

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial #: NDA 210565/Original

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Indication(s): Treatment of post-operative inflammation and pain following ocular surgery

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1 EXECUTIVE SUMMARY

This review evaluates the statistical evidence of efficacy for Inveltys (loteprednol etabonate [LE] ophthalmic suspension 1%), dosed twice daily (BID), for the treatment of post-operative inflammation and pain following ocular surgery. LE as a corticosteroid is marketed in the United States (US) for over 20 years and LE 0.5% is approved under the trade name Lotemax for the same indication.

This review focuses on the two Phase 3, randomized, multicenter, double-masked, vehicle-controlled studies (Studies 001 and 005) with similar designs. Study 001 randomized 380 subjects to receive either LE 0.25% four times a day (QID) (N = 129), LE 1% BID (N = 125), vehicle QID (N = 60), or vehicle BID (N = 66) for 2 weeks. Study 005 randomized 520 subjects to receive either LE 1% BID (N = 261) or the vehicle BID (N = 259) for 2 weeks. The primary endpoints in both studies were as follows:

- The proportion of the subjects with complete resolution (grade 0) of anterior chamber (AC) cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15
- The proportion of the subjects with complete resolution (grade 0) of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15

The two primary endpoints were tested sequentially in both studies to maintain an overall Type I error of 0.05. In Study 001, the two vehicle groups were pooled for all efficacy analyses.

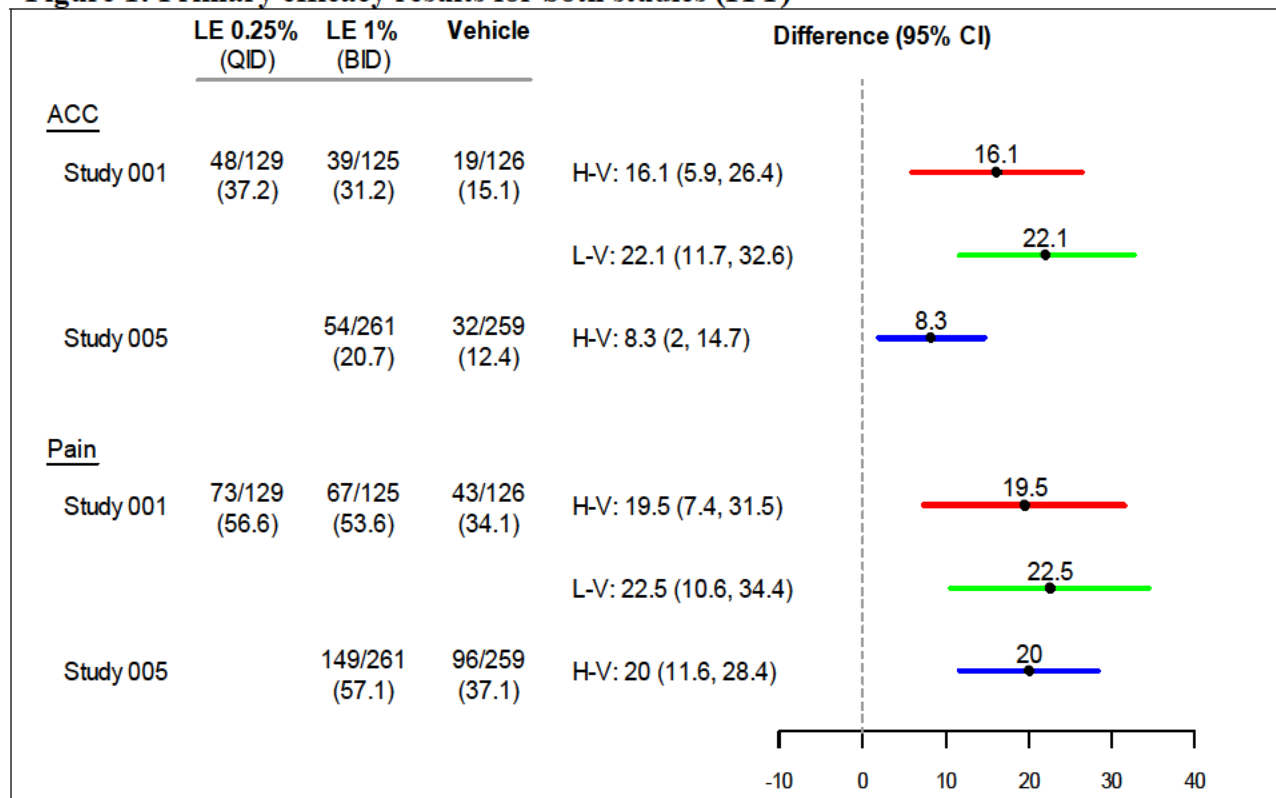
Figure 1 below displays the efficacy results for the primary endpoints. Study 001 demonstrated superiority of both LE groups to the vehicle for both primary endpoints. The proportions of subjects with complete resolution of AC cells at Day 8 and maintained through Day 15 were 37.2%, 31.2% and 15.1% in the LE 0.25% QID, LE 1% BID, and vehicle groups, respectively; the treatment difference was 22.1% (95% confidence interval [CI]: 11.7%, 32.6%) between the LE 0.25% QID and vehicle and was 16.1% (95% CI: 5.9%, 26.4%) between the LE 1% BID and vehicle. The proportions of subjects with complete resolution of ocular pain at Day 8 and maintained through Day 15 were 56.6%, 53.6% and 34.1% in the LE 0.25% QID, LE 1% BID, and vehicle groups, respectively; the treatment difference between the LE 0.25% QID and vehicle was 22.5% (95% CI: 10.6%, 34.4%) and between the LE 1% BID and vehicle was 19.5% (95% CI: 7.4%, 31.5%).

Study 005 also demonstrated superiority of LE 1% BID to the vehicle for both primary endpoints. The proportions of subjects with complete resolution of AC cells at Day 8 and maintained through Day 15 were 20.7% and 12.4% in the LE 1% BID and vehicle groups, respectively; the treatment difference was 8.3% (95% CI: 2%, 14.7%). The proportion of subjects with complete resolution of ocular pain at Day 8 and maintained through Day 15 were 57.1% and 37.1% in the LE 1% BID and vehicle groups, respectively; the treatment difference was 20% (95% CI: 11.6%, 28.4%).

The significant primary results were supported by the analysis of the primary endpoints in the Per-Protocol population and by the analyses of majority of the non-primary endpoints.

In conclusion, the results of the two studies provide sufficient evidence of efficacy for LE 1% BID for the treatment of post-operative inflammation and pain following ocular surgery.

Figure 1: Primary efficacy results for both studies (ITT)



Source: KPI-121-001 CSR, Table 16 and KPI-121-005 CSR Table 15

Note: ITT = Intent-to-Treat population, which included all randomized subject. ACC = primary endpoint of AC cells. Pain = primary endpoint of ocular pain. H = LE 1% BID. L = LE 0.25% QID. Missing data was treated as failures.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

According to the submission, intraocular inflammation is an anticipated sequela of ocular surgery and is manifested principally as conjunctival erythema, corneal edema, ciliary flush, and the presence of inflammatory cells in the aqueous humor. In the United States (US), topical corticosteroids are routinely prescribed after ocular surgery for 2 weeks to inhibit the inflammatory response.

Loteprednol etabonate (LE) as an ester-based corticosteroid is marketed in the US for over 20 years. LE 0.5% was approved by the US Food and Drug Administration (FDA) to treat the post-operative pain and inflammation under the trade name Lotemax 0.5%. The marketed dosing

frequency of Lotemax 0.5% is four times daily (QID), and three different dosage forms have been approved: suspension (NDA 20583 and 20841; approved in 1998), ointment (NDA 200738; approved in 2011), and gel (NDA 202872; approved in 2012). In addition, LE 0.2% was approved under the trade name Alrex (NDA 20803; approved in 1998) for the temporary relief of signs and symptoms of seasonal allergic conjunctivitis.

The proposed drug product, Inveltys, is LE 1%, dosed twice daily (BID) for 2 weeks. Inveltys utilizes a novel, proprietary drug-delivery technology known as mucus penetrating particles (MPP). According to the applicant, MPP allows for prolonged drug presence on the ocular surface and increased drug penetration into ocular tissues, and thus supports the reduced dosing frequency of LE 1% BID compared with marketed formulation of Lotemax 0.5% QID.

2.1.2 History of Drug Development

The applicant first submitted its clinical development program for Inveltys to Division of Transplant and Ophthalmology Products (DTOP) on April 04, 2013 via a pre-IND meeting (IND 117192). In the meeting package, the applicant proposed to conduct two pivotal studies. The first study was planned to compare two dosing regimens (0.25% QID and 1.0% BID) to the vehicle controls (vehicle QID and vehicle BID); the second study was planned to compare a single dosage identified in the first study to the vehicle. The applicant proposed to pool the two vehicle groups in the first study. DTOP agreed on the pooling only if the two vehicle groups were not statistically different. DTOP also recommended that the primary analysis population be the Intent-to-Treatment (ITT) population, which included all randomized subjects, and subjects received rescue therapy be treated as failures. The full protocol for the first pivotal study (KPI-121-C001, also referred to as Study 001) was subsequently submitted to DTOP on December 19, 2013 as a part of the initial IND.

On June 15, 2015, a Type C meeting was held. At the meeting, the applicant reported that Study 001 was completed and asked if Study 001 as the sole pivotal study could be adequate to support a 505(b)2 NDA filing. DTOP disagreed and stated that it expected an additional pivotal study. On May 31, 2016, the applicant submitted the protocol for the second pivotal Study (KPI-121-C-005, also referred to as Study 005) comparing LE 1% BID to the vehicle. LE 1% BID was selected over 0.25% QID because LE 1% BID yielded lower adverse event (AE) incidence than LE 0.25% QID in Study 001 and because the applicant believes that a BID product could meaningfully benefit the patients treated with multiple medicines following ocular surgery.

