CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 211950
Product Name:	CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL
Indication(s):	Treatment of macular edema associated with non-infectious uveitis
Applicant:	Clearside Biomedical, Inc.
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Key words: Macular Edema, Non-Infectious Uveitis, Best Corrected Visual Acuity, Corticosteroid

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1 EXECUTIVE SUMMARY

1.1 Introduction and Background

Clearside Biomedical, Inc. (Applicant) submitted this 505(b)(2) NDA seeking approval of CLS-TA for the treatment of macular edema (ME) associated with non-infectious uveitis. CLS-TA is a preservative-free, (b) (4) sterilized, suprachoroidal injectable aqueous suspension of triamcinolone acetonide (TA), a synthetic corticosteroid with an anti-inflammatory action. Per the Applicant, suprachoroidal administration of TA is likely to provide enhanced efficacy and safety results over the outcomes seen from other local methods of corticosteroid administration to the eye. The primary evidence for the efficacy of CLS-TA comes from one Phase 3 study (Study CLS1001-301). The submission also includes literature summary from 27 publications and two small studies conducted by the Applicant (CLS-1001-201 and CLS-1001-302) as supportive evidence (See Appendix). The main objective of this review is to evaluate whether the efficacy results in Study CLS1001-301 support the proposed indication.

1.2 Summary of Study CLS1001-301

CLS1001-301 was a Phase 3, randomized, masked, sham-controlled, multicenter study. The primary objective of this study was to evaluate the efficacy of CLS-TA in subjects with ME associated with non-infectious uveitis. The study enrolled 160 adult subjects in 53 sites located across three countries (80 subjects in the Unites States, 70 subjects in India, and 10 subjects in Israel). Eligible subjects were randomized in a 3:2 ratio to receive either 2 unilateral suprachoroidal injections of CLS-TA (96 subjects) or 2 unilateral suprachoroidal injections of a sham Control (64 subjects), administered to the study eye approximately 12 weeks apart. The total duration of the study was approximately 27 weeks. Efficacy and safety assessments were conducted at Weeks 4, 8, 12, 16, 20 and 24. Beginning at Week 4, subjects were eligible for rescue medication if they met one of the following criterion: (1) a decline from baseline of 10 letters or more in best corrected visual acuity (BCVA) (2) an increase from baseline in central subfield retinal thickness of more than 100 microns or 20% (whichever was lower) (3) a ≥1.5-step increase from baseline in the level of inflammation or (4) a determination by the investigator that uveitic complications have not improved.

The primary efficacy endpoint of the study was the proportion of subjects with 15 letters or more improvement from baseline at Week 24. The primary efficacy analysis was conducted using a Cochran-Mantel-Haenszel (CMH) test adjusting for a country subgroup (US+Israel vs. India). The treatment difference (CLS-TA-Control) in the proportion of subjects with 15 letters or more improvement from baseline at Week 24 together with an exact 95% confidence interval for proportions was also provided. The primary efficacy analysis was conducted based on all randomized subjects (ITT population). For subjects with missing BCVA data at Week 24, the last non-missing BCVA data from a prior visit was used. For subjects who received a rescue medication prior to the evaluation of the primary efficacy endpoint, the BCVA data collected prior to the receipt of rescue medication was used in the primary efficacy analysis.

This study showed that the proportion of subjects with 15 letters or more improvement from baseline at Week 24 was significantly higher in the CLS-TA arm compared with the Control arm (45% vs 16%; diff (95% CI): 31 (15%, 46%]). In addition, substantially higher proportion of subjects in the Control arm (72%) received rescue medication compared to subjects in the CLS-TA arm (13%). In both arms, the main reason for administration of rescue medication was the investigators' judgment that uveitic complications have not improved.

Per the safety results, the proportion of subjects who reported at least one ocular adverse event in the study eye was slightly lower in the CLS-TA arm [49 (51%)] compared to the Control arm [37 (58%)]. However, subjects in the CLS-TA arm experienced a higher number of ocular adverse events compared to subjects in the Control arm. Specifically, a combined total of 122 events were reported by the 49 CLS-TA randomized subjects who reported at least one ocular adverse event. The corresponding figure for the 37 subjects in the Control arm was 54 events. The most common ocular adverse events reported in the CLS-TA arm were intraocular pressure (17.7%), eye pain (14.6%), cataract (8.3%), and vitreous detachment (5.2%). The incidence rates of these events in the Control arm were: 6.3% (intraocular pressure), 0.0% (eye pain), 6.3% (cataract), and 1.6% (vitreous detachment). No death was reported in either arm, but three (3.1%) subjects, all in the CLS-TA arm, experienced serious adverse events (sialoadenitis, lumbar vertebral fracture and retinal detachment), of which one, retinal detachment, was an ocular adverse event.

No subject in either arm discontinued the study due to an adverse event. However, the study reported that five subjects in each arm experienced adverse events that lead to treatment discontinuation. The most frequent adverse events in the CLS-TA arm that led to treatment discontinuation were ocular hypertension, uveitis, visual acuity reduced, vitreous haemorrhage and increased intraocular pressure, all of which occurred in about 1% of the randomized subjects. Uveitis (6.3%), iridocyclitis (1.6%), and increased intraocular pressure (1.6%) were the most frequent adverse events that led to treatment discontinuation in the Control arm. Because all randomized subjects received the first of the two planned injections, "treatment discontinuation" likely refers to not receiving the planned second injection.

1.3 Labeling Recommendation

The Applicant's proposed text presented in Section 14 of the drug label (see below) together with the summary of the primary efficacy endpoint as presented in *Table A0* is acceptable.

The efficacy of XIPERE™ was assessed in a 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with uveitis. The primary efficacy endpoint was the proportion of subjects in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up (Table A0). A statistically significantly greater proportion of patients treated with XIPERE achieved a ≥15-letter improvement in BCVA than control patients (p<0.001) at Week 24.

Table A0: Number and Percent of Patients with ≥15 Letters Improvement from Baseline in BCVA at Week 24

XIPERE (N = 96)	***Control (N = 64)***	***% Difference (95% CI)***
45 ((b) (4)%)	*10 ((b) (4)%)*	*31 (b) (4)% (15(b) (4)%, (b) (4)%)*

The Applicant also claimed that there are “statistically significant” treatment differences in favor of CLA-TA for the secondary efficacy endpoint and the additional efficacy endpoints (including the mean BCVA at all post-baseline study visits, the percentage of patients with resolution of inflammation at Week 24, and the percentage of patients with a reduction in inflammation of 2 steps or more at Week 24). However, because the study did not specify a testing procedure that adjusted for multiplicity due to testing of these additional endpoints, per this reviewer, the Applicant cannot make claims of “statistical significance” for treatment differences associated with the additional efficacy endpoints. If the additional endpoints are deemed relevant and are believed to add value to the prescribing physician, the results could be presented in the drug label as descriptive summaries (See Section 4.3 for Details).

2 INTRODUCTION

Clearside Biomedical, Inc. submitted this 505(b)(2) NDA to support the safety and efficacy of CLS-TA for the treatment of macular edema associated with non-infectious uveitis. The submission included data from one Phase 3 study (CLS-1001-301). This study enrolled 160 subjects globally: 80 subjects in the United States, 70 subjects in India and 10 subjects in Israel. The Applicant also provided literature summary from 27 publications and two small Phase 2 studies (CLS-1001-201 and CLS-1001-302) as supportive evidence.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the specific studies reviewed.

2.1.1 Drug Class and Indication

CLS-TA is a preservative-free, (b) (4) sterilized, aqueous suspension of the corticosteroid triamcinolone acetonide (TA). CLS-TA is developed for the treatment of macular edema (ME) associated with non-infectious uveitis. The active ingredient in CLS-TA, TA, is a synthetic glucocorticoid corticosteroid with marked anti-inflammatory action. Per the Applicant, CLS-TA is formulated for ocular administration and is optimized for suprachoroidal (SC) injection. The Applicant states that, uveitis is commonly treated systemically or locally with corticosteroids and other immunomodulatory agents administered topically or via intravitreal injection. Per the Applicant, while an intravitreal route of administration enables availability of the drug to the posterior segment, the procedure leads to significant exposure of the administered corticosteroid to anterior segment ocular structures. The state that this could lead to cataract formation and elevated intraocular pressure (IOP) in addition to inconsistent efficacy. Per the Applicant, the unique distribution of TA following suprachoroidal administration of CLS-TA is likely to provide a differentiating benefit to risk profile where both efficacy and safety outcomes have the potential to be enhanced over the outcomes seen from other local methods of corticosteroid administration to the eye.

2.1.2 History of Drug Development

The protocol and the statistical analysis plan for study CLS-1001-301 were reviewed under IND115683. The Applicant had one End-of-Phase 2 meeting with the agency on April 23, 2015. During this meeting, the Applicant inquired if a single study together with a literature summary would suffice for this indication. In response, the Agency stated that, a single Phase 3 pivotal clinical study in conjunction with comprehensive literature review of the use of TA for the treatment of macular edema will support a 505(b)(2) NDA for the stated indication. The Applicant also discussed the design of Study CLS1001-301. The Agency recommended that the intent-to-treat (ITT) population which includes all randomized subjects be used for the primary efficacy analysis. The Agency also recommended that subjects who receive rescue medication

prior to the evaluation of the primary efficacy endpoint should be treated as treatment failures in the primary efficacy analysis.

Reviewer's remark: After the NDA for this product was submitted, it was noted that the Applicant was basing their submission on their own clinical data and the findings from the approval of Triesence (NDA 22048). The Agency informed the Applicant that since the approval of Triesence was based on the original DESI review for steroids, the review for CLS-TA will also be based on the single Phase 3 study and the Agency's finding of safety and efficacy in the DESI review, not Triesence. The Applicant's literature summary submitted to support efficacy and safety of CLS-TA and presented in the Appendix is thus considered as supportive evidence only.

The Applicant also had a pre-NDA meeting with the Agency on August 7, 2018. This meeting was primarily focused on the contents of the impending NDA submission. During this pre-NDA meeting, the Applicant also requested guidance on how to present results of the inflammation endpoints in the drug label. In response, the Agency recommended that, to facilitate review, data showing the proportion of subjects with a complete resolution of vitreous haze at Week 24 among those who had vitreous haze scores ≥ 2 (Sun Criteria) at baseline should be presented.

2.1.3 Studies Reviewed

The summary of Study CLS-1001-301, which is the basis for this NDA, is presented in Table 1. The summaries of the 27 publications and the two small studies conducted by the Applicant (CLS-1001-201 and CLS-1001-302) are presented in the Appendix.

Table 1: Summary of Study CLS-1001-301

Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
A Phase 3, randomized, masked, sham-controlled, multicenter study to assess the safety and efficacy of 4 mg of CLS-TA administered via suprachoroidal injection compared to a sham injection procedure in the treatment of subjects with ME associated with non-infectious uveitis.	– CLS-TA: N=96 – Control: N=64	Primary Endpoints: Proportion of subjects with a >=15 letters improvement from baseline at Week 24. The primary efficacy analysis of evaluating superiority of CLS-TA against control was conducted using the CMH test stratified for country group.	This Phase 3 study met its primary endpoint [sic] demonstrating the efficacy of CLS-TA as shown by the proportion of subjects with a change from Baseline of ≥15 ETDRS letters in BCVA at Week 24. The proportion of successes in the CLS-TA arm (46.9%) was much greater than in the Control arm (15.6%). The CMH test was statistically significant ($p<0.001$) showing that subjects treated with suprachoroidal injections of CLS-TA had an improved vision from Baseline (≥15 ETDRS letters score) compared to subjects treated with sham injection procedures (Control arm).

Source: Applicant's Study Report

2.2 Data Sources

The data sources for this review included the Applicant's clinical study reports and SAS datasets submitted both as SDTM and ADAM data formats. The datasets used in this review are located at: \\Cdsesub1\evsprod\NDA211950\0001\m5\datasets\. The visual acuity outcome at baseline and subsequent measurement times were included in the "adoe.xpt" dataset. An indicator variable (PARAMCD) was included to distinguish between the different outcomes. A data type variable DTYPE was also included to distinguish between imputed and observed values. The treatment variable, given both as numeric (TRTP) and character (TRTPN), was also included in the above dataset. The adverse events and treatment exposures were included in the "adae.xpt" dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data were generally of decent quality. The reviewer replicated the Applicant's analyses results based on the submitted data. The final statistical analysis plan and the amended protocols were all submitted.

3.2 Evaluation of Efficacy

This section summarizes the design of the study CLS1001-301 and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

CLS1001-301 was a randomized, masked, sham-controlled, multicenter, Phase 3 study. The objective of this study was to assess the safety and efficacy of 4 mg of CLS-TA administered via suprachoroidal injection compared to a sham injection procedure in the treatment of subjects with macular edema associated with non-infectious uveitis. Eligible subjects for study CLS1001-301 were 18 years or older with macular edema associated with non-infectious uveitis of any etiology. Eligible subjects were also expected to have a BCVA score of between 5 and 70 letters read in the study eye at baseline.

