Sub-study, corneal endothelial cell parameters were measured in both eyes at Screening and in the study eye only at Visit 6 (POD22) and Visit 7 (POD85).

[2] Surgery occurred between 1 to 28 days after Visit 1 (Screening), preferably in the morning. If, due to unexpected events, surgery was postponed and would occur > 28 days past the Screening visit, the Study Medical Monitor was contacted to discuss which, if any, of the screening procedures should be repeated. Subjects were determined to be a suitable candidate for surgery during a pre-surgery medical assessment, where the routine medication list prescribed by the cataract surgeon was reviewed to rule out prohibited medications.

[3] Visit 2 (POD1) was scheduled between 18 to 34 hours following conclusion of surgery on Day 0. All assessments done on POD1 were done prior to Randomization to ensure eligibility. Note: Women-of-childbearing-potential were eligible for enrollment if they had a negative urine pregnancy test on POD1 prior to Randomization and they agreed to abstinence from sexual activity or use of highly effective method of contraception.

[4] Visit 5 (POD15) occurred on the day after the subject completed the study drug administration for 14 days. Women-of-childbearing-potential had a urine pregnancy test.

[5] Visit 6 (POD22) was the last visit for subjects participating in the Main Study only. Subjects who were withdrawn early had the Visit 6 assessments and a urine pregnancy test performed prior to their release from the study.

Source: Table 4 of Study 301 CSR.

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/s/

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