On May 02, 2017, a Type B pre-NDA meeting was held to obtain agreement on the format and content of clinical and nonclinical modules of NDA submission. At the meeting, DTOP agreed that the applicant could provide analysis datasets that were not in the standardized Analysis Data Model (ADaM) format.

2.1.3 Specific Study Reviewed

This review focuses on the two Phase 3 studies: Studies 001 and 005. Table 1 below contains a brief summary of these two studies.

Table 1: Summary of Study 001 and Study 005

Trial ID	Design*	Treatment /Sample Size	Primary Endpoint /Analysis	Applicant's primary analysis results
Study 001 /Primary objective: To evaluate the efficacy and safety of LE 1% BID and 0.25% QID as compared to the pooled vehicle	MC, R, DB, VC trial	• LE 1% BID / N=125 • LE 0.25% QID / N=129 • Vehicle BID / N=66 • Vehicle QID / N=60	• Proportion of study eyes with complete resolution of anterior chamber (AC) cells (grade = 0) at Day 8 maintained through Day 15 with no rescue medication prior to Day 15 • Proportion of study eyes with pain grade = 0 at Day 8 maintained through Day 15 with no rescue medication prior to Day 15	• Superiority of both LE 1% BID (31.2%) and 0.25% QID (37.2%) to the pooled vehicle (15.1%) was demonstrated for the primary endpoint of AC cells (p-values = 0.0024 and < 0.0001, respectively) • Superiority of both LE 1% BID (53.6%) and 0.25% QID (56.6%) to the pooled vehicle (34.1%) was demonstrated for the primary endpoint of ocular pain (p-values = 0.0019 and 0.0003, respectively)
Study 005 /Primary objective: To evaluate the efficacy and safety of LE 1% BID as compared to the vehicle BID	MC, R, DB, VC trial	• LE 1% BID / N=261 • Vehicle BID / N=259	• Proportion of study eyes with pain grade = 0 at Day 8 maintained through Day 15 with no rescue medication prior to Day 15	• Superiority of LE 1% BID (20.7%) to the vehicle (12.4%) was demonstrated for the primary endpoint of AC cells (p-value = 0.0105) • Superiority of LE 1% BID (57.1%) to the vehicle (37.1%) was demonstrated for the primary endpoint of ocular pain (p-value < 0.0001)

** MC: multi-center, R: randomized, DB: double-blind, VC: vehicle controlled.

2.2 Data Sources

The data sources for this review included clinical study reports, protocols, statistical analysis plan (SAP), and datasets. All data sources were electronic submitted and are located at <\\CDSESUB1\evsprod\NDA210565\0001>, <\\CDSESUB1\evsprod\NDA210565\0004>, and <\\CDSESUB1\evsprod\NDA210565\0011>. The latter two links are for the analysis datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The original submission included the SDTM and raw CRF datasets but not an analysis dataset. The define files in the original submission were not sufficiently detailed. Upon our information request, the applicant submitted the analysis dataset along with a new define file on November 28, 2017. Although the analysis dataset was not in a standardized format, the dataset was of sufficient quality for this reviewer to perform efficacy analyses. On January 19, 2018, the

applicant resubmitted the analysis dataset with additional details on how each variable was derived.

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 various non-primary analyses.

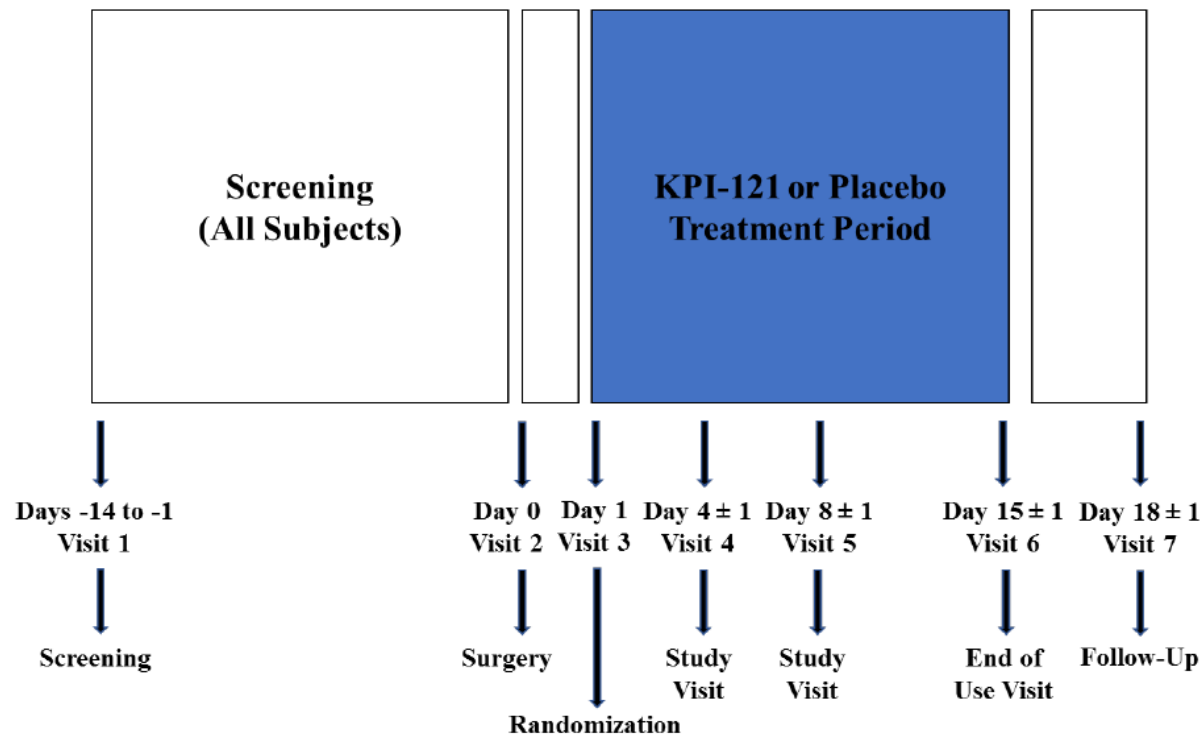
3.2.1 Study Design and Endpoints

i) Study Design

Studies 001 and 005 were both randomized, double-masked, vehicle-controlled Phase 3 studies conducted in the US. In Study 001, the first subject was randomized on (b) (6) and the last subject completed the trial on (b) (6). In Study 005, the first subject was randomized on (b) (6) and the last subject completed the study on (b) (6). These two studies share similar designs with the main difference being that Study 001 compared two dosage of LE (0.25% QID and 1% BID) to the pooled group of vehicles dosed QID and BID (hereinafter referred to as vehicle), while Study 005 compared only the LE 1% BID to the vehicle.

Both studies had seven study visits: screening, Day 0 (surgery), Day 1 (randomization), Day 4, Day 8, Day 15 (end of treatment), and Days 18 (follow up). At screening, subjects need to meet the following key inclusion criteria: 1) at least 18 years of age, 2) candidates for a routine, uncomplicated cataract surgery, and 3) at least 20/200 in Snellen Distance visual acuity, which is equivalent to ETDRS best corrected visual acuity (BCVA) of 35 letters, in the study eye. The study eye was defined as the eye received surgery and each subject has one study eye. At Day 1, to be qualified for randomization, subjects need to have undergone cataract surgery and had AC cell grade ≥ 2 . Figure 2 below displays the study design for both studies. A detailed schedule of study assessments is shown in Appendix 1.

Figure 2: Study design for Studies 001 and 005



Source: Summary of Clinical Efficacy, Figure 1.

Note: KPI-121 is the applicant's internal product name for Inveltys.

In Study 001, 380 subjects were randomized from 24 sites to one of the following treatment groups in a 2:2:1:1 ratio: LE 0.25% QID, LE 1% BID, vehicle QID, and vehicle BID. In Study 005, 520 subjects were randomized from 35 sites to receive either LE 1% BID or vehicle BID in a 1:1 ratio. Randomization in both studies was stratified by study site.

Subjects could also receive rescue therapy if they did not respond adequately to the study treatment anytime during the study at the investigator's discretion. The choice of rescue therapy was also at the investigator's discretion. However, if any non-anti-inflammatory medications were designated as rescue medication, this designation was disregarded prior to locking the database.

ii) Study Endpoints

The two primary endpoints in both studies were:

- The proportion of study eyes with complete resolution (grade 0) of AC cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15
- The proportion of study eyes with complete resolution (grade 0) of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15

Table 2 shows the grade of AC cell and ocular pain.

Table 2: AC cell grade and ocular pain grade

AC cell	Ocular pain
0 = No cells seen	0 = None
1 = 1 to 5 cells	1 = Minimal
2 = 6 to 15 cells	2 = Mild
3 = 16 to 30 cells	3 = Moderate
4 = Greater than 30 cells	5 = Severe

Source: Summary of Clinical Efficacy, page 11-12

The SAP-defined secondary endpoints in Study 001 included the proportion of study eyes with complete resolution of both AC cells (grade = 0) and ocular pain (grade = 0) at Days 8 with no rescue medication prior to Day 8, the proportion of study eyes with complete resolution of both AC cells and ocular pain at Day 15 with no rescue medication prior to Day 15, and composite mean of AC cell and pain (average of AC cell grade and pain grade) at each visit.