The total duration of the study was 27 weeks and included 8 clinic visits. Subject eligibility was evaluated during the screening visit (Day -14 to -1). Eligible subjects were randomized to receive 2 unilateral suprachoroidal injections of CLS-TA administered to the Study eye or 2 unilateral sham suprachoroidal injection procedures administered to the Study eye, approximately 12 weeks apart. Follow-up visits were conducted every 4 weeks up to 24 weeks. Subjects had final evaluations conducted 24 weeks following initial randomization. Per the study protocol, beginning at Week 4, investigators had discretion to prescribe rescue medication for subjects who met one of the following criterion: (1) a BCVA decline from baseline of ≥10 letters, (2) an increase from baseline in central subfield retinal thickness of more than 100 microns or 20% (whichever was lower), (3) a ≥1.5-step increase from baseline in the level of

inflammation, or (4) a determination by the investigator that uveitic complications have not improved. The primary efficacy endpoint of this study was the proportion of subjects with at least 15 letters improvement from baseline at Week 24. The mean change from baseline in central subfield retinal thickness at Week 24 was the secondary efficacy endpoint.

3.2.2 Statistical Methods

3.2.2.1 Analysis Populations

The protocol defined the following 4 analysis populations for the evaluation of efficacy, safety and Pharmacokinetic (PK):

- Intent-to-treat (ITT): Includes all randomized subjects.
- Per-protocol (PP): Includes all subjects in the ITT population who did not have significant protocol deviations and who have completed the 24-week visit.
- Safety: Includes all subjects in the ITT population who are administered at least one dose of study drug, either active or sham Control.
- Pharmacokinetic (PK): Includes all subjects enrolled in the PK portion of the study that provided blood samples for TA concentration analysis and were randomized to CLS-TA arm.

3.2.2.2 Analysis Methods

The primary efficacy analysis compared the efficacy of CLS-TA arm against Control using a Cochran-Mantel-Haesnezl (CMH) test adjusting for a country subgroup (US+Israel vs. India). The proportion of subjects in each arm with 15 letters or more improvement from baseline at Week 24, a treatment difference together with an exact 95% confidence interval for proportions was also provided. The primary efficacy analysis was conducted based on the ITT population. For subjects with missing BCVA data at Week 24, the last non-missing BCVA data from a prior visit was used in the primary efficacy analysis. For subjects who received a rescue medication prior to the evaluation of the primary efficacy endpoint, the BCVA data prior to the receipt of rescue medication was used in the primary efficacy analysis.

As sensitivity analyses, the Applicant conducted the analysis of the primary efficacy endpoint on the ITT population using all observed data regardless of whether the data was collected before or after rescue medication. In this analysis, subjects who had missing BCVA data at Week 24 were treated as treatment failures. The Applicant also conducted the analyses of the primary efficacy endpoint on the ITT population using what they referred to as “the worst-case imputation” and “the best-case imputation.” In the worst-case imputation, the baseline BCVA data was used for missing BCVA at Week 24 and data collected after rescue medications for subjects in the CLS-TA arm; while, the last non-missing BCVA data from a prior visit was used for similar subjects in the Control arm. For the best case-imputation, the reverse was done.

The Applicant used an analysis of covariance (ANCOVA) model to compare the two treatment arms with respect to the secondary efficacy endpoint, the mean change from baseline in central subfield retinal thickness at Week 24. The model included treatment group and country as factors, and baseline central subfield retinal thickness as covariate. This analysis was performed based on the ITT population with the last non-missing data from a prior visit used for missing data and data collected after the receipt of rescue medication. The same analysis was also conducted on the PP population using observed data only. In both these analyses, the Applicant provided a treatment difference together with a 95% confidence interval.

As additional analyses, the Applicant compared the two treatment arms with respect to the mean change from baseline in BCVA at Week 24 using an analysis of variance (ANOVA) model with treatment considered as the only factor. The Applicant also presented treatment differences together with 95% confidence intervals for the proportion of subjects with complete resolution of three inflammation symptom measures: anterior chamber flare, cell and vitreous haze at Week 24 (See Appendix for inflammation Scales). These analyses were performed based on the ITT population with the last non-missing data from a prior visit used for missing data and data collected after the receipt of rescue medication. No multiplicity adjustments were applied for the analyses of the secondary and additional efficacy endpoints.

To be consistent with the recommendations given during the End-of-Phase 2 meeting, the reviewer provided the result of the primary efficacy endpoint on the ITT population by treating subjects who received rescue medication and those with missing BCVA data for other reasons as treatment failures. Additionally, this reviewer conducted a descriptive risk-benefit analysis at the subject level. This analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best-case scenario is the case in which a BCVA improvement of 15 letters or more is achieved at Week 24 without incurring an adverse event (AE) during the study (benefit without harm). The worst-case scenario is incurring an AE during the study without a BCVA improvement from baseline of 15 letters or more at Week 24 (no benefit but harm). The other two scenarios are a case where BCVA improvement from baseline of 15 letters or more is achieved at Week 24 with AE (benefit with harm); and a case where BCVA improvement from baseline of 15 letters or more is not achieved, and no AE is reported (no benefit and no harm).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Demographic and Baseline Characteristics

There were no significant baseline imbalances between the two arms in the demographics of age, gender, race or iris color. In both arms, there were more female participants than male participants; and most of the study participants were white. A larger proportion of subjects in both arms had brown eyes and were younger than 65 years. (Table 2).

Table 2: Baseline and Demographic Characteristics (ITT)

	Treatments		
	CLS-TA N=96	**Control N=64**	**Total N=160**
Sex			
Male	42 (43.8%)	30 (46.9%)	72 (45.0%)
Female	54 (56.3%)	34 (53.1%)	88 (55.0%)
Age			
Mean (STD)	50.4 (14.18)	50.00 (15.08)	50.24 (14.50)
Median	52.0	49.50	51.0
Min, Max	18.0, 92.0	22.0, 85.0	18.0, 92.0
Age Group[1]			
<65 Years	80 (83.3%)	52 (81.2%)	132 (82.5%)
>=65 to <75 Years	13 (13.4%)	8 (12.5%)	21 (13.1%)
≥ 75 Years	3 (3.1%)	4 (6.2%)	7 (4.4%)
Race			
White	40 (41.7%)	25 (39.1%)	65 (40.6%)
Black/ African American	11 (11.5%)	11 (17.2%)	22 (13.8%)
Asian	44 (45.8%)	28 (43.8%)	72 (45.0%)
Other	1 (1.0%)	0 (0.0%)	1 (0.6%)
Iris Color			
Blue	12 (12.5%)	4 (6.3%)	16 (10.0%)
Brown	55 (57.3%)	47 (73.4%)	102 (63.8%)
Black	23 (24%)	7 (10.9%)	30 (18.8%)
Hazel	5 (5.2%)	2 (3.1%)	7 (4.4%)
Green	0 (0.0%)	3 (4.7%)	3 (1.9%)
Gray	1 (1.0%)	0 (0.0%)	1 (0.6%)
Other	0 (0.0%)	1 (1.6%)	1 (0.6%)
Ethnicity			
Hispanic or Latino	10 (10.4%)	6 (9.4%)	16 (10.0%)
Not Hispanic or Latino	86 (89.6%)	58 (90.6%)	144 (90.0%)
BCVA			
Mean (STD)	54.7 (13.92)	53.5 (12.91)	54.20 (13.50)
Median	57.00	54.00	56.00
Min, Max	8, 16	23.0, 93.0	9.0, 89.0
Uveitis Location [2]			
Anterior	27 (28.1%)	14 (21.9%)	41 (25.6%)
Intermediate	34 (35.4%)	23 (35.9%)	57 (35.6%)
Posterior	22 (22.9%)	13 (20.3%)	35 (21.9%)
Pan	28 (29.2%)	24 (37.5%)	52 (32.5%)

Source: Table 14.1.2 and Table 14.1.5 of the Applicant's Study Report. [1]The age categories are provided by the reviewer. [2] 22 subjects had uveitis in two locations and one subject had uveitis in all four locations. These subjects are counted in multiple categories.

3.2.3.2 Patient Disposition and Analysis Populations

The summary of subject disposition is presented in Table 3. Over 95% of subjects in each arm completed the study.

Table 3: Patient Disposition (ITT)

	CLS-TA	**Control**	**Total**
Randomized	96	64	160
Completed the Study	92 (95.8%)	63 (98.4%)	155 (96.9%)
Discontinued the Study	4 (4.2%)	1 (1.6%)	5 (3.1%)
Reason for Subject Withdrawal			
Adverse Event(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Non-Compliance	1 (1.0%)	0 (0.0%)	1 (0.6%)
Lost to Follow-Up	1 (1.0%)	0 (0.0%)	1 (0.6%)
Consent Withdrawn	2 (2.0%)	1 (1.6%)	3 (1.9%)

Source: Table 14.1.1 of the Applicant's Study Report.

The summary of subjects included in the different analyses populations is presented in Table 4. The Intent-to-Treat (ITT) population was used as the primary efficacy analysis population with subjects analyzed under the treatment to which they were randomized.

Table 4: Number of Subjects Included in the Analyses Populations (All Randomized)

Analysis population	**CLS-TA N=96**	**Control N=64**	**Total N=160**
Intent-to-Treat (ITT)	96 (100%)	64 (100%)	160 (100%)
Per-Protocol (PP)	56 (58.3%)	13 (20.3%)	69 (43.1%)
Safety	96 (100%)	64 (100%)	160 (100%)
Pharmacokinetic (PK)	23 (24%)	0 (0%)	23 (14.4%)

Source: Table 14.1.1 of the Applicant's Study Report.

The number of subjects with missing and observed BCVA data at each study visit is presented in Table 5. In both arms, few subjects had missing BCVA data at each visit. For example, at Week 24, BCVA data was missing for only 5 subjects (4 subjects in the CLS-TA arm and one subject in the Control arm). However, BCVA data at Week 24 was collected after 46 (72%) subjects in the Control arm and 13 (14%) subjects in the CLS-TA arm have received rescue medications (*Observed (Treatment + Rescue*). Note that, BCVA data collected after rescue medications use was not included in the primary efficacy analysis.

Table 5: Summary of Subjects by Data Type: (ITT)

Visit	**Data Category**	**CLS-TA N=96**	**Control N=64**	**Total N=160**
Week 4	Observed (On Treatment only)	95(99%)	57(89%)	152(95%)
	Observed (Treatment + Rescue)	0(0%)	6(9%)	6(4%)
	Missing	1(1%)	1(2%)	2(1%)
Week 8	Observed (On Treatment)	94(98%)	37(58%)	131(82%)
	Observed (Treatment + Rescue)	0(0%)	26(41%)	26(16%)
	Missing	2(2%)	1(2%)	3(2%)
Week 12	Observed (On Treatment only)	89(93%)	32(50%)	121(76%)
	Observed (Treatment + Rescue)	4(4%)	30(47%)	34(21%)
	Missing	3(3%)	2(3%)	5(3%)
Week 16	Observed (On Treatment only)	85(89%)	28(44%)	113(71%)
	Observed (Treatment + Rescue)	8(8%)	34(53%)	42(26%)
	Missing	3(3%)	2(3%)	5(3%)
Week 20	Observed (On Treatment only)	81(84%)	26(41%)	107(67%)
	Observed (Treatment + Rescue)	9(9%)	36(56%)	45(28%)
	Missing	6(6%)	2(3%)	8(5%)
Week 24	Observed (On Treatment only)	79(82%)	17(27%)	96(60%)
	Observed (Treatment + Rescue)	13(14%)	46(72%)	59(37%)
	Missing	4(4%)	1(2%)	5(3%)

Source: Reviewer's Analysis. Missing: data not collected; Observed (On Treatment only): data collected without any rescue medication; Observed (Treatment + Rescue): data collected after a subject has received a rescue medication.

The summary of subjects who received rescue medication on or prior to a given visit is presented in Table 6. As shown, more Control randomized subjects received rescue medication

compared to those in the CLS-TA arm. Moreover, most Control randomized subjects received rescue medication at earlier time points compared to subjects in the CLS-TA arm. In the CLS-TA arm, rescue medication use increased starting around Week 12. Note that subjects received the second injection of their assigned treatment around Week 12.

Table 6: Proportion of Subjects Who Received Rescue Medication (ITT)

Visit	CLS-TA N=96	Control N=64	Total N=160
Week 4	0(0%)	24(38%)	24(15%)
Week 8	4(4%)	31(48%)	35(22%)
Week 12	8(8%)	34(53%)	42(26%)
Week 16	10(10%)	38(59%)	48(30%)
Week 20	13(14%)	46(72%)	59(37%)
Week 24	13(14%)	46 (72%)	59 (37%)

Source: Reviewer's Analysis. A total of 11 subjects received their first rescue medication during unscheduled visits that were outside the prespecified visit window. For these subjects, the study week at which the rescue medication was used is set as the week closer to the unscheduled visit.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

3.2.4.1.1 *Primary Efficacy Analysis*

A significantly higher proportion of subjects in the CLS-TA arm achieved 15 letters or more improvement from baseline at Week 24 compared with the sham Control arm (45% vs 16%; diff (95% CI): 31 (15%, 46%]).

3.2.4.1.2 *Sensitivity Analyses*

The number of subjects who discontinued the study, and the number of subjects who had missing BCVA data at Week 24 were very minimal (Table 3 and Table 5). On the other hand, 72% of Control randomized subjects and 13% of CLS-TA randomized subjects received rescue medications (Table 6). Therefore, as can be seen from the sensitivity analyses conducted by the Applicant and this reviewer, use of rescue medication was the single important intercurrent event of interest. Overall, the sensitivity analyses results are supportive of the primary efficacy analysis result.