The SAP-defined secondary endpoints in Study 005 included the proportions of study eyes with complete resolution of ocular pain at Day 4 and maintained through Day 15 with no rescue medication prior to Day 15, the proportion of study eyes with complete resolution of AC flare (grade = 0) at Day 4 and maintained through Day 15 with no rescue medication prior to Day 15, and change from baseline in mean AC cell grade at Day 4.

3.2.2 Statistical Methodologies

i) Analysis Population

Three analysis populations were defined in both studies: ITT population, which included all randomized subjects, Per-Protocol (PP) population, which included ITT subjects who completed the treatment period without major protocol deviation, and safety population, which included all subjects who received at least 1 dose of the study drug and from whom at least 1 safety assessment was obtained after randomization.

ii) Efficacy Analysis

The primary efficacy analyses in both studies were performed on the ITT population. In Study 001, the applicant conducted a chi-square test to test the two primary endpoints in the following hierarchical order to control the Type I error (α) at the 0.05 level: LE 0.25% QID vs. vehicle with regard to the AC cells endpoint, LE 1% BID vs. vehicle with regard to the AC cells endpoint, LE 1% BID vs. vehicle with regard to the pain endpoint, and LE 0.25% QID vs. vehicle with regard to the pain endpoint. In Study 005, the chi-square test was also used to test the two primary endpoints hierarchically: AC cell endpoint first and pain endpoint second. For analyses of the primary endpoints, missing values were considered as treatment failures. The SAP also stated that if the amount of missing data is less than 5%, no sensitivity analysis would be conducted.

For analyses of the three SAP-defined secondary endpoints in Study 005, although the SAP stated that these endpoints would be tested at $\alpha = 0.0167$ (0.05/3), the applicant actually

presented the results for these endpoints based on $\alpha = 0.05$. In this review, all non-primary analyses results will be presented based on $\alpha = 0.05$.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Table 3 shows a summary of subject disposition by study and by treatment group. In Study 001, 380 subjects were randomized to the LE 0.25% QID (N = 129), LE 1% BID (N = 125), and vehicle (N = 126) groups, respectively. Only a small percentage of randomized subjects in all three treatment groups (1.6%, 0.8%, and 1.6% in the LE 0.25% QID, LE 1% BID, and vehicle groups, respectively) discontinued early from the study. No subject was discontinued due to an AE.

In Study 005, 520 subjects were randomized to the LE 1% BID (N = 261) and vehicle (N = 259) groups, respectively. Similar to Study 001, the percentage of randomized subjects who discontinued early from the study was small (1.1% in the LE 1% BID and 1.9% in the vehicle). Only 1 subject (0.4%) discontinued from the study due to AE.

Table 3: Subject disposition (all randomized subjects)

	Study 001			Study 005	
	0.25% QID (N=129)	1% BID (N=125)	Vehicle (N=126)	1% BID (N=261)	Vehicle (N=259)
ITT Population	129 (100%)	125 (100%)	126 (100%)	261 (100%)	259 (100%)
PP Population	126 (97.7%)	123 (98.4%)	124 (98.4%)	251 (96.2%)	251 (96.9%)
Safety Population	129 (100%)	125 (100%)	126 (100%)	261 (100%)	259 (100%)
Discontinued early from the study	2 (1.6%)	1 (0.8%)	2 (1.6%)	3 (1.1%)	5 (1.9%)
Adverse Event	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Withdrawal by Subject	2 (1.6%)	0 (0%)	1 (0.8%)	1 (0.4%)	4 (1.5%)
Lost to Follow-Up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Physician	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Other	0 (0%)	1 (0.8%)	0 (0%)	1 (0.4%)	0 (0%)
Completed Study	127 (98.4%)	124 (99.2%)	124 (98.4%)	258 (98.9%)	254 (98.1%)

Source: KPI-121-001 CSR, Tables 7 and 9 and KPI-121-005, Tables 7 and 9

Note: all subjects discontinued during the treatment period and no subject discontinued during the follow-up period.

3.2.3.2 Demographic and Baseline Characteristics

In both studies, demographic and baseline characteristics were generally balanced across treatment groups in both studies, except that in Study 005, the baseline ocular pain grade was slightly higher in the vehicle group than that in the LE 1% BID group (Table 4).

Table 4: Demographic and baseline characteristics (ITT)

	Study 001			Study 005	
	0.25% QID (N=129)	1% BID (N=125)	Vehicle (N=126)	1% BID (N=261)	Vehicle (N=259)
Age at randomization (years)					
Mean (SD)	68.4(9.7)	67.9(9.4)	69.8(7.3)	67.5(8.7)	69.3(8.5)
Median	69	68	70	69	70
Min, Max	34, 88	41, 89	52, 87	38, 89	40, 90
Age group (years)					
< 69	58(45%)	64(51.2%)	53(42.1%)	129(49.4%)	105(40.5%)
≥ 69	71(55%)	61(48.8%)	73(57.9%)	132(50.6%)	154(59.5%)
Sex					
Female	73(56.6%)	75(60%)	78(61.9%)	144(55.2%)	144(55.6%)
Male	56(43.4%)	50(40%)	48(38.1%)	117(44.8%)	115(44.4%)
Race					
White	96(74.4%)	91(72.8%)	87(69%)	206(78.9%)	207(79.9%)
Non-White	33(25.6%)	34(27.2%)	39(31%)	53(20.3%)	51(19.7%)
Ethnicity					
Hispanic or Latino	8(6.2%)	15(12%)	13(10.3%)	38(14.6%)	36(13.9%)
NOT Hispanic or Latino	121(93.8%)	110(88%)	113(89.7%)	223(85.4%)	223(86.1%)
Baseline AC cell grade					
Mean (SD)	2.3(0.5)	2.3(0.5)	2.3(0.4)	2.3(0.5)	2.3(0.5)
Median	2	2	2	2	2
Min, Max	2, 3	2, 4	2, 3	2, 4	2, 4
Baseline AC flare grade					
Mean (SD)	0.9(0.6)	0.9(0.6)	0.9(0.6)	0.9(0.7)	0.9(0.6)
Median	1	1	1	1	1
Min, Max	0, 2	0, 2	0, 2	0, 3	0, 2
Baseline ocular pain grade					
Mean (SD)	1(0.9)	1.1(1.1)	1(1.1)	1.1(1.1)	1.3(1.1)
Median	1	1	1	1	1
Min, Max	0, 4	0, 4	0, 5	0, 5	0, 5

Source: KPI-121-001 CSR, Tables 14.1.4.1, 14.2.1.5.1, 14.2.1.6.1, 14.2.1.7.1 and KPI-121-005, Tables 14.1.4.1, 19, 14.2.1.4, 14.2.1.5

Note: SD stands for standard deviation. In Study 005, 2 subjects in the LE 1% BID group and 1 subject in the vehicle group had unknown race. According to KPI-121-001 CSR, iris color was noted in the SAP as a planned demographic. However, this was not collected during the both studies.

3.2.4 Results and Conclusion

3.2.4.1 Primary Efficacy Results

In Study 001, the two vehicle groups (BID and QID) were pooled for all efficacy analyses because the two groups had similar results for both primary endpoints (Appendix 2).

Figure 1 in Section 1 presents the primary efficacy results in the ITT population for both studies. Study 001 demonstrated superiority of both LE 0.25 QID and 1% BID to the vehicle for both primary endpoints. Complete resolution of AC cells at Day 8 and maintained through Day 15 were achieved by 37.2%, 31.2%, and 15.1% of subjects in the LE 0.25% QID, LE 1% BID, and the vehicle groups, respectively. The treatment difference in the primary endpoint of AC cells was 22.1% (95% CI: 11.7%, 32.6%) between the LE 0.25% QID and the vehicle and was 16.1% (95% CI: 5.9%, 26.4%) between the LE 1% BID and the vehicle. Complete resolution of ocular

pain at Day 8 and maintained through Day 15 was achieved by 56.6%, 53.6%, and 34.1% of subjects in the LE 0.25% QID, LE 1% BID, and vehicle, respectively. The treatment difference in the primary endpoint of pain was 22.5% (95% CI: 10.6%, 34.4%) between the LE 0.25% QID and the vehicle and was 19.5% (95% CI: 7.4%, 31.5%) between the LE 1% BID and the vehicle.

Study 005 also showed superiority of LE 1.0 % BID to the vehicle for both primary endpoints. Complete resolution of the AC cells at Day 8 and maintained through Day 15 was achieved by 20.7% and 12.4% of subjects in the LE 1% BID and the vehicle, respectively. The treatment difference (LE 1% BID - vehicle) in the primary endpoint of AC cells was 8.3% with a 95% CI from 2% to 14.7%. Complete resolution of pain at Day 8 and maintained through Day 15 was achieved by 57.1% and 37.1% of subjects in the LE 1% BID and the vehicle, respectively. The estimated treatment difference (LE 1% BID - vehicle) in the primary endpoint of pain was 20% with a 95% CI from 11.6% to 28.4%.

The above primary results in the ITT population were supported by the analyses of both primary endpoints in the PP population (see Appendix 3). The applicant did not conduct any sensitivity analyses for missing data because the amount of missing was less than 5%.

Use of rescue medication was also reported by the applicant (Table 5). In both studies, subjects in the LE groups received less rescue medication than subjects in the vehicle group at Days 4, 8, and 15.