The results from the primary efficacy analysis (*Primary*) and the reviewer's sensitivity analysis which treated all rescue users and subjects with missing BCVA data at Week 24 as treatment failures (*Rescue and Missing as failure*) were only slightly different. The *treatment policy analysis*, which included all observed data regardless of rescue use, however provided a treatment difference that was substantially lower than the difference observed in the primary efficacy analysis. This is because, 13 subjects in the Control arm, whose BCVA improvement from baseline was less than 15 letters (failure) prior to rescue use, has changed to an improvement of more than 15 letters (success) after rescue use. There was only one such subject in the CLS-TA arm. In fact, three subjects in the CLS-TA arm who had a more than 15 letters

improvement in BCVA (success) prior to rescue had an improvement of less than 15 letters after rescue use (failure) (Table 7).

Table 7: Sensitivity Analysis Results for the Primary Efficacy Endpoint (ITT)

Approaches	Treatments		Difference (95% CI)
	CLS-TA	**Control**	
Primary[1]	45/96 (47%)	10/66 (16%)	31% (15%, 46%)
Rescue and Missing Failure[2]	41/96 (43%)	6/66 (9%)	33% (18%, 48%)
Worst-Case Imputation[3]	41/96 (43%)	10/66 (16%)	27% (11%, 42%)
Treatment policy[4]	43/96 (45%)	23/66 (36%)	9% (-7%, 25%)

[1]Source: Table 12 of the Applicant's Study Report. The last non-missing BCVA data from a prior visit was used for missing data at Week 24 and for Week 24 data collected after receiving rescue medication

[2] Source: Reviewer's Analysis. Subjects with missing data at Week 24 and subjects who received rescue medication are considered as treatment failures (< 15 letters improvement from baseline).

[3]Source: Adapted from Table 14.2.1.3 of the Applicant's Study Report. For subjects in the CLS-TA arm with missing data at Week 24 and those who received rescue medications prior to the evaluation of the primary efficacy endpoint, the baseline BCVA value was used. For similar subjects in the Control arm, the last non-missing BCVA data from a prior visit was used.

[4] Source: Adapted from Table 14.2.2.1 of the Applicant's Study Report. All observed data regardless of rescue medication use is used.

Reviewer's remarks: *Note that, neither the protocol nor the statistical analysis plan clearly specified the treatment difference of interest that was to be estimated in the primary efficacy analysis. However, because BCVA data collected after rescue medications use was not included in the primary efficacy analysis, the interest was likely to evaluate the effect of the randomized treatment without the confounding effect of rescue medications.*

Reviewer's remarks: *Note also that, because the primary and sensitivity analyses estimated different quantities of treatment effect, they are interpreted differently. For example, the treatment difference estimated by the protocol defined primary efficacy analysis could be interpreted as "the difference in the proportion of subjects with a BCVA improvement of at least 15 letters from baseline at the last time through Week 24 prior to receiving a rescue medication."*

On the other hand, the analysis listed as treatment-policy estimates "the difference in the proportion of subjects with a BCVA improvement of at least 15 letters from baseline at Week 24 in all subjects in the ITT population, regardless of whether rescue medication was used." Similarly, the reviewer's analysis which treated all subjects who received a rescue medication and those who had missing BCVA as treatment failures could be viewed as "the difference between CLS-TA and Control in the proportion of subjects in the ITT population with a BCVA improvement of at least 15 letters from baseline at Week 24 without a need for a rescue medication."

3.2.4.1.3 *Secondary Efficacy Endpoint*

The mean change from baseline in central subfield retinal thickness at Week 24 was the only secondary efficacy endpoint in this study. The mean reduction in central subfield retinal thickness from baseline at Week 24 was 162.2 μm in the CLS-TA arm compared to 4.5 μm in the Control arm providing a treatment difference (CLS-TA-Control) of 157.71 μm (95% CI: -198.86, -116.57). The observed differences in mean changes from baseline central subfield retinal thickness at all study visits were consistently favorable to the CLS-TA arm (Figure 3).

3.2.4.1.4 *Additional Efficacy Endpoints*

The Applicant presented results of treatment comparisons in the mean change from baseline in BCVA at all visits. The Applicant's treatment comparisons were however performed without adjusting for baseline BCVA. The reviewer provided treatment differences in the mean change from baseline in BCVA estimated using an ANCOVA model adjusting for baseline BCVA. These results showed that the CLS-TA arm had consistently higher BCVA improvement from baseline for all study visits. The improvements ranged from 9.7 letters at Week 4 to 13.9 letters at Week 24, compared to an increase of 1.2 letters (Week 4) to 3 letters (Week 24), in the Control arm (Figure 4 and Figure 5). The Applicant also provided the mean change from baseline in BCVA by uveitis anatomic location (Anterior, Intermediate, Posterior and Pan). At Week 24, subjects in the CLS-TA arm had consistently higher mean change from baseline in BCVA for all four uveitis anatomic locations [14.4 vs 2.9 (Anterior), 13.4 vs 7 (Intermediate), 12 vs -1.6 (Pan) and 15.6 vs 1.4 (Posterior)].

The treatment differences in the proportions of subjects with complete resolution of signs of inflammation (anterior chamber cells, anterior chamber flare and vitreous haze) were consistently favorable to the CLS-TA arm compared to the Control arm at all study visits. The treatment differences in the signs of inflammation ranged between 11% and 34% (Figure 6- Figure 8).

As stated earlier, during the pre-NDA meeting, the Agency recommended that data showing the proportion of subjects with a complete resolution of vitreous haze at Week 24 among those who had vitreous haze scores ≥ 2 (Sun Criteria) at baseline be presented. It however appears that there were very few subjects with vitreous haze scores of 2 or more at baseline in this study. Thus, the Applicant instead provided the proportions of subjects with complete resolutions of vitreous haze among those who had any signs of inflammation at baseline (score>0). They also provided the proportions of subjects with complete resolution of anterior chamber cells and the proportion of subjects with complete resolution of flare among those with anterior chamber cell score and flares score of greater than zero at baseline, respectively. These results also favor the CLS-TA arm (Figure 9- Figure 11). In addition, treatment comparisons based on the health assessment scores of VFQ-25 and EQ-5D were also provided. The results for the composite VFQ-25 score presented in Figure 12 show a numerically higher improvement from baseline (7.3 units) in VFQ-25 score in the CLS-TA arm compared to subjects in the Control arm (3.8 units).

3.2.4.1.5 *Subgroup Analyses*

The subgroup analyses results are consistent with the result of the primary efficacy analysis. The CLS-TA arm had consistently higher proportion of subjects with an improvement of 15 letters or more from baseline at Week 24 for subgroups formed based on age, sex, iris color, race and country group (Figure 15). Note, because only 10 subjects were enrolled from Israel, the country subgroup was formed by combining the 10 subjects from Israel with the 80 subjects from the US (US+Israel versus India).

3.3 Evaluation of Safety

3.3.1 Treatment Exposure

Per the study protocol, subjects were to receive two suprachoroidal injections of their assigned treatments, approximately 12 weeks apart (at baseline and Week 12). All randomized subjects (96 in the CLS-TA arm and 64 in the Control arm) received their respective first scheduled injection at baseline. Of these, 84 (87.5%) and 29 (45.3%) subjects received CLS-TA and sham injections at Week 12, respectively.

3.3.2 Protocol Deviations

A total of 30 (31.3%) subjects in the CLS-TA arm and 12 (18.8%) subjects in the Control arm had major protocol deviations. The main protocol deviations reported were non-compliance with the inclusion and exclusion criteria, non-compliance with masking, not performing Week 24 assessment and use of prohibited concomitant therapy.

3.3.3 Adverse Events

The proportion of subjects who reported at least one ocular adverse event in the study eye was slightly lower in the CLS-TA arm [49 (51%)] compared to the Control arm [37 (58%)]. However, individual subjects in the CLS-TA arm experienced a higher number of ocular adverse events compared to subjects in the Control arm. Specifically, a combined total of 122 events were reported by the 49 CLS-TA randomized subjects who reported at least one ocular adverse event. The corresponding figure for the 37 subjects in the Control arm was 54 events.

The most common ocular adverse events reported in the CLS-TA arm were intraocular pressure (17.7%), eye pain (14.6%), cataract (8.3%), and vitreous detachment (5.2%). The incidence rates of these events in the Control arm were: 6.3% (intraocular pressure), 0.0% (eye pain), 6.3% (cataract), and 1.6% (vitreous detachment). No death was reported in either arm, however, 3 (3.1%) subjects, all in the CLS-TA arm, experienced serious adverse events (sialoadenitis, lumbar vertebral fracture and retinal detachment) of which one (retinal detachment) was an ocular adverse event (Table 8).

No subject in either arm discontinued the study due to an adverse event. However, the study reported that 5 (5.2%) subjects in the CLS-TA arm and 5 (7.8%) subjects in the Control arm experienced adverse events that lead to treatment discontinuations. Because all randomized subjects received the first of the two planned injections, “treatment discontinuation” likely refers to not receiving the planned second injection. The most frequent adverse events reported in the CLS-TA arm that led to treatment discontinuation were ocular hypertension, uveitis, visual acuity reduced, vitreous haemorrhage and increased intraocular pressure, all of which occurred in about 1% of the subjects. Uveitis (6.3%), iridocyclitis (1.6%), and increased intraocular pressure (1.6%) were the most frequent adverse events that led to treatment discontinuation in the Control arm.

Table 8: Summary of Adverse Events

Adverse event (AE)	Treatment: N (%) CLS-TA N=96	Control N=64	Total N=160
Any AE (Ocular and non-ocular)[1]	67 (70%)	45 (70%)	112 (70.0%)
Any serious AE (SAE)	3 (3%)	0 (0%)	3 (2%)
Any ocular AE in the Study eye[2]	49 (51%)	37 (58%)	86 (54%)
Intraocular pressure increased	17(18%)	4(6%)	21(13%)
Eye pain	14(15%)	0 (0.0%)	14(9%)
Cataract[3]	8 (8%)	4(6%)	12(8%)
Vitreous detachment	5(5%)	0 (0.0%)	5(3%)
Conjunctival haemorrhage	4(4%)	2(3%)	6(4%)
Injection site pain	4(4%)	2(3%)	6(4%)
Visual acuity reduced	4(4%)	1(2%)	5(3%)
Vitreous floaters	3(3%)	0 (0.0%)	3(2%)
Anterior capsule contraction	2(2%)	0 (0.0%)	2(1%)
Chalazion	2(2%)	0 (0.0%)	2(1%)
Conjunctival hyperaemia	2(2%)	1(2%)	3(2%)
Conjunctival oedema	2(2%)	0 (0.0%)	2(1%)
Dry eye	2(2%)	1(2%)	3(2%)
Eye irritation	2(2%)	0 (0.0%)	2(1%)
Eyelid ptosis	2(2%)	0 (0.0%)	2(1%)
Ocular hypertension	2(2%)	5(8%)	7(4%)
Photophobia	2(2%)	0 (0.0%)	2(1%)
Photopsia	2(2%)	0 (0.0%)	2(1%)
Punctate keratitis	2(2%)	1(2%)	3(2%)
Uveitis	2(2%)	7(11%)	9(6%)
Vision blurred	2(2%)	0 (0.0%)	2(1%)
Conjunctival disorder	1(1%)	0 (0.0%)	1(1%)
Erythema of eyelid	1(1%)	0 (0.0%)	1(1%)
Eye pruritus	1(1%)	0 (0.0%)	1(1%)
Injection site discomfort	1(1%)	1(2%)	2(1%)
Injection site erythema	1(1%)	0 (0.0%)	1(1%)
Iridocyclitis	1(1%)	1(2%)	2(1%)
Macular pseudohole	1(1%)	0 (0.0%)	1(1%)
Meibomianitis	1(1%)	0 (0.0%)	1(1%)
Ocular hyperaemia	1(1%)	0 (0.0%)	1(1%)
Periorbital haemorrhage	1(1%)	0 (0.0%)	1(1%)
Posterior capsule opacification	1(1%)	0 (0.0%)	1(1%)
Retinal detachment	1(1%)	0 (0.0%)	1(1%)
Retinal tear	1(1%)	0 (0.0%)	1(1%)
Scleral hyperaemia	1(1%)	0 (0.0%)	1(1%)
Visual field defect	1(1%)	0 (0.0%)	1(1%)
Vitreous haemorrhage	1(1%)	0 (0.0%)	1(1%)
Vitritis	1(1%)	0 (0.0%)	1(1%)

Source: Tables 19 and 20 of the Applicant's Study Report. [1] includes ocular AEs reported in both the study and the fellow eyes. [2]Ocular AEs are for the study eye only. If the subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE, using the closest relationship to study treatment.[3] Includes cataract, cataract cortical and cataract subcapsular.

Increased IOP was one of the main adverse events reported in subjects randomized to the CLS-TA arm. The summary of the treatment comparisons with respect to the change from baseline in

IOP at each time point is presented in Figure 14. The results are provided from an analysis of covariance (ANCOVA) model with baseline IOP and treatment as covariates. Per the results, both arms showed an increase in IOP from baseline; with higher increases observed in the CLS-TA arm compared to the Control arm. The increases in IOP ranged from 1.6 to 5.4 mm Hg in the CLS-TA arm compared to 1.2 to 3 mm Hg in the Control arm. The highest increase in IOP of 5.4 mm Hg was observed after the second injection was administered at Week 12.