Table 5: Use of rescue medication by visit (ITT; OBS)

	Study 001			Study 005	
	0.25% QID	1% BID	Vehicle	1% BID	Vehicle
Day 4	0/129 (0%)	0/125 (0%)	1/126 (0.8%)	3/258 (1.2%)	6/258 (2.3%)
Day 8	7/129 (5.4%)	8/125 (6.4%)	27/125 (21.6%)	18/258 (7.0%)	53/257 (20.6%)
Day 15	15/128 (11.7%)	14/124 (11.3%)	48/125 (38.4%)	45/258 (17.4%)	95/254 (37.4%)

Source: KPI-121-001 CSR, Table 14.1.9.1 and KPI-121-005, Table 14.1.8.1

Note: OBS = observed data

3.2.4.2 Results for Non-Primary Efficacy Endpoints

This section presents the efficacy results for the following non-primary efficacy endpoints:

- Complete resolution of both AC cells and pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15
- Complete resolution of AC flare at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15
- Complete resolution of AC cells at Day 4 and maintained through Day 15 with no rescue medication prior to Day 15

- Complete resolution of ocular pain at Day 4 and maintained through Day 15 with no rescue medication prior to Day 15
- Complete resolution of AC flare at Day 4 and maintained through Day 15 with no rescue medication prior to Day 15
- Complete resolution of AC cells at Days 4, 8, and 15 (regardless of the maintenance) with no rescue medication prior to the corresponding visit
- Complete resolution of ocular pain at Days 4, 8, and 15 (regardless of the maintenance) with no rescue medication prior to the corresponding visit
- Complete resolution of AC flare at Days 4, 8, and 15 (regardless of the maintenance) with no rescue medication prior to the corresponding visit
- Mean reduction from baseline in AC cell grade, ocular pain grade, composite mean of AC cell and ocular pain, and AC flare grade

Among the above non-primary endpoints, the applicant considered complete resolution of ocular pain at Day 4 and maintained through Day 15, complete resolution of AC cells at Day 15, and complete resolution of ocular pain at Day 15 as the key non-primary endpoints. Note that the applicant did not pre-specify these three endpoints as key non-primary endpoints in the protocol or SAP, but presented their results in the Summary of Clinical Efficacy and Clinical Overview as the key non-primary results [REDACTED] ^{(b) (4)}. The efficacy results for these three endpoints are summarized separately in Sections 3.2.4.2.2 and 3.2.4.2.3 and together in Mock-up Figures 1 and 2 in Section 5.4.

3.2.4.2.1 Complete Resolution at Day 8 and Maintained through Day 15 with No Rescue Medication prior to Day 15 for 1) Both AC Cells and Ocular Pain and 2) AC Flare

As shown in Table 6 below, in Study 001, there were statistically significant treatment differences between the two LE groups and vehicle for the endpoint complete resolution of both AC cells and ocular pain at Day 8 and maintained through Day 15 and for the endpoint of complete resolution of AC flare at Day 8 and maintained through Day 15. In Study 005, the significant treatment differences between the LE 1% BID and the vehicle were also observed for these two endpoints.

Table 6: Complete resolution at Day 8 and maintained through Day 15 for 1) both AC cells and pain and 2) AC flare (ITT)

Endpoint	Endpoint	LE 0.25% QID	LE 1% BID	Vehicle	LE 0.25% QID - vehicle		LE 1% BID - vehicle	
		n/N (%)	n/N (%)	n/N (%)	Difference (95% CI)	P-value	Difference (95% CI)	P-value
Study 001	Both AC cells and pain	34/129 (26.4%)	28/125 (22.4%)	12/126 (9.5%)	16.8% (7.7%, 26%)	<0.001	12.9% (3.9%, 21.8%)	0.0053
	AC flare	93/129 (72.1%)	82/125 (65.6%)	52/126 (41.3%)	30.8% (19.3%, 42.4%)	0	24.3% (12.4%, 36.3%)	<0.001
Study 005	Both AC cells and pain	NA	39/261 (14.9%)	18/259 (6.9%)	NA		8% (2.7%, 13.3%)	0.0035
	AC flare		159/261 (60.9%)	87/259 (33.6%)			27.3% (19.1%, 35.6%)	0

Source: KPI-121-001 CSR, Table 14.2.3.1 and reviewer's analyses (colored in blue)

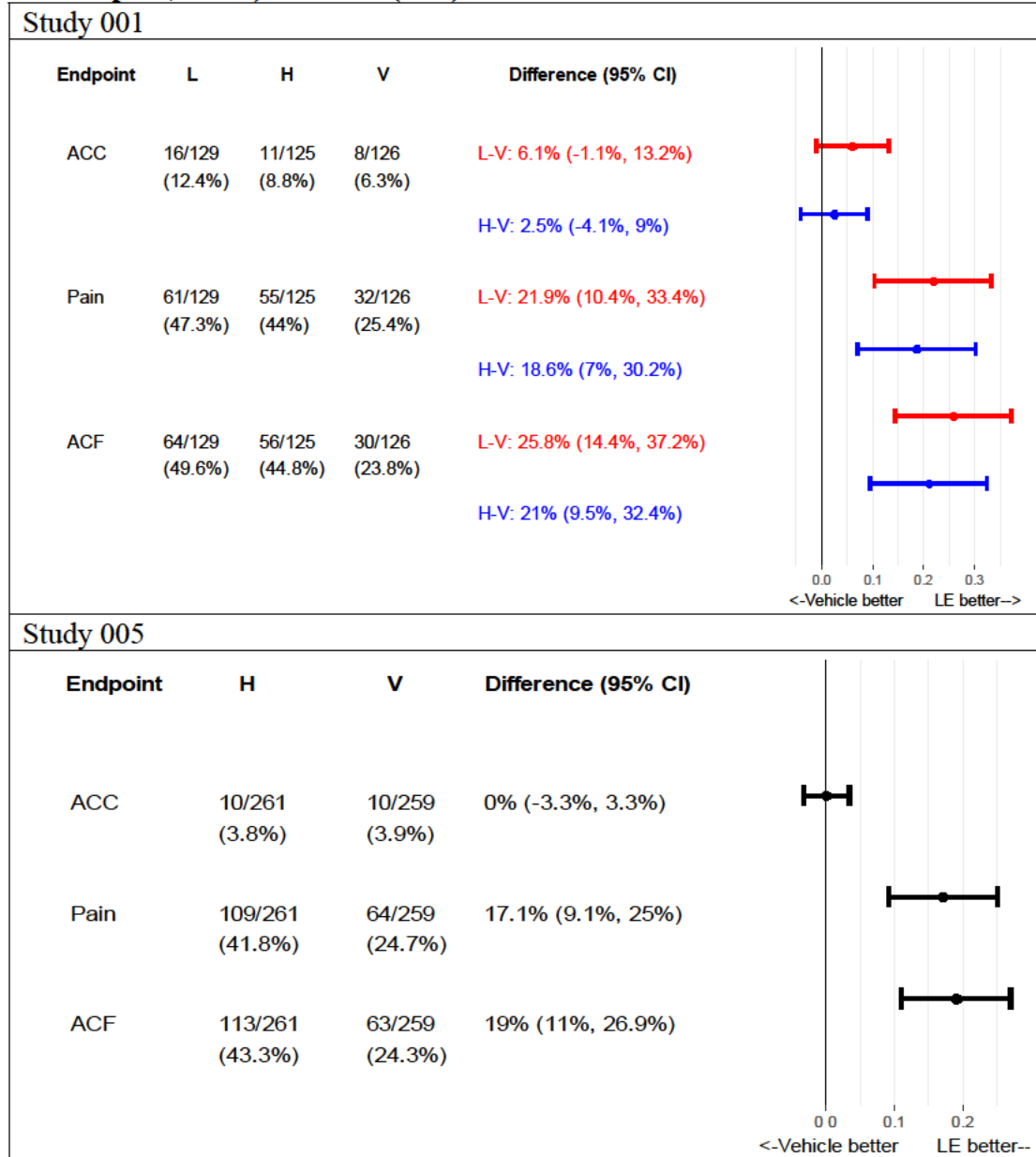
Note: Missing observations were treated as failures.

3.2.4.2.2 Complete Resolution at Day 4 and Maintained through Day 15 with No Rescue Medication prior to Day 15 for 1) AC Cells, 2) Ocular Pain, and 3) AC Flare

As shown in Figure 3 below, in Study 001, the treatment differences were statistically significant between the two LE groups and the vehicle for the endpoint of complete resolution of ocular pain at Day 4 and maintained through Day 15 and for the endpoint of complete resolution of AC flare at Day 4 and maintained through Day 15. For the endpoint of complete resolution of AC cells at Day 4 and maintained through Day 15, neither the LE 0.25% QID nor the LE 1% BID demonstrated significant treatment effect over the vehicle.

Similar trend was observed in Study 005. The treatment differences between the LE 1% BID and the vehicle were statistically significant for the endpoints of complete resolution of ocular pain and complete resolution of AC flare at Day 4 and maintained through Day 15, but not for the endpoint of complete resolution of AC cells at Day 4 and maintained through Day 15.