3.4 Risk-Benefit Summary

Per the Applicant, the unique distribution of TA following suprachoroidal administration of CLS-TA is likely to provide a differentiating benefit to risk profile where both efficacy and safety outcomes have the potential to be enhanced over the outcomes seen from other local methods of corticosteroid administration to the eye. As the safety results in this study and the literature summary (See Appendix) showed, IOP related adverse events were the most common adverse events reported following the use of CLS-TA. Thus, for this descriptive risk-benefit summary, incurring IOP related adverse events (increased IOP or ocular hypertension) was considered as the most relevant treatment related risk.

The proportion of subjects who have benefited from the drug (achieved a 15 letters improvement from baseline at Week 24) without incurring IOP related adverse events was 38% in the CLS-TA arm compared to 16% in the Control arm. On the other hand, 10% of CLS-TA randomized subjects experienced increased IOP related adverse events without achieving 15 letters or more improvement from baseline at Week 24 compared to 14% in the Control arm. With benefit measured as a 10 letters improvement from baseline, the proportion of subjects who have benefited from the drug (achieved a 10 letters improvement from baseline) without incurring the risk of developing IOP related adverse events was 47% in the CLS-TA arm compared to 28% in the Control arm. On the other hand, 6% of CLS-TA randomized subjects compared to 13% in the Control arm, experienced IOP related adverse events without achieving 10 letters or more improvement from baseline (Figure 16).

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

No major statistical issues were encountered in this review.

4.2 Collective Efficacy Evidence

A higher proportion of subjects in the CLS-TA arm achieved a BCVA improvement of at least 15 letters from baseline at Week 24. The results from the analyses of the secondary efficacy endpoint and the additional efficacy endpoints of the study are all supportive of the efficacy of CLS-TA. The CLS-TA arm had a higher mean reduction in subfield retinal thickness from baseline at Week 24. Moreover, a higher proportion of subjects in the CLS-TA arm showed clearance of signs of inflammation at all study visits compared to subjects randomized to the Control arm. In addition, a substantially higher proportion of subjects in the Control arm needed a rescue medication compared to subjects in the CLS-TA arm.

4.3 Labeling Recommendations

The Applicant's proposed text presented in Section 14 of the drug label (see below) together with the summary of the primary efficacy endpoint as presented in *Table A0* is acceptable.

*The efficacy of **XIPERE** was assessed in a 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with uveitis. The primary efficacy endpoint was the proportion of subjects in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up (Table A0). A statistically significantly greater proportion of patients treated with XIPERE achieved a ≥15-letter improvement in BCVA than control patients (p<0.001) at Week 24.*

Table A0: Number and Percent of Patients with ≥15 Letters Improvement from Baseline in BCVA at Week 24

XIPERE (N = 96)	***Control (N = 64)***	***% Difference (95% CI)***
45 ((b) (4)%)	*10 ((b) (4)%)*	*31 (b) (4)% (15(b) (4)%, (b) (4)%)*

The Applicant also claimed that there are "statistically significant" treatment differences in favor of CLA-TA for the secondary efficacy endpoint (the mean change from baseline in subfield retinal thickness at week 24) and the additional efficacy endpoints listed below:

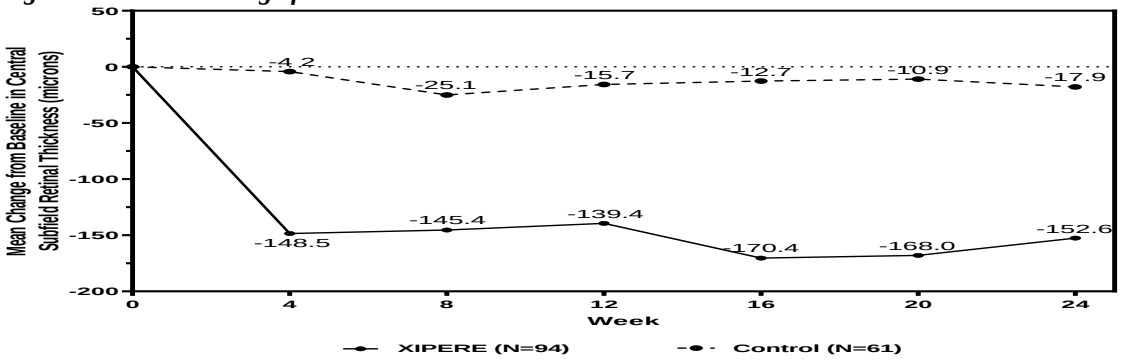
- The mean change from baseline in BCVA at all post-baseline study visits (for the overall population)
- The mean change in BCVA at Week 24 by anatomical locations (Anterior, Intermediate, Posterior and Pan)
- The proportion of subjects with clearing of each of the three signs of inflammation (anterior chamber cell, flare and vitreous haze)
- The proportion of subjects with a 2-step reduction in each of the three signs of inflammation.

However, because the study did not specify a testing procedure that adjusted for multiplicity due to testing these additional endpoints, per this reviewer, the Applicant cannot make claims of "statistical significance" for the treatment differences associated with the additional efficacy endpoints. If the additional endpoints are deemed relevant and believed to add value to the

prescribing physician, this reviewer recommends that the results be presented in the drug label as descriptive summaries as follows:

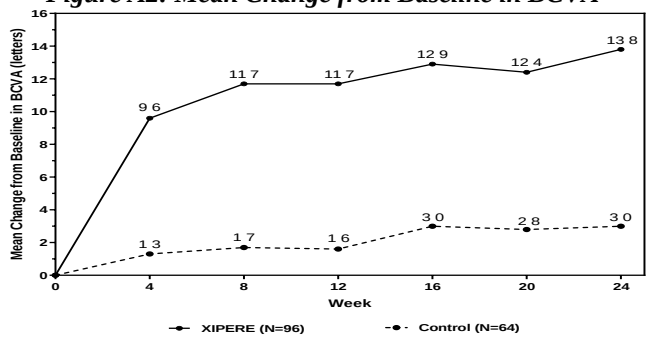
Descriptive summaries for the mean change from baseline in subfield retinal thickness at week 24, the mean change from baseline in BCVA for the overall population and by uveitis anatomic locations are presented in Figures A1-A3.

Figure A1: Mean Change from Baseline in CST



(b) (4)

Figure A2: Mean Change from Baseline in BCVA



(b) (4)

(b) (4)

Applicant's Summary presented in Section 14 of the drug label

*The efficacy of **XIPERE** was assessed in a 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with uveitis.*

The primary efficacy endpoint was the proportion of subjects in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up (Table A1).

Table A1: Number and Percent of Patients with ≥15 Letters Improvement from Baseline in BCVA at Week 24

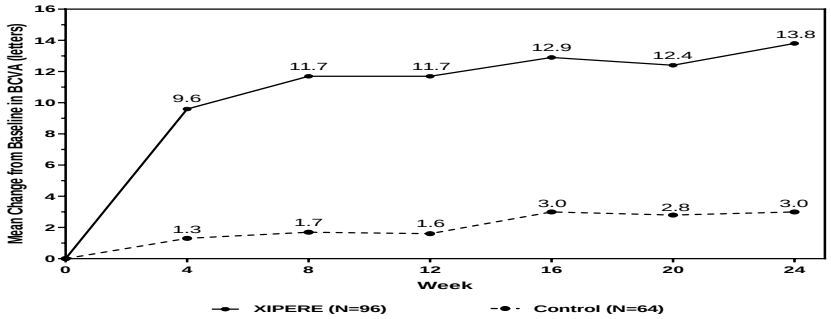
Patients Who Gained ≥ 15 Letters from Baseline at Week 24	***XIPERE (N = 96)***	***Control (N = 64)***
n (%)	*45 ((b) (4)%)*	*10 ((b) (4)%)*
Estimated Difference (95% CI)	*31 (b) (4)% (15 (b) (4)%, (b) (4)%)*	
*CMH p-value**	*<0.001*	

** The p-value was based on a Cochran Mantel Haenszel test for general association between treatment and response with stratification by country.*

*A statistically significantly greater proportion of patients treated with **XIPERE** achieved a ≥15-letter improvement in BCVA than control patients (p<0.001) at Week 24.*

(b) (4)

Figure A1: Mean Change from Baseline in BCVA

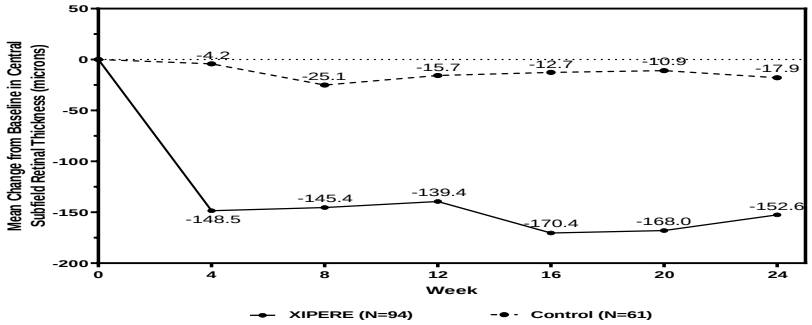


(b) (4)

(b) (4)

(b) (4)

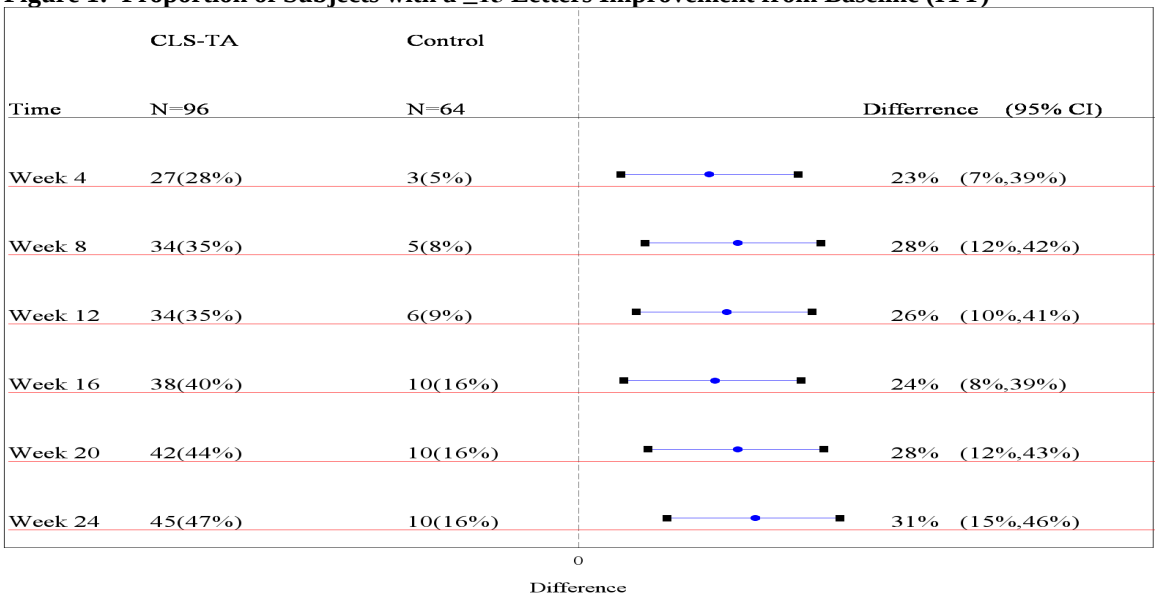
Figure A3: Mean Change from Baseline in CST



(b) (4)

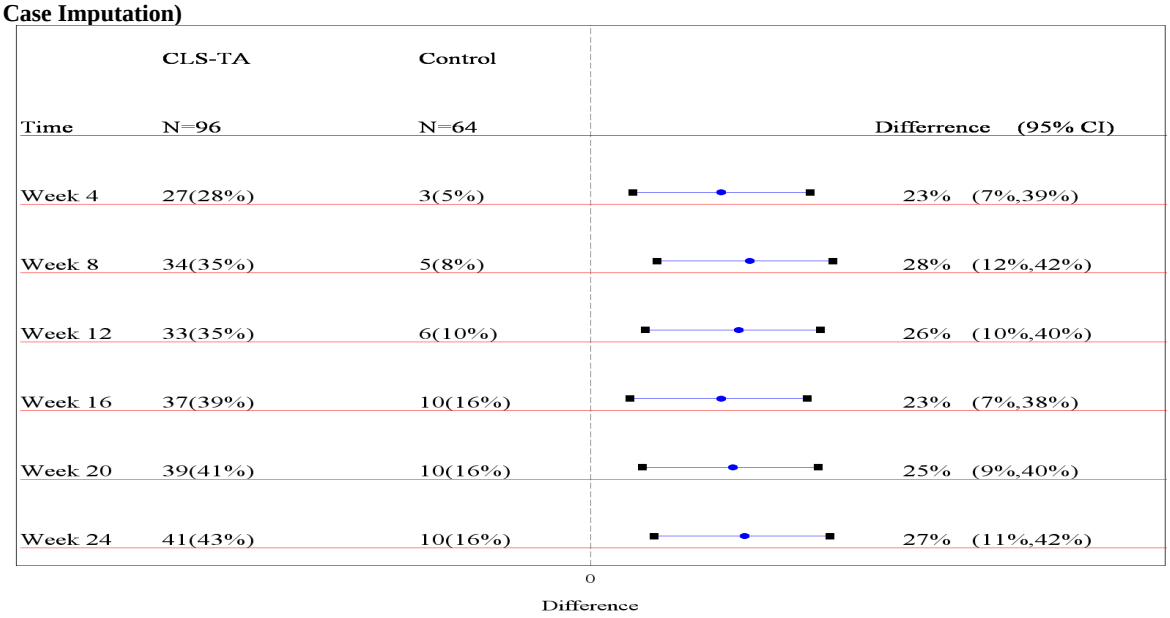
5 Appendix 1: Selected Efficacy and Safety Summaries

Figure 1: Proportion of Subjects with a ≥15 Letters Improvement from Baseline (ITT)



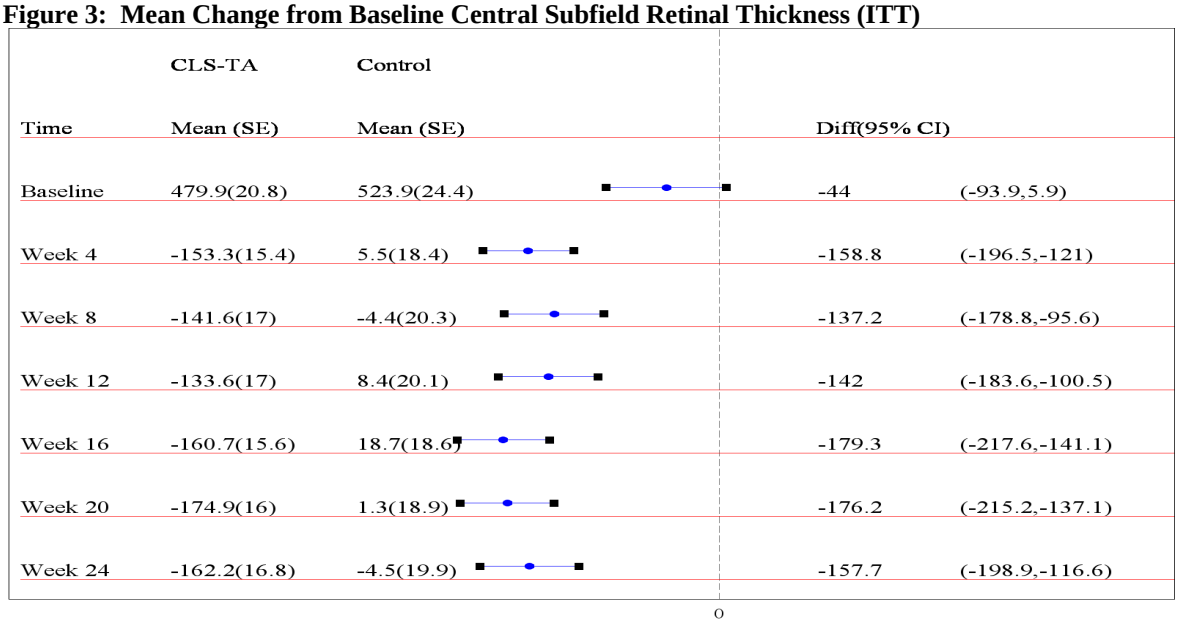
Source: Adapted from Table 15 of the Applicant's Study Report. Treatment differences and 95% confidence intervals for timepoints other than Week 24 provided by the reviewer. For missing BCVA data and data collected after rescue medication, the last non-missing data from a prior visit is used.

Figure 2: Proportion of Subjects with a ≥15 Letters Improvement from Baseline (ITT: Applicant's Worst-Case Imputation)



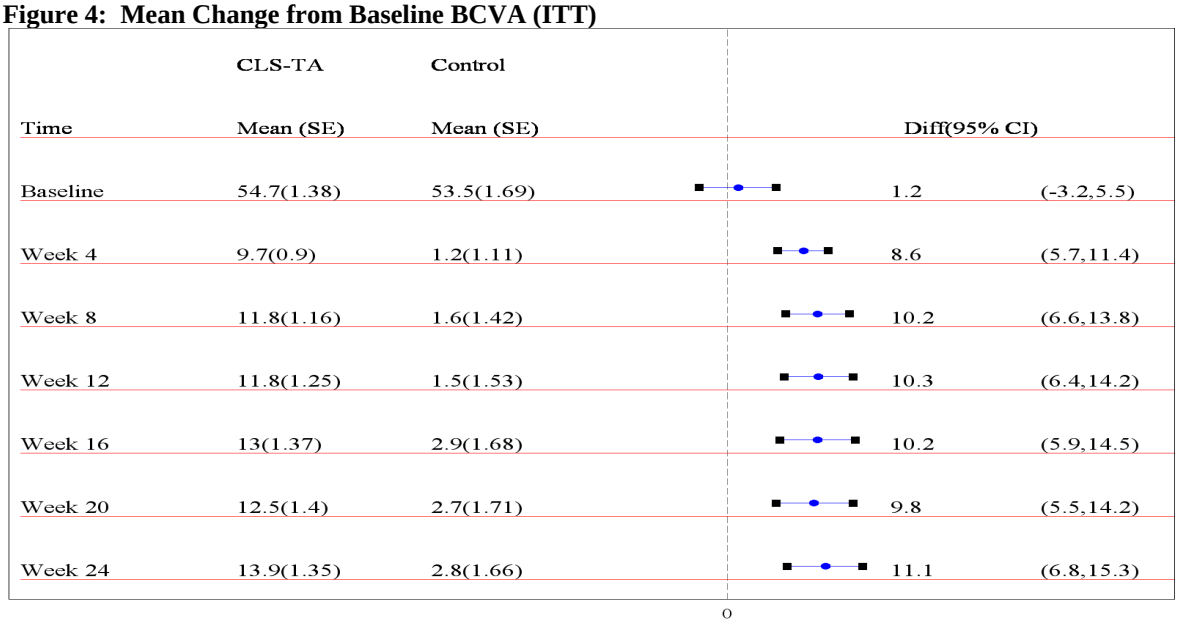
Source: Reviewer's Analysis. Treatment differences and 95% confidence intervals for timepoints other than Week 24 provided by the reviewer. For the Control arm, missing BCVA data and data collected after rescue medication, the last non-missing data from a prior visit is used. For the CLS-TA arm, for missing BCVA data and data collected after rescue medication, the baseline values are used.

Figure 3: Mean Change from Baseline Central Subfield Retinal Thickness (ITT)



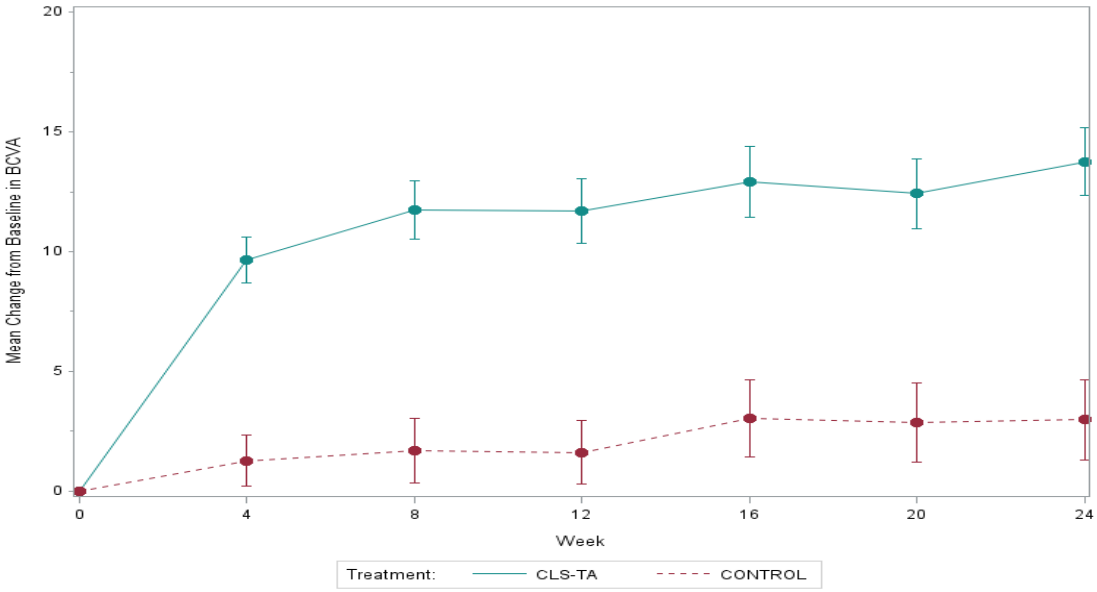
Source: Reviewer's Analysis. Mean (SE), treatment differences and confidence intervals are provided from an ANCOVA model with treatment, country and baseline central subfield retinal thickness used as covariates. For missing central subfield retinal thickness data and data collected after rescue medication, the last non-missing data from a prior visit is used.

Figure 4: Mean Change from Baseline BCVA (ITT)



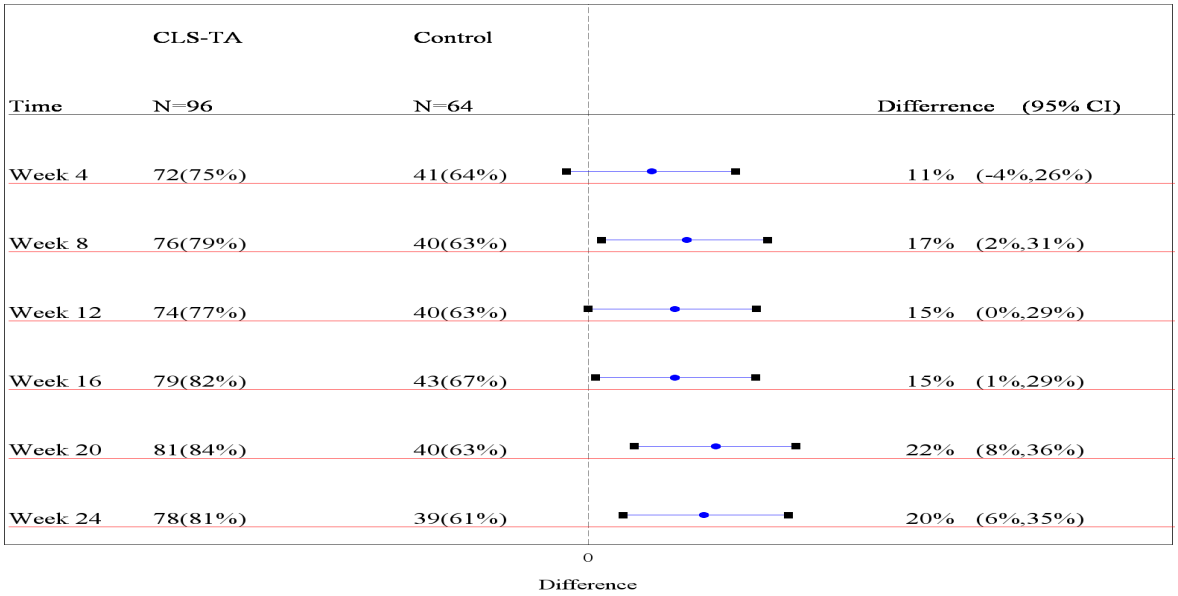
Source: Reviewer's Analysis. Mean (SE), treatment differences and confidence intervals are provided from an ANCOVA model with treatment and baseline BCVA used as covariates. For missing BCVA data and data collected after rescue medications, the last non-missing data from a prior visit is used.

Figure 5: Plot of Mean Change from Baseline BCVA Over Time (ITT)



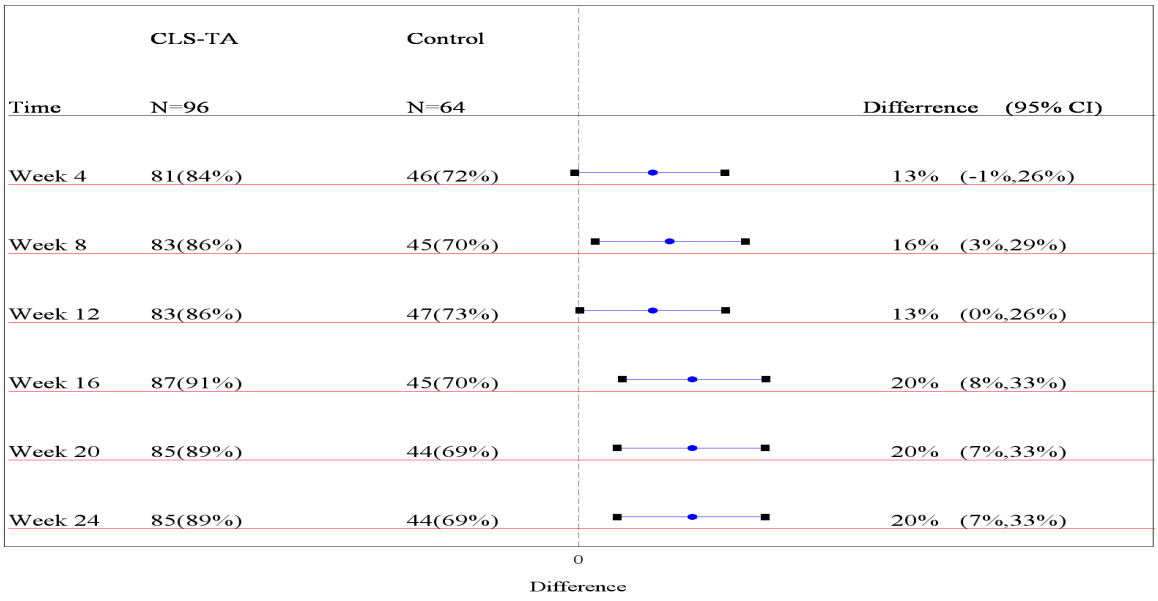
Source: Reviewer's Analysis. For missing BCVA data and data collected after rescue medications, the last non-missing data from a prior visit is used.