Figure 3: Complete resolution at Day 4 and maintained through Day 15 for 1) AC cells, 2) ocular pain, and 3) AC flare (ITT)



Source: KPI-121-001 CSR, Table 14.2.3.4 and KPI-121-005, Tables 14.2.3.1, 14.2.3.2, 14.2.3.3, and reviewer's analysis for ACC and ACF endpoint in Study 001

Note: ACC = AC cell, ACF = AC flare, L = LE 0.25% QID, H = LE 1% BID, and V = vehicle

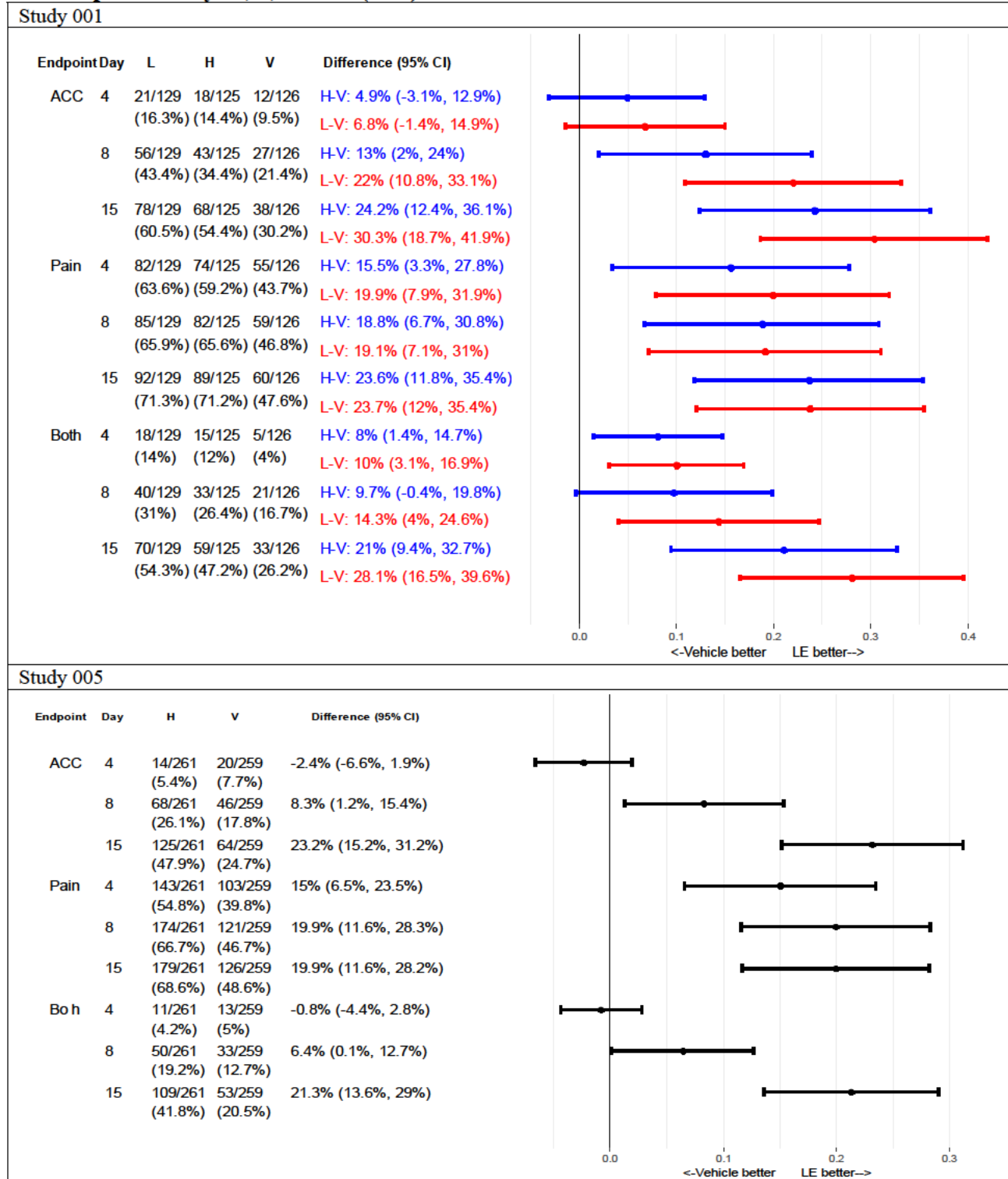
3.2.4.2.3 Complete Resolution at Days 4, 8, and 15 regardless of the maintenance for: 1) AC Cells, 2) Ocular Pain, and 3) Both AC cells and Ocular Pain

In Study 001, the two LE groups had statistically higher percentages of subjects who achieved complete resolution of AC cells than the vehicle at Days 8 and 15, but not at Day 4. The two LE groups also had statistically higher percentages of subjects who achieved complete resolution of

ocular pain at Days 4, 8, and 15. For the endpoint of complete resolution of both AC cells and ocular pain, the lower dosage group, LE 0.25% QID, had significantly higher percentages of subjects who achieved this endpoint than the vehicle at all three visits; the LE 1% BID group had significantly higher percentages of subjects who achieved this endpoint than the vehicle only at Days 4 and 15 (Figure 4).

In Study 005, the LE 1% BID group had statistically significantly higher percentages of subjects who achieved the complete resolution of ocular pain at Days 4, 8, and 15 than the vehicle. The LE 1% BID group also had significantly higher percentages of subjects who achieved the complete resolution of AC cells and who achieved complete resolution of both AC cells and ocular pain at Days 8 and 15, but not at Day 4.

Figure 4: Complete resolution of 1) AC cells, 2) ocular pain, and 3) both AC cells and ocular pain at Days 4, 8, and 15 (ITT)



Source: KPI-121-001 CSR, Tables 14.2.1.3, 14.2.1.4, 14.2.3.2, and 14.2.3.3, KPI-121-005, Tables 14.2.4.1 and 14.2.4.2 and reviewer's analyses (Study 001: ACC and pain endpoints at Days 4 and 8, both ACC and pain endpoint at Day 4; Study 005: ACC and pain endpoints at Days 4 and 8, both ACC and pain endpoint at Days 4, 8, and 15)

Note: ACC = AC cells, ACF = AC flare, L = LE 0.25% QID, H = LE 1% BID, and V = vehicle

3.2.4.2.4 Mean Reductions from Baseline in AC Cell Grade, Ocular Pain Grade, Composite Mean of AC Cell and Pain, and AC Flare Grade by Visit

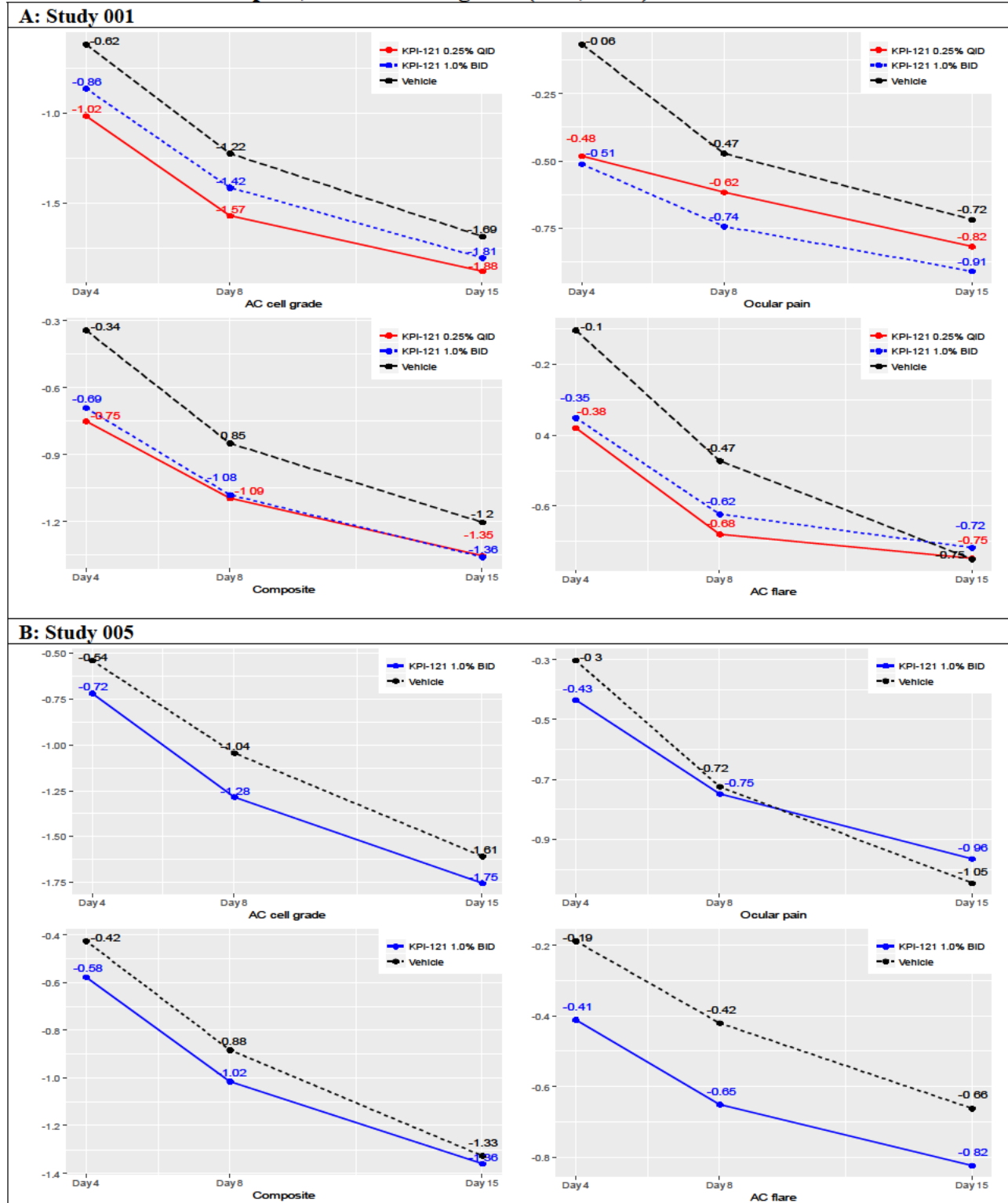
The applicant also reported the mean reductions from baseline in AC cell grade, ocular pain grade, composite mean of AC cell and ocular pain, and AC flare grade at Days 4, 8, and 15 (Figure 5). All observed data were used regardless of the use of rescue medication. In Study 001, the two LE groups had consistently greater mean reductions from baseline in AC cell grade, ocular pain grade, and composite mean score of AC cell and ocular pain than the vehicle at Days 4, 8, and 15. The two LE groups also had greater mean reductions from baseline in AC flare grade than the vehicle at Days 4 and 8, but not at Day 15. At Day 15, the AC flare grade was similar among three treatment groups.

In Study 005, the LE 1% BID group had consistently greater mean reductions from baseline in AC cell grade, composite mean score of AC cell and ocular pain, and AC flare grade than the vehicle at Days 4, 8, and 15. The LE 1% BID also had greater mean reductions from baseline in ocular pain grade at Days 4 and 8 compared to the vehicle, but not at Day 15. At Day 15, the vehicle appeared to have slightly greater mean reduction in ocular pain grade as compared to the LE 1% BID group.

The results in Figure 5 were also supported by the applicant's analyses of these four endpoints using the analysis of covariance (ANCOVA) model (see Appendix 4 for details). The applicant's ANCOVA model included treatment, site, and baseline score as independent variables. In Study 001, the LE 0.25% QID group had statistically greater least squares (LS) mean reductions from baseline in AC cell grade and in composite mean score of AC cell and ocular pain than the vehicle at Days 4, 8, and 15. The LE 0.25% QID group also had a statistically greater LS mean reduction from baseline in ocular pain grade at Day 4 and statistically greater AC flare grade at Days 4 and 8 than the vehicle. The LE 1% BID group had statistically greater LS mean reductions from baseline in AC cell grade, ocular pain grade, composite mean score of AC cell and pain, and AC flare grade, as compared to the vehicle, at Days 4 and 8, but not at Day 15.

In Study 005, the LE 1% BID group had significantly greater LS mean reductions from baseline in AC cell grade, composite mean score of AC cell and pain, and AC flare at Days 4, 6, and 8. The LE 1% BID group also had significantly greater LS mean reductions in ocular pain from baseline at Days 4 and 8, but not at Day 15. This is consistent with what we observed in Figure 5.

Figure 5: Mean change from baseline in AC cell grade, ocular pain grade, composite mean of AC cell and ocular pain, and AC flare grade (ITT; OBS)



Source: KPI-121-001 CSR, Tables 14.2.1.5.2, 14.2.1.7.1, 14.2.1.8.1, and 14.2.1.6.1 and KPI-121-005 CSR, Tables 14.2.1.3, 14.2.1.5, 14.2.1.6 and 14.2.1.4

Note: OBS = observed cases

3.2.4.3 Efficacy Conclusion

In Study 001, both LE 0.25% QID and 1% BID were statistically superior to the vehicle for both primary endpoints. In Study 005, the LE 1% BID was also statistically superior to the vehicle for both primary endpoints.

Analyses of non-primary endpoints in both studies were in general supportive of the primary results. For example, the following non-primary results were statistically significant in favor of the LE groups:

- Results for the endpoint of complete resolution of both AC cells and pain at Day 8 and maintained through Day 15 statistically favored both LE groups in Study 001 and favored the LE 1% BID group in Study 005
- Results for the endpoint of complete resolution of AC flare at Day 8 and maintained through Day 15 statistically favored both LE groups in Study 001 and favored the LE 1% BID group in Study 005
- Results for the endpoint of complete resolution of ocular pain at Day 4 and maintained through Day 15 statistically favored both LE groups in Study 001 and favored the LE 1% BID group in Study 005
- Results for the endpoint of complete resolution of AC flare at Day 4 and maintained through Day 15 statistically favored both LE groups in Study 001 and favored the LE 1% BID group in Study 005
- Results for the endpoint of complete resolution of AC cells statistically favored both LE groups at Days 8 and 15 in Study 001 and favored the LE 1% BID group at Days 8 and 15 in Study 005
- Results for the endpoint of complete resolution of ocular pain statistically favored both LE groups at Days 4, 8 and 15 in Study 001 and favored the LE 1% BID group at Days 4, 8, and 15 in Study 005
- Results for the endpoint of complete resolution of both AC cells and ocular pain statistically favored both LE groups at Days 4 and 15 and favored only the LE 0.25% QID group at Day 8 in Study 001. Results for this same endpoint statistically favored the LE 1% BID group at Days 8 and 15 in Study 005
- Results for the endpoints of mean reduction from baseline in AC cell grade statistically favored both LE groups at Days 4 and 8 and favored only the LE 0.25% QID group at Day 15 in Study 001. Results for this same endpoint statistically favored the LE 1% BID group at Days 4, 8, and 15 in Study 005

- Results for the endpoint of mean reduction from baseline in ocular pain grade statistically favored both LE groups at Day 4 and favored only the LE 1% BID group at Day 8 in Study 001. Results for this same endpoint statistically favored the LE 1% BID group at Days 4 and 8 in Study 005
- Results for the endpoint of mean reduction from baseline in composite mean score of AC cell and ocular pain statistically favored both LE groups at Days 4 and 8 and favored only the LE 0.25% QID group at Day 15 in Study 001. Results for this same endpoint statistically favored the LE 1% BID group at Days 4, 8, and 15 in Study 005
- Results for the endpoint of mean reduction from baseline in AC flare grade statistically favored both LE groups at Days 4 and 8 in Study 001 and favored the LE 1% BID group at Days 4, 8, and 15 in Study 005.

3.3 Safety Evaluation

This section briefly summarizes the safety in the two studies. For a comprehensive review of safety, please refer to Dr. Martin Nevitt's clinical review.

As shown in Table 7, in Study 001, the LE 1% BID group had fewer incidences of AEs and serious AEs than the other two treatment groups. In Study 005, the LE 1% BID also had fewer incidences of AEs and serious AEs than the vehicle. No death was reported in both studies.

Table 8 below summarizes the types of common ($\geq 1\%$ in either treatment group) AEs in the LE 1% BID and vehicle BID groups in the pooled safety population. The most common AE in the LE 1% BID group was headache, and the most common AE in the vehicle BID group was eye pain. The applicant also reported that the serious AEs in the LE 1% BID group were cholelithiasis and pneumonia (1 subject each) and serious AEs in the vehicle BID group were angina pectoris and hypertensive emergency (1 subject reported both) and cerebrovascular accident (1 subject).

In Studies 001 and 005, Snellen distance visual acuity and intraocular pressure (IOP) were analyzed as the two safety outcomes. The applicant stated that in both studies, there was no clinically important differences between the LE 1% BID and vehicle in terms of change from baseline in visual acuity at any post-baseline visit. The applicant also states that based on the pooled analysis of IOP, the mean IOP values were similar between the LE 1% BID group and vehicle BID at all study visits. The percentage of subjects experiencing IOP elevation of > 5 mmHg from baseline was numerically higher in the LE 1% BID group ($19/386 = 4.9\%$) than that in the vehicle BID ($8/325 = 2.5\%$).

Table 7: Summary of all AEs (safety population)

	Study 001			Study 005	
	0.25% QID (N=129)	1% BID (N=125)	Vehicle (N=126)	1% BID (N=261)	Vehicle (N=259)
Any AEs, n (%)	22 (17.1)	15 (12.0)	26 (20.6)	38 (14.6)	42 (16.2)
Number of AEs Reported	31	22	41	50	69
Severe AEs	3 (2.3)	1 (0.8)	5 (4.0)	3 (1.1)	4 (1.5)
AEs Related to Treatment	3 (2.3)	1 (0.8)	9 (7.1)	9 (3.4)	7 (2.7)
AEs Leading to Discontinuation from Treatment, n (%) ¹	3 (2.3)	2 (1.6)	12 (9.5)	5 (1.9)	10 (3.9)
AEs Leading to Interruption of Study Treatment Use	0	1 (0.8)	0	0	0
Serious AEs	2 (1.6)	1 (0.8)	2 (1.6)	1 (0.4)	2 (0.8)
Deaths	0	0	0	0	0

Source: KPI-121-001 CSR, Table 23 and KPI-121-005 CSR, Table 24

Table 8: Number of subjects reporting common AEs (pooled safety population)