Figure 6: Proportion of Subjects with a Complete Resolution of Anterior Chamber Cells (Score=0)



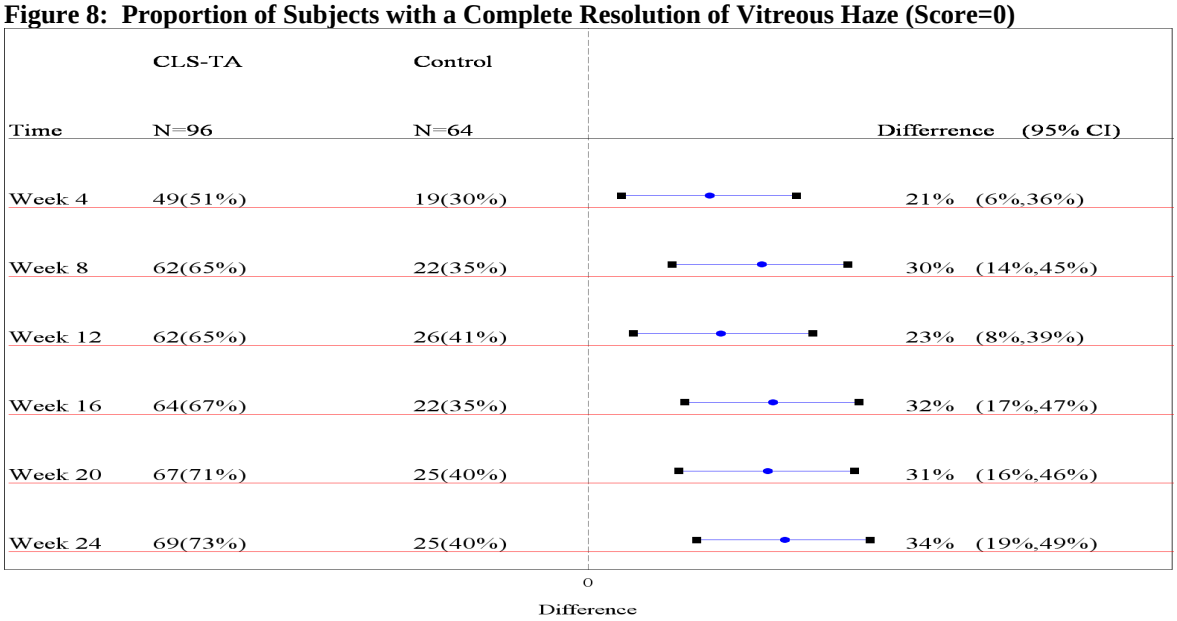
Source: Table 14.2.11.1 of the Applicant's Study Report. For missing data and data after rescue medication use, the last-non-missing data from a prior visit is used.

Figure 7: Proportion of Subjects with a Complete Resolution of Flare (Score=0)



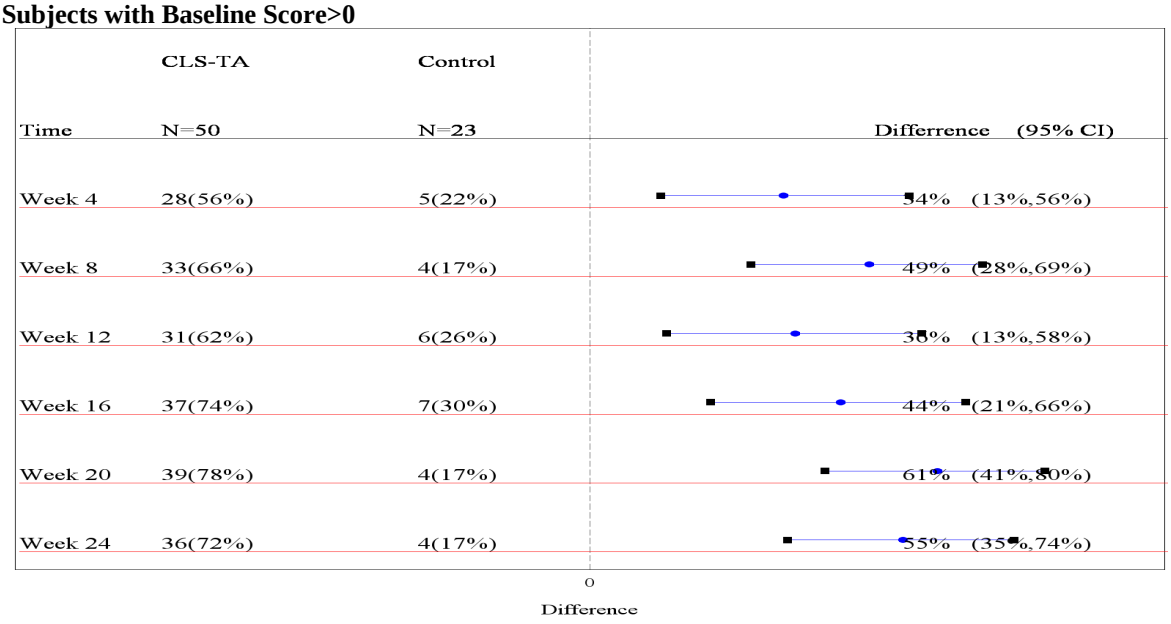
Source: Table 14.2.11.3 of the Applicant's Study Report. For missing data and data after rescue medication use, the last-non-missing data from a prior visit is used.

Figure 8: Proportion of Subjects with a Complete Resolution of Vitreous Haze (Score=0)



Source: Table 14.2.11.5 of the Applicant's Study Report. For missing data and data after rescue medication use, the last-non-missing data from a prior visit is used.

Figure 9: Proportion of Subjects with a Complete Resolution of Anterior Chamber Cells (Score=0) Among Subjects with Baseline Score>0



Source: Table 14.2.11.2 of the Applicant's Study Report. For missing data and data after rescue medication use, the last-non-missing data from a prior visit is used. Only subjects with baseline anterior chamber cell score of >0 are included.

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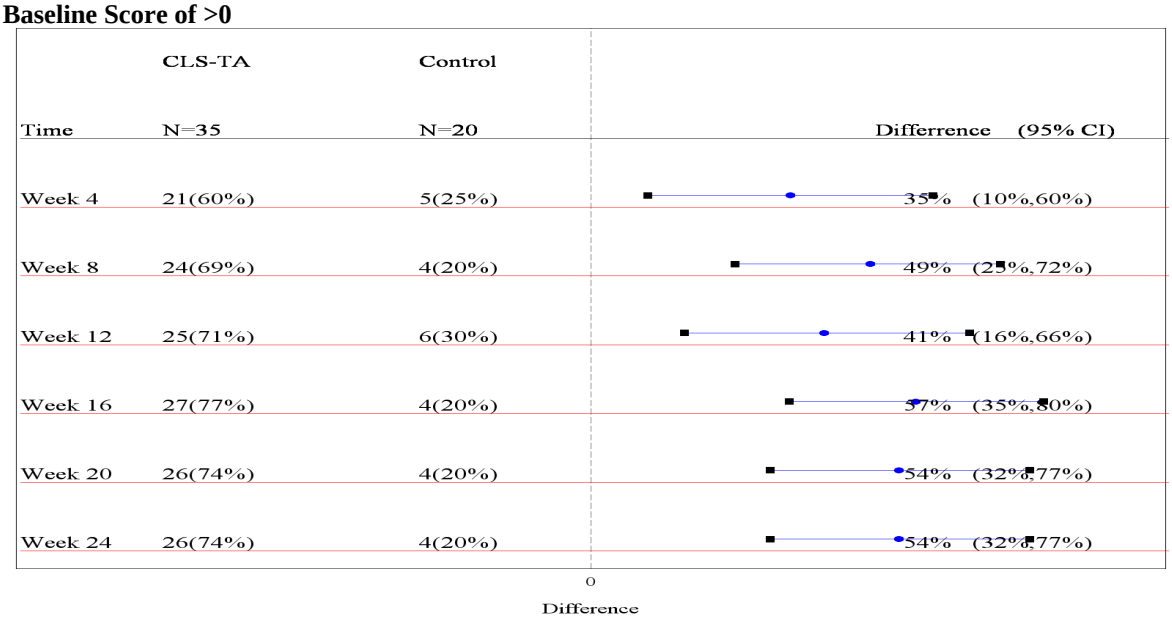
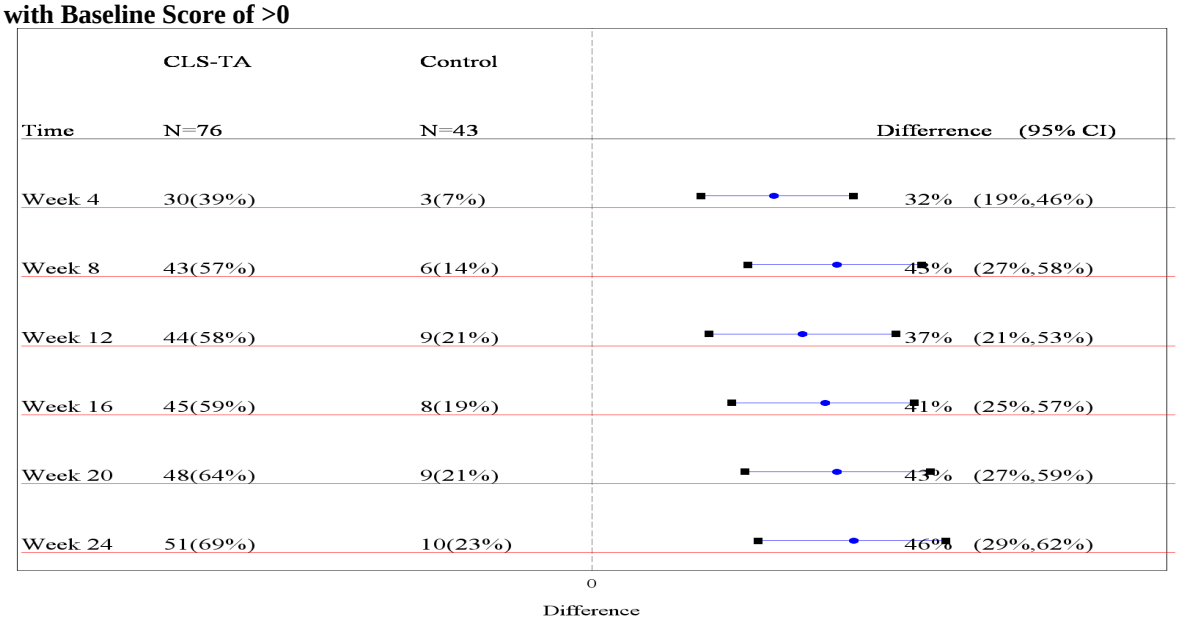
Figure 10: Proportion of Subjects with a Complete Resolution of Flare (Score=0) Among Subjects with Baseline Score of >0



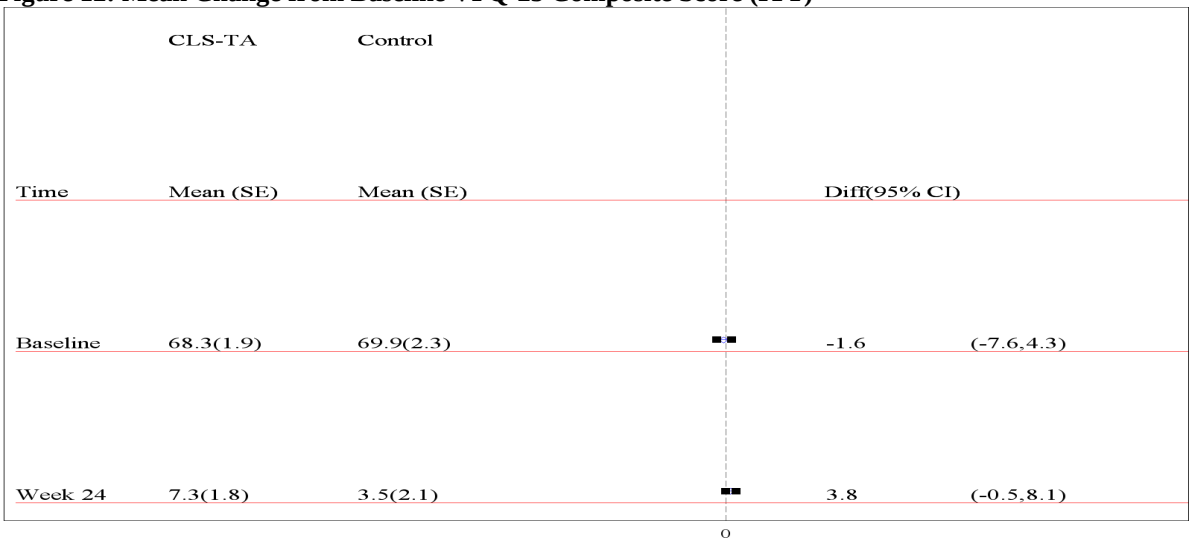
Source: Table 14.2.11.4 of the Applicant's Study Report. For missing data and data after rescue medication use, the last-non-missing data from a prior visit is used. Only subjects with baseline flare score of >0 are included.