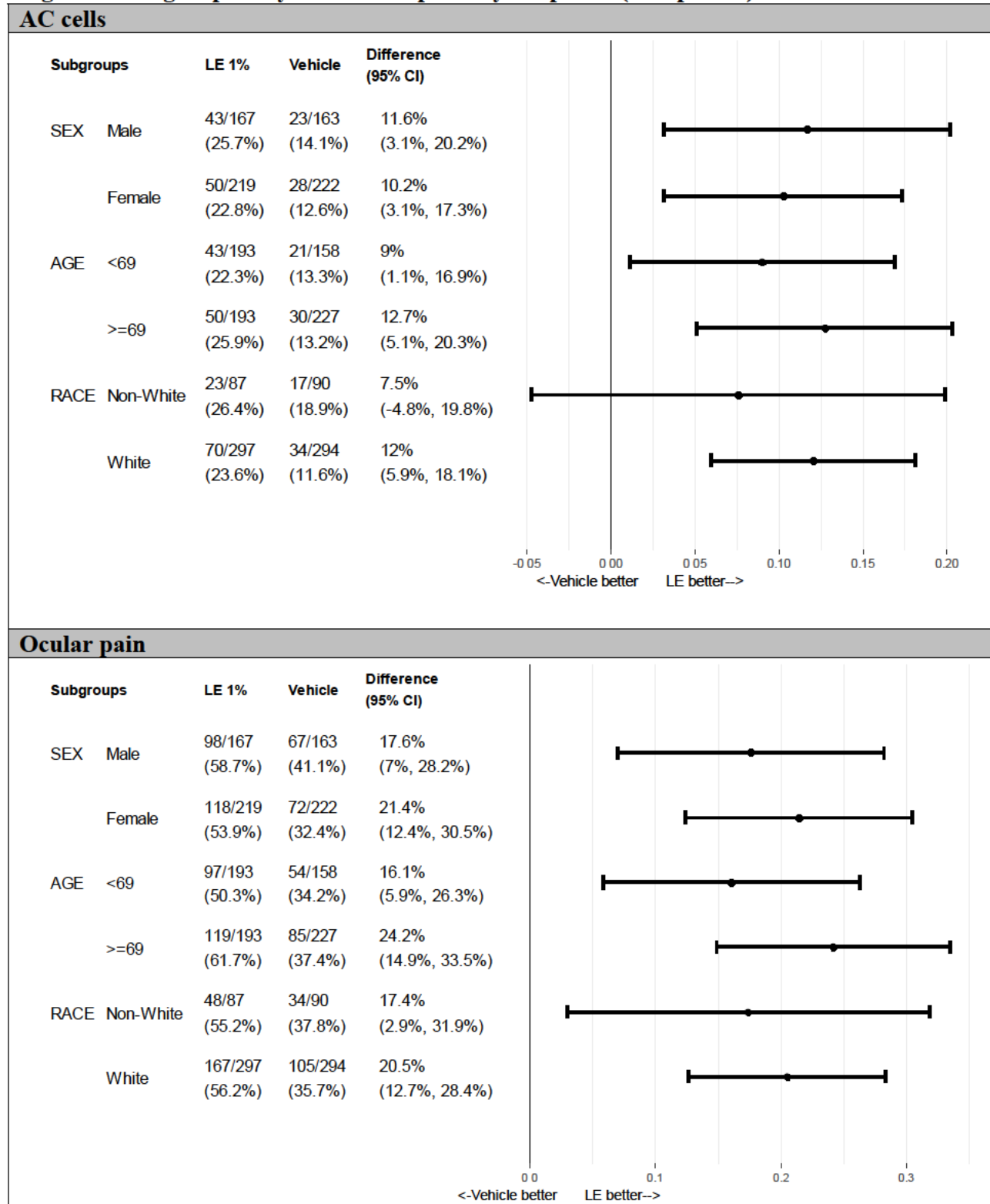
	LE 1% BID (N = 386)	Vehicle BID (N = 325)
Number (%) of Subjects Reporting Any AEs	53 (13.7)	57 (17.5)
Eye Disorders	26 (6.7)	38 (11.7)
Eye Pain	4 (1.0)	9 (2.8)
Posterior Capsule Opacification	4 (1.0)	4 (1.2)
Photophobia	2 (0.5)	6 (1.8)
Corneal Oedema	2 (0.5)	4 (1.2)
Nervous System Disorder	7 (1.8)	8 (2.5)
Headache	6 (1.6)	6 (1.8)
Infections and Infestations	12 (3.1)	3 (0.9)
Nasopharyngitis	4 (1.0)	1 (0.3)

Source: Summary of clinical safety, Table 12

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Figure 6 displays the results for the primary endpoints in demographic subgroups of the pooled ITT population. For the primary endpoint of AC cells, the results statistically favored the LE 1% BID group in most of the subgroups, except for the subgroup of subjects who were non-white. Yet, even in this subgroup, the result still numerically favored the LE 1% BID group. For the primary endpoint of ocular pain, the results statistically favored the LE 1% BID group in all subgroups.

Figure 6: Subgroup analyses for both primary endpoints (ITT pooled)



Source: Reviewer's analysis. Note: three subjects in Study 005 have race identified as unknown and were excluded from the subgroup analysis by race.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were identified.

5.2 Collective Evidence

Both Studies 001 and 005 demonstrated superiority of LE 1% BID to the vehicle for the two primary endpoints. The analyses of non-primary efficacy endpoints also provide further assurance that the LE 1% BID is effective. For example, the treatment difference between the LE 1% BID and vehicle was statistically significant for the following non-primary endpoints:

- Complete resolution of both AC cells and pain and complete resolution of AC flare at Day 8 and maintained through Day 15 in both studies
- Complete resolution of ocular pain and complete resolution of AC flare at Day 4 and maintained through Day 15 in both studies
- Complete resolution of AC cells at Days 8 and 15 in both studies
- Complete resolution of ocular pain at Days 4, 8, and 15 in both studies
- Complete resolution of both AC cells and ocular pain at Days 4 and 15 in Study 001 and at Days 8 and 15 in Study 005
- Mean reduction in AC cell grade, composite mean score of AC cell and pain, and AC flare grade at Days 4 and 8 in Study 001 and at Days 4, 8, and 15 in Study 005
- Mean reduction in ocular pain grade at Days 4 and 8 in both studies

The lower dosage, LE 0.25% QID, also demonstrated significant treatment benefit on the primary endpoints and many non-primary endpoints in Study 001. For example, the treatment difference between the LE 0.25% QID and vehicle was significant for the following non-primary endpoints:

- Complete resolution of both AC cells and pain and complete resolution of AC flare at Day 8 and maintained through Day 15
- Complete resolution of ocular pain and complete resolution of AC flare at Day 4 and maintained through Day 15
- Complete resolution of AC cells at Day 8 and 15
- Complete resolution of ocular pain and complete resolution of both AC cells and ocular pain at Days 4, 8, and 15
- Mean reduction in AC cell grade and composite mean score of AC cell and pain at Days 4, 8 and 15
- Mean reduction in ocular pain at Day 4
- Mean reduction in AC flare grade at Days 4 and 8

Moreover, subgroup analyses showed a consistent treatment effect of the LE 1% BID across subgroups of sex, age, and race.

5.3 Conclusions and Recommendations

In conclusion, the two studies together provide sufficient evidence that the LE 1% BID is effective for the treatment of post-operative inflammation and pain following ocular surgery.

5.4 Labeling Recommendation

(b) (4)

This reviewer recommends presenting the results from the two studies separately as in Mock-up Figures 1 and 2 below.

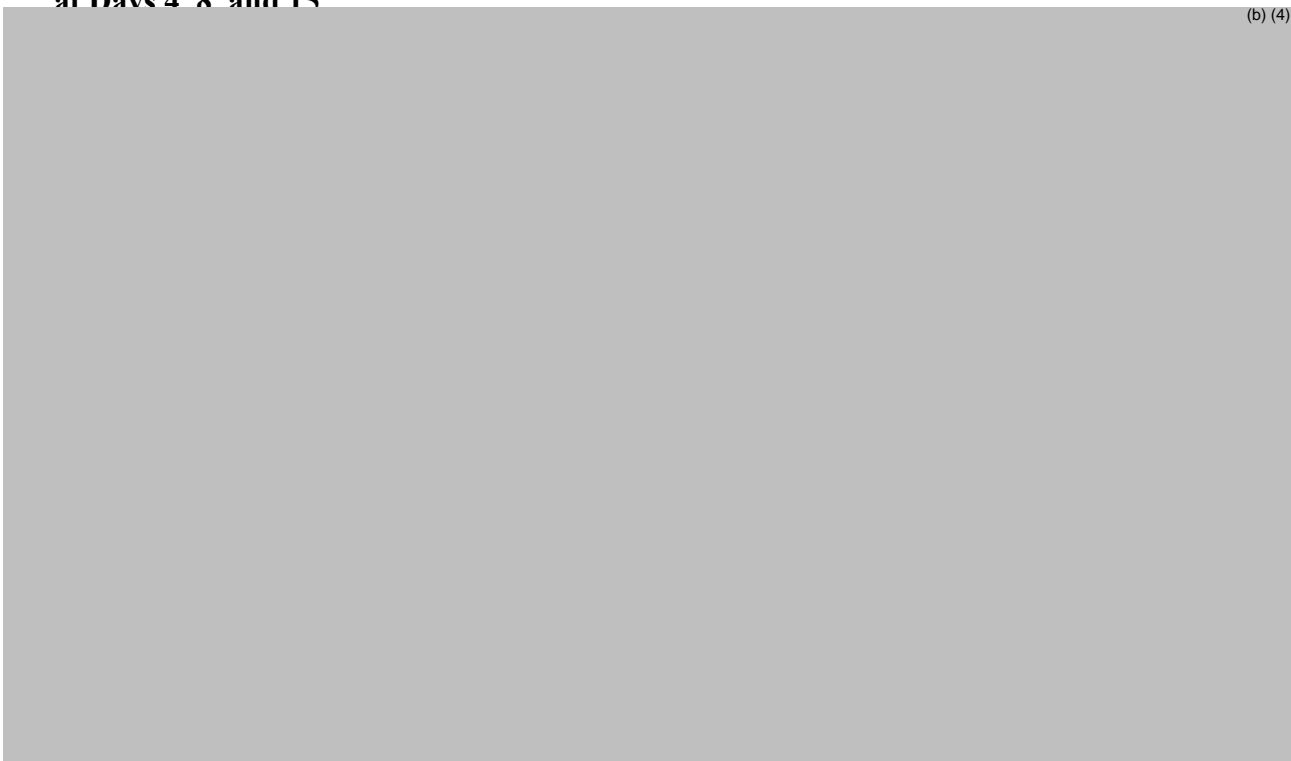
Mock-up Figure 1: Percentage of patients with complete resolution of anterior chamber cells (cell count = 0) at Days 8 and 15

(b) (4)

**Mock-up Figure 2: Percentage of patients
at Days 4, 8, and 15**

(b) (4)

(b) (4)



APPENDICES

Appendix 1: Summary of Assessments for Both Studies

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening	Surgery	Randomization	Study Visit	Study Visit	End of Study Product Use Visit	Follow-Up
	Days -14 to -1	Day 0	Day 1	Day 4 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Days 17 - 19
Informed Consent, HIPAA Authorization and Medical History	X						
Concomitant Medication Query	X	X	X	X	X	X	X
Pregnancy Test ^a	X					X	
Inclusion/Exclusion	X		X				
AE Assessment		X ^b	X	X	X	X	X
Surgery		X					
Subject-Rated Ocular Pain Assessment			X	X	X	X	X
Snellen Distance Pinhole Visual Acuity	X		X	X	X	X	X
Slit-lamp Biomicroscopy	X		X	X	X	X	X
IOP Measurement	X		X	X	X	X	X
Dilated Ophthalmoscopy	X					X	
Randomization			X				
Study Product Administration in Clinic			X				
Dispense Study Product			X				
Collect Study Product						X	
Dosing Compliance Assessment				X	X	X	

AE = adverse event; IOP = intraocular pressure

^a Women of childbearing potential only

^b Assessments of AEs pre-surgery and post-surgery

Source: KPI-121-001 CSR, Table 6 and KPI-121-005 CSR, Table 6

Note: both studies shared the same schedule of assessments.

Appendix 2: Vehicle Comparison for Primary Efficacy Endpoints (ITT)

	Vehicle A QID (N=60)	Vehicle B BID (N=66)	Vehicle Comparison (Vehicle A QID minus Vehicle B BID) % Responders (95% CI) p-value
Complete Resolution of Anterior Chamber Cells, n (%)	9 (15.0)	10 (15.2)	-0.2 (-12.7, 12.4) 0.9811
Complete Resolution of Ocular Pain, n (%)	22 (36.7)	21 (31.8)	4.8 (-11.7, 21.4) 0.5665

Note: Subjects with complete resolution (Grade 0) of anterior chamber cells or of ocular pain at Day 8 and Day 15 without rescue medication (ie, no rescue medication prior to Day 15) are counted as responders ("yes"). P-values are based on 2-sided chi-square tests, unadjusted, wherein the significance level was 0.05.

Source: Tables 14.2.1.18 and 14.2.1.19

Source: Source: KPI-121-001 CSR, Table 15

Appendix 3: Results for the Primary Efficacy Endpoints in the PP Population

Study 0001					
Hierarchical Testing Order	KPI-121 0.25% QID (N=126)	KPI-121 1% BID (N=123)	Vehicle (N=124)	Between-Group Difference for % Responders ^a (95% CI)	p-value
Complete Resolution (Grade 0) of Anterior Chamber Cells, n (%)	47 (37.3)	39 (31.7)	19 (15.3)		
1) KPI-121 0.25% QID vs. Vehicle				22.0 (11.4, 32.5)	<0.0001
2) KPI-121 1% BID vs. Vehicle				16.4 (6.0, 26.8)	0.0024
Complete Resolution (Grade 0) of Pain, n (%)	73 (57.9)	66 (53.7)	43 (34.7)		
3) KPI-121 1% BID vs. Vehicle				19.0 (6.8, 31.1)	0.0027
4) KPI-121 0.25% QID vs. Vehicle				23.3 (11.2, 35.3)	0.0002

BID = twice daily; QID = four times daily
^a KPI-121 minus vehicle
 Note: Subjects with complete resolution (Grade 0) of anterior chamber cells or of ocular pain at Day 8 and Day 15 without rescue medication (ie, no rescue medication prior to Day 15) are counted as responders. P-values are based on 2-sided chi-square tests, unadjusted.
 Source: [Tables 14.2.2.1](#) and [14.2.2.2](#)

Study 005				
	KPI-121 1% (N=251)	Vehicle (N=251)	Between-Group Difference for % Responders (95% CI)	P-value
Complete Resolution of Anterior Chamber Cells, n (%)	50(19.9%)	31(12.4%)	7.6% (1.2, 14.0)	0.0212
Complete Resolution of Ocular Pain, n (%)	145(57.8%)	94(37.5%)	20.3% (11.8, 28.9)	<0.0001

CI = confidence interval
 Note: Subjects with complete resolution (Grade 0) of anterior chamber cells or of ocular pain at Day 8 and maintained through Day 15 without rescue medication (ie, no rescue medication prior to Day 15) were counted as responders. P-values are based on 2-sided chi-square tests, unadjusted, wherein the significance level was 0.05.
 Source: [Tables 14.2.2.1](#) and [14.2.2.2](#)

Source: KPI-121-001 CSR, Table 17 and KPI-121-005, Table 16

Appendix 4: Mean Reduction in AC Cell Grade, Ocular Pain Grade, Composite Mean Score of AC Cell and Pain, and AC Flare Grade (ITT; OBS)

Endpoint	Study	Visit	LE 0.25%	LE 1%	Vehicle	LE 0.25% - vehicle		LE 1% - vehicle	
			LS mean (SE)	LS mean (SE)	LS mean (SE)	Difference in LS means (95% CI)	P-value	Difference in LS means (95% CI)	P-value
AC cell grade	Study 001	Day 4	-1(0.07)	-0.9(0.08)	-0.6(0.08)	-0.4 (-0.6, -0.2)	2.00E-04	-0.3 (-0.4, -0.1)	0.0141
		Day 8	-1.6(0.07)	-1.4(0.07)	-1.2(0.07)	-0.3 (-0.5, -0.1)	7.00E-04	-0.2 (-0.4, 0)	0.044
		Day 15	-1.8(0.06)	-1.8(0.06)	-1.7(0.06)	-0.2 (-0.3, 0)	0.0391	-0.1 (-0.3, 0.1)	0.1811
	Study 005	Day 4	NA	-0.7(0.05)	-0.5(0.05)	NA	NA	-0.2 (-0.3, 0)	0.0078
		Day 8	NA	-1.3(0.05)	-1(0.05)	NA	NA	-0.2 (-0.4, -0.1)	5.00E-04
		Day 15	NA	-1.7(0.05)	-1.6(0.05)	NA	NA	-0.2 (-0.3, 0)	0.0169
Ocular Pain grade	Study 001	Day 4	-0.5(0.08)	-0.5(0.08)	-0.1(0.08)	-0.4 (-0.6, -0.2)	2.00E-04	-0.4 (-0.6, -0.2)	6.00E-04
		Day 8	-0.6(0.07)	-0.7(0.06)	-0.5(0.07)	-0.1 (-0.3, 0.1)	0.1953	-0.2 (-0.4, 0)	0.0307
		Day 15	-0.8(0.06)	-0.9(0.06)	-0.7(0.06)	-0.1 (-0.2, 0.1)	0.2589	-0.1 (-0.2, 0.1)	0.2132
	Study 005	Day 4	NA	-0.5(0.06)	-0.3(0.06)	NA	NA	-0.2 (-0.4, -0.1)	0.0053
		Day 8	NA	-0.8(0.05)	-0.6(0.05)	NA	NA	-0.2 (-0.3, 0)	0.0157
		Day 15	NA	-1(0.03)	-1(0.03)	NA	NA	-0.1 (-0.2, 0)	0.1694
Composite mean score of AC cell and pain	Study 001	Day 4	-0.8(0.06)	-0.7(0.06)	-0.4(0.06)	-0.4 (-0.5, -0.2)	0	-0.3 (-0.5, -0.2)	1.00E-04
		Day 8	-1.1(0.05)	-1(0.05)	-0.8(0.05)	-0.2 (-0.4, -0.1)	0.002	-0.2 (-0.3, -0.1)	0.0059
		Day 15	-1.3(0.05)	-1.3(0.05)	-1.2(0.05)	-0.1 (-0.2, 0)	0.0394	-0.1 (-0.2, 0)	0.1021
	Study 005	Day 4	NA	-0.6(0.04)	-0.4(0.04)	NA	NA	-0.2 (-0.3, -0.1)	9.00E-04
		Day 8	NA	-1(0.04)	-0.8(0.04)	NA	NA	-0.2 (-0.3, -0.1)	3.00E-04
		Day 15	NA	-1.4(0.03)	-1.3(0.03)	NA	NA	-0.1 (-0.2, 0)	0.0123
AC flare grade	Study 001	Day 4	-0.4(0.06)	-0.4(0.06)	-0.1(0.06)	-0.3 (-0.4, -0.1)	7.00E-04	-0.3 (-0.4, -0.1)	0.0012
		Day 8	-0.7(0.04)	-0.7(0.05)	-0.5(0.04)	-0.2 (-0.4, -0.1)	1.00E-04	-0.2 (-0.3, -0.1)	0.0027
		Day 15	-0.8(0.03)	-0.8(0.04)	-0.7(0.03)	0 (-0.1, 0)	0.3291	0 (-0.1, 0.1)	0.7326
	Study 005	Day 4	NA	-0.4(0.04)	-0.2(0.04)	NA	NA	-0.2 (-0.3, -0.1)	0.0013
		Day 8	NA	-0.6(0.03)	-0.5(0.04)	NA	NA	-0.2 (-0.3, -0.1)	1.00E-04
		Day 15	NA	-0.8(0.03)	-0.7(0.03)	NA	NA	-0.1 (-0.2, 0)	0.0018

Source: KPI-121-001 CSR, Tables 14.2.1.5.1, 14.2.1.7.1, 14.2.1.8.1, and 14.2.1.6.1 and KPI-121-005, Tables 14.2.1.3, 14.2.1.4, 14.2.1.6, and 14.2.1.5, and reviewer's analysis (in blue)

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/s/

QING N ZHOU
06/14/2018

YAN WANG
06/14/2018
I concur.