Figure 11: Proportion of Subjects with a Complete Resolution of Vitreous Haze (Score=0) Among Subjects with Baseline Score of >0



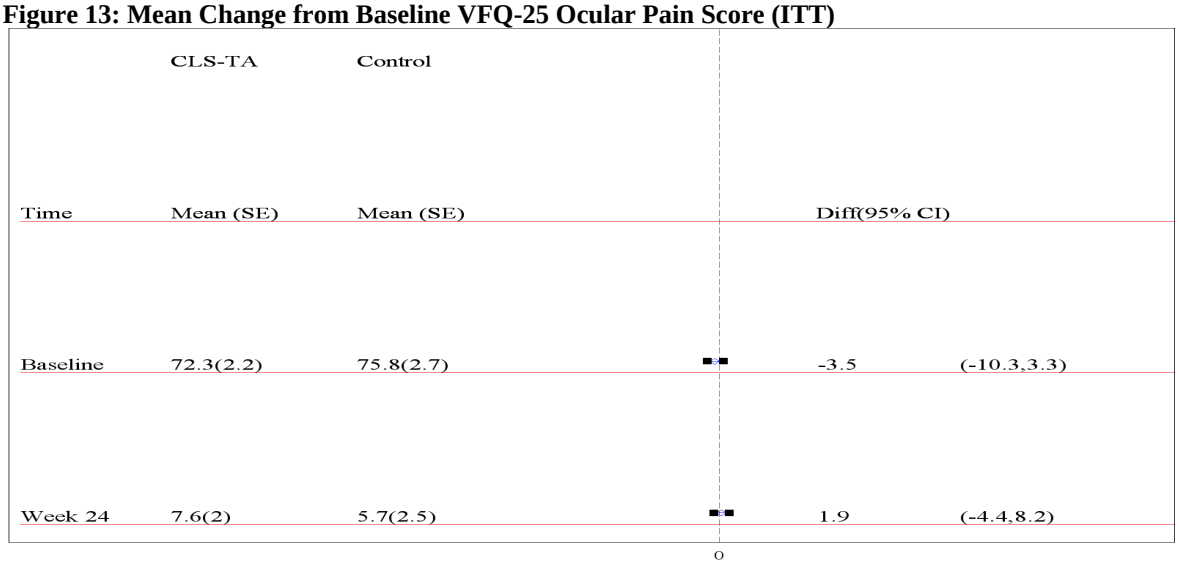
Source: Table 14.2.11.6 of the Applicant's Study Report. For missing data and data after rescue medication use, the last-non-missing data from a prior visit is used. Only subjects with baseline vireos haze score of >0 are included.

Figure 12: Mean Change from Baseline VFQ-25 Composite Score (ITT)



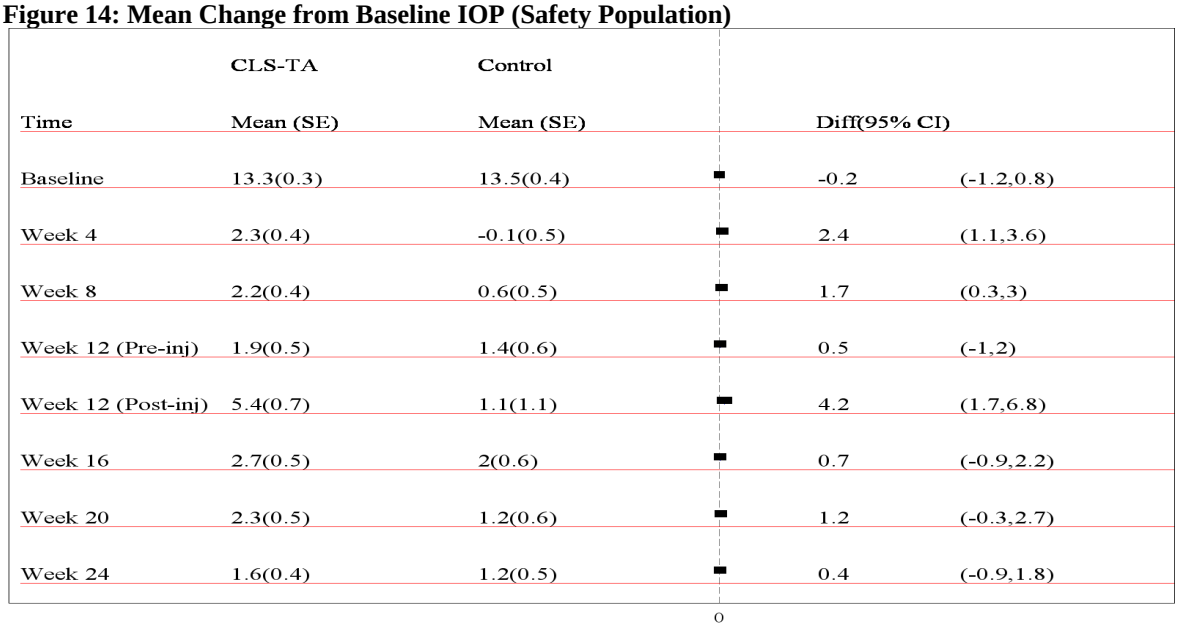
Source: Adapted from Table 14.2.7.1.1 of the Applicant's Study Report. Mean (SE), treatment differences and confidence intervals are provided from an ANCOVA model with treatment, country and baseline score used as covariates. For missing VFQ-25 data at a given visit, the last non-missing data from a prior visit is used.

Figure 13: Mean Change from Baseline VFQ-25 Ocular Pain Score (ITT)



Source: Adapted from Table 14.2.7.1.1 of the Applicant's Study Report. Mean (SE), treatment differences and confidence intervals are provided from an ANCOVA model with treatment, country and baseline score used as covariates. For missing VFQ-25 ocular pain data at a given visit, the last non-missing data from a prior visit is used.

Figure 14: Mean Change from Baseline IOP (Safety Population)



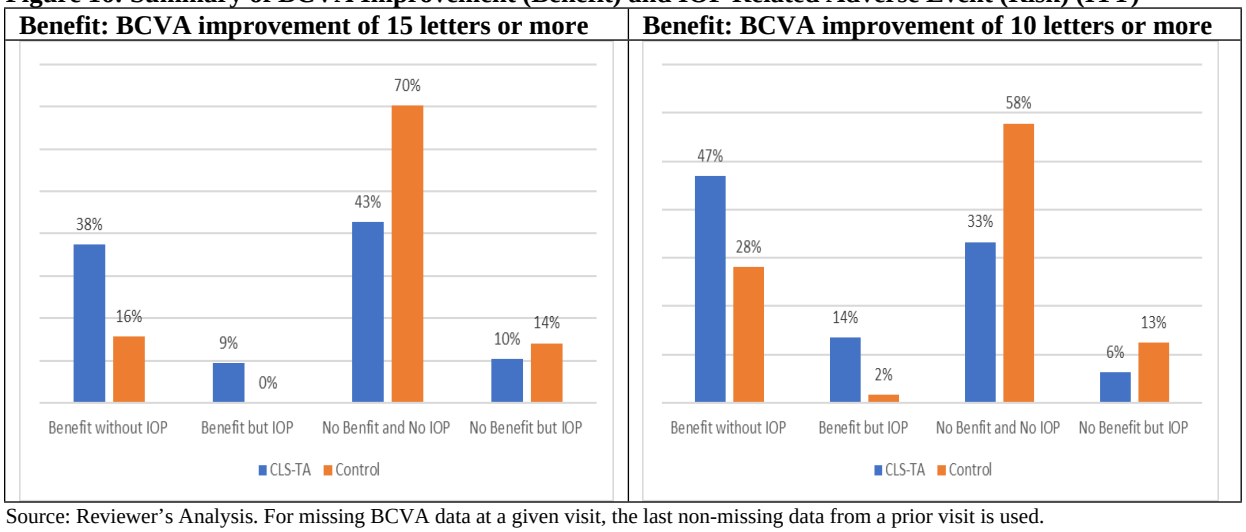
Source: Adapted from Table 14.3.5.1.1 of the Applicant's Study Report. Mean (SE), treatment differences and confidence intervals are provided from an ANCOVA model with treatment and baseline IOP used as covariates. Pre-inj and Post-inj refer to pre and post second injection IOP values.

Figure 15: Subgroup Analysis: Proportion of Subjects with >=15 letters Improvement from Baseline at Week 24 (ITT)

Subgroups	CLS-TA N (%)	Control N (%)	Difference(95% CI)	
Overall	45(47%)	10(16%)	31%	(15%,46%)
Sex: F	26(48%)	5(15%)	33%	(12%,52%)
Sex: M	19(45%)	5(17%)	29%	(5%,50%)
Age: 65-75 Years	6(50%)	1(13%)	38%	(-9%,76%)
Age: <65 Years	38(47%)	8(15%)	32%	(15%,47%)
Age: >75 Years	1(33%)	1(25%)	8%	(-63%,76%)
Race: ASIAN	24(55%)	8(29%)	26%	(2%,48%)
Race: BLACK OR AM	7(64%)	1(9%)	55%	(9%,84%)
Race: WHITE	14(35%)	1(4%)	31%	(6%,53%)
Ethnicity: Hispanic	5(50%)	0(0%)	50%	(-2%,88%)
Ethnicity: Non-Hispanic	40(47%)	10(17%)	29%	(13%,45%)
Region: INDIA	23(53%)	8(30%)	24%	(0%,46%)
Region: USA-ISR	22(42%)	2(5%)	36%	(16%,54%)

Source: Applicant's integrated summary of efficacy (ISE) Tables 1.1.1 to Table 1.1.13. AM: African American. For missing BCVA data and data collected after rescue medication, the last non-missing data from any prior visit is used.

Figure 16: Summary of BCVA Improvement (Benefit) and IOP Related Adverse Event (Risk) (ITT)



Source: Reviewer's Analysis. For missing BCVA data at a given visit, the last non-missing data from a prior visit is used.

Inflammation Scales

Vitreous Haze Scale

Score	Description
0	No inflammation
+0.5	Trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fiber layer reflex)
+1	Mild blurring of the retinal vessels and optic nerve
+1.5	Optic nerve head and posterior retina view obscuration greater than +1 but less than +2
+2	Moderate blurring of the optic nerve head
+3	Marked blurring of the optic nerve head
+4	Optic nerve head not visible

Anterior Chamber Flare Grading Scale

Score	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Anterior Chamber Cells Grading Scale

Score	Cells in Field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

6 Appendix 2: Summary of the 27 Publications and Two Additional Studies

6.1 Summary of Publications

As supporting evidence, the Applicant submitted a literature summary based on 27 publications. The design of the studies summarized in the 27 publications together with baseline characteristics of subjects enrolled in these studies is presented in Table 11. Of the 27 studies, 2 (7.4%) were randomized controlled trials (Shin and Yu, 2015; Soheilian, 2010), 9 (33.3%) were non-randomized prospective studies, and 16 (59.3%) were retrospective studies. Per the Applicant's summary, the 27 studies included a total of 1013 eyes with a diagnosis of uveitis, of which 840 were treated with TA alone or TA in combination with other therapy. The patient follow-up time ranged from 3 weeks to more than 2 years. A minimum follow-up of at least 3 months was frequently reported. Most of the studies included more females than males (Table 11). The main efficacy outcomes of interest in the published literatures were visual acuity and macular edema measured by retinal thickness. The visual acuity and macular edema efficacy summaries for the 27 studies are presented in Table 12 and Table 13, respectively.

As stated earlier, of the 27 studies, only 2 were randomized and controlled studies (Shin and Yu, 2015 and Soheilian, 2010). Shin and Yu, 2015 summarized a prospective, double-masked, randomized study. In this study, 50 patients were randomized equally into the intravitreal (IV) TA injection group (4 mg/0.1mL) and the sham group. The two groups were comparable with respect to baseline characteristics of age and sex (Table 12). Per the summary, follow-up visits were performed monthly within a 1-week window period for 6 months. At the baseline and follow-up visits, all patients underwent a complete ophthalmologic assessment, including BCVA measurement. The study showed that there was no statistically significant difference between the two groups with respect to mean BCVA throughout the follow-up period. In addition, the study reported that BCVA did not improve significantly from baseline in either group. The Authors also conducted a treatment comparison on a subgroup of subjects formed based on baseline lens status (pseudophakic and phakic). The results showed that there was also no significant difference in BCVA change in these subgroups. Soheilian, 2010 summarized a randomized pilot study which compared intravitreal bevacizumab (IVB) versus triamcinolone acetonide (IVTA) in subjects with refractory uveitic. In this study, 31 eyes of 26 patients were randomly assigned to the two groups. Per the study summary, subjects allocated into the IVB group received 1-3 injections of 1.25 mg bevacizumab [15 eyes] and the IVTA group received 1–3 injections of 2 mg triamcinolone [16 eyes]. The primary efficacy outcome of interest in this study was change in BCVA from baseline at Week 36. The study reported that there was no statistically significant difference between the two treatment groups with respect to visual acuity change from baseline at 12, 24 and 36 weeks.

Per the Applicant, the safety profile reported in the 27 articles was characterized by elevations in IOP. They state that these elevations were predictable and generally managed with IOP-lowering medications. Per the summary, cataract was the most common non-IOP ocular event reported in the literature review. Based on the efficacy and safety summary in the 27 publications, the Applicant concluded that, the data presented in this literature review are

favorable and support the use of TA in subjects with macular edema associated with non-infectious uveitis.

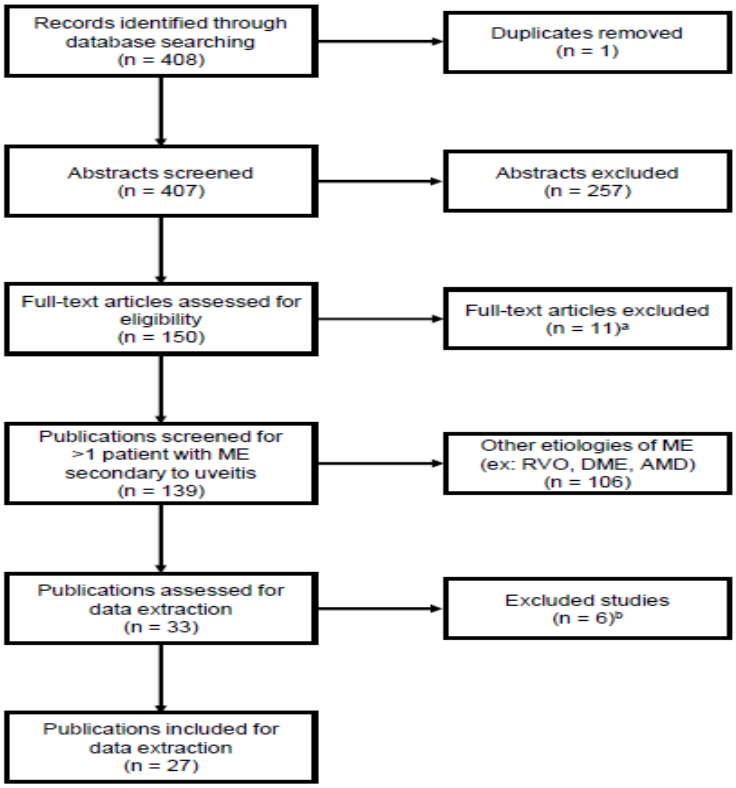
Table 9: Summary of Search Terms Used for the 27 Publications (Study CLS1001-304)

Triamcinolone Acetonide	Macular Edema	Disease Descriptors
triamcinolone acetonide (Emtree and MeSH)	macular edema (Emtree 2014)	uveitis (Emtree)
triamcinolone	macular edema (MeSH 1984)	uveitis (MeSH)
TA	retina macula edema (Emtree pre-2014)	non-infectious uveitis
	macula lutea AND edema (MeSH)	diabetic macular edema OR DME
	macular edema OR macula edema	retinal vein occlusion OR RVO
	oedema	panuveitis OR cyclitis
		inflammation

Abbreviations: DME = diabetic macular edema; Emtree = subject headings unique to Embase; MeSH = Medical Subject Headings used for indexing articles for MEDLINE/PubMed; RVO = retinal vein occlusion; TA = triamcinolone acetonide.

Source: Table 1 of the Applicant's summary

Figure 17: Flow Diagram of Publications Selections Process (Study CLS1001-304)



Abbreviations: AMD = age-related macular degeneration; DME = diabetic macular edema; ME = macular edema; n = number; RVO = retinal vein occlusion; TA = triamcinolone acetonide.

[a] Did not meet the prespecified eligibility criteria upon evaluation of the full text (included letters to the editor, conference abstracts, reviews, and studies that did not use TA).

[b] Included 3 studies reporting already published results and 3 studies with uninterpretable results (reported only combined results for multiple drug treatment regimens).

Source: Figure 1 of the Applicant's summary

Table 10: Summary of Clinical Publications (Study CLS1001-304)

Etiology	Total Eyes per Etiology	Total Eyes per Treatment		Total No. Articles[a]	Specific Publications
		TA[b]	OT		
BRVO	2879	1789	1090	67	Adelman, 2015; Asano, 2007; Avitabile, 2005; Bearelly, 2006; Beer, 2003; Byun, 2010; Cakir, 2008; Cekiç, 2007; Cekiç, 2010; Cekiç, 2005a; Channa, 2017; Chen, 2010; Chen, 2006; Cheng, 2006; Cheng, 2009a; Chung, 2008; Demir, 2014b; Gokce, 2014; Guthoff, 2010a; Hayashi and Hayashi, 2005; He, 2011; Higashiyama, 2013; Hirano, 2007; Hou, 2009; Iwao, 2007; Jonas, 2005; Karadžić, 2015; Kawaji, 2005; Kawaji, 2008; Kelkar, 2009; Kim and Park, 2009; Kogure, 2008; Kola, 2016; Krepler, 2005b; Kunikata, 2012; Kwon, 2013; Lee and Shah, 2005; Lee, 2014; Lee and Yang, 2004; Lim, 2011a; Ma, 2008; Gurram, 2013; Moon, 2016; Noma, 2012a; Noma, 2012b; Noma, 2012c; Oh, 2007; Ozdek, 2008; Ozkiris, 2005; Ozkiris, 2006; Ozkok, 2015; Park and Ahn, 2008; Patel, 2008; Riese, 2008; Scott, 2009; Senturk, 2013; Sohn, 2014; Tewari, 2005; Uemura, 2009; Wei, 2012b; Yamashita, 2007; Yepremyan, 2005; Yoo, 2015; Yoon, 2014; Yumusak, 2016a; Yumusak, 2016b; Zhang, 2016
CRVO	1784	1273	511	51	Adelman, 2015; Alshareef, 2014; Asano, 2007; Avitabile, 2005; Bashshur, 2004; Batioglu, 2007; Cekiç, 2007; Cekiç, 2005b; Cheng, 2009b; Demir, 2014a; Ding, 2011; Fan, 2014; Furino, 2005; Gelston, 2006; Goff, 2006; Gokce, 2013; Gregori, 2006; Guthoff, 2010b; He, 2011; Ip, 2004; Ip, 2009; Iwao, 2007; Kaushik, 2004; Krepler, 2005a; Lee and Yang, 2004; Lim, 2011a; Lim and Na, 2011b; Lin, 2007; Lucatto, 2017; Gurram, 2013; Moschos, 2007; Muni, 2010; Ozdek, 2005; Ozkok, 2015; Park, 2003; Parodi, 2008; Patel, 2008; Senturk, 2010; Tao, 2010; Tewari, 2005; Wang and Song, 2009; Wei, 2012a; Wei, 2012b; Williamson and O'Donnell, 2005; Wu, 2009; Yamamoto, 2011; Yamashita, 2007; Yan, 2016; Yoo, 2015; Yoon, 2014; Yumusak, 2016a
Unspecified/ Other RVO	691	509	182	6	Aref, 2015; Bhurayanontachai, 2009; Cekiç, 2005b; Jonas, 2004; Patel 2008; Wang, 2008
DME	367	333	34	14	Avitabile, 2005; Beer, 2003; Bhurayanontachai, 2009; Cekiç, 2007; He, 2011; Iwao, 2007; Jonas, 2004; Jonas, 2005; Kogure, 2008; Lee and Yang, 2004; Sonoda, 2011; Tewari, 2005; Wang, 2008; Yamashita, 2007
Other Etiologies	125	125	0	6	Beer, 2003; Bhurayanontachai, 2009; Iwao, 2007; Jonas, 2004; Jonas, 2005; Lee and Yang, 2004

Abbreviations: BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DME = diabetic macular edema; RVO = retinal vein occlusion; OT = other treatment; TA = triamcinolone acetonide

[a] Publications may have reported >1 etiology.

[b] Counts for treatment with TA includes eyes that received combination therapy (TA+OT).

Source: Table 2 of the Applicant's summary

Table 11: Study Designs and Baseline Characteristics (Publications Selected for Data Extraction: Study CLS1001-304)

Publication	Study Design	Treatment	N (Subjects)	N (Eyes)	Mean Age (Range)	Gender	Follow-Up
Randomized Controlled Trials							
Shin and Yu, 2015	Prospective, DM, randomized study (RCT)	4 mg IVTA Sham	25 25	25 25	53.60 50.56	M/F: 12/13 M/F: 11/14	6 m
Soheilian, 2010	Masked RCT	1.25 mg IVB 2 mg IVTA	26	15 16	33.1 44.0	M/F: 7/8 M/F: 7/9	36 w
Nonrandomized Prospective Studies							
Antcliff, 2001	Self-controlled trial	2 mg IVTA	6	6	46.7 (33–59)	M/F: 1/5	Three subjects were followed for more than 1 yr, and the other 3 for between 3 and 9 m.
Choudhry and Ghosh, 2007	Interventional case series	4 mg IVTA in 1 eye 20 mg PSTA in other eye	10	20	43.9 (33–59)	M/F: 7/3	Of the 10 subjects, 9 completed the 6 m follow up period, and 1 subject who was a steroid responder, was withdrawn from the study after 1 w.
Goldstein, 2016	Phase 1/2 OL study	4 mg suprachoroidally injected TA	9 enrolled with 11 attempted injections/ 8 treated	8	Median 60 (42–78)	M/F: 3/8 (attempted injections)	All subjects completed the 26-w follow-up, except for 1 subject who was lost to follow-up 16 w following re-enrollment.
Jennings, 1988	Comparative study	40 mg PS methylprednisone 20 mg PSTA	10	10 2	36 (18–64)	M/F: 5/5	Up to 3–4 w
Jovanović, 2017	Interventional case series	40 mg PSTA	25	30	40.5 (15–66)	M/F: NR	Mean: 12.4 m Range: 10–26 m
Munk, 2013	Observational study	4 mg IVTA	24	29	48.4	M/F: 10/14	3 m
Morrison, 2007	Interventional consecutive case series	20 mg IVTA	7	8 (13 injections)	50	M/F: 5/2	Minimum 9 m

Publication	Study Design	Treatment	N (Subjects)	N (Eyes)	Mean Age (Range)	Gender	Follow-Up
Venkatesh, 2007	Observational study	40 mg PSTA 1 mg/kg oral prednisolone	11 11	11 22	33.6 41.8	M/F: 10/1 M/F: 5/6	3 m
Young, 2001	OL, unmasked, pilot study	4 mg IVTA	6	6	36.5 (23–57)	M/F: NR	Range: 15-20 m
Retrospective Studies							
Androudi, 2005	Retrospective review	4 mg IVTA	16	20	45.3 (21–73)	M/F: 3/13	Mean: 34 w Median: 32 w Range: 19-56 w
Bae, 2011	Retrospective comparative review	1.25 mg IVB 4 mg IVTA 40 mg PSTA	10 11 10	10 11 10	47.6 (18–77)	M/F: 14/17	Mean: 22.3 w Range: 14–37 w
Das-Bhaumik and Jones, 2006	Case series	2 mg IVTA	29	33	51.4 (13–72)	M/F: 5/24	Mean: 13.5 m Range: 2–26 m
Gutfleisch, 2007	Retrospective review	4 mg IVTA	19	19	55 (16–76)	M/F: 4/15	Up to 1 yr
Hogewind, 2008	Noncomparative, interventional case series	~10mg IVTA	23	33 (40 injections)	54.7	M/F: 7/16	Up to 1 yr
Jea, 2006	Chart review	4 mg IVTA 40 mg PSTA	41 25	42[a] 43[b]	58.5 (39–75) 48.3 (33–80)	M/F: 20/21 M/F: 16/9	Minimum 3 m
Kok, 2005	Noninterventional comparative case series	4 mg IVTA	54	65	44 (14–76)	M/F: NR	Mean: 8.0 m Range: 3-51 m
Lasave, 2009	Multicenter interventional comparative study	2.5 mg IVB 4 mg IVTA	28	16 20	45.6 (28–64) 41.9 (21–64)	M/F: 7/5 M/F: 8/7 1 unknown	6 m
Lasave, 2017	Multicenter interventional comparative study	1.25 mg IVB 4 mg IVTA	16 21	20 24	42.6 (19–65)	M/F: 7/9 M/F: 9/12	24 m

Publication	Study Design	Treatment	N (Subjects)	N (Eyes)	Mean Age (Range)	Gender	Follow-Up
Leder, 2011	Cohort study	PSTA or OFTA (79% and 21% of injections, respectively); dose of 40 mg or 20 mg (96% and 4% of injections, respectively)	126	156	44 (median) (8–80)	M/F: 31/95	Minimum 12 m
Maca, 2009	Retrospective review	4 mg IVTA	18	24 (1-3 injections)	53.9	M/F: 6/12	Mean: 11 m Range: 3-25 m
Radwan, 2013	Comparative case series	Br BID 25 mg/mL IVB/Br BID 4 mg IVTA/Br BID	55	34 21 12	56.1 54.6 52.1	M/F: 4/22 M/F: 4/14 M/F: 7/4	3 m
Roesel, 2009	Retrospective study	4 mg IVTA 40 mg OFTA	92	48 49	53.9 48.8	M/F: 21/27 M/F: 13/36	12 m
Sallam, 2012	Consecutive case series	4 mg IVTA	35	41	NR	M/F: NR	Minimum 3 m
Sreekantam, 2017	Retrospective study	40 mg Sub-tenon TA	22	22	47.4 (23–74)	M/F: 5/17	Median: 7 w Range: 4–19 w
Steeples, 2017	Single center cohort study	2-5 mg IVTA	40	44 (66 injections)	52.5 (16–85)	M/F: 16/24	Minimum 6 m

Abbreviations: BID = twice a day; Br = bromfenac drops; DM = double-masked; F = female; IVB = intravitreal bevacizumab; IVTA = intravitreal TA; M = male; m = month(s); N = number; NR = not reported; OFTA = orbital floor TA; OL = open-label; PS = posterior sub-tenon; PSTA = posterior sub-tenon TA; RCT = randomized controlled trial; TA = triamcinolone acetonide; w = week(s); yr = year(s)

[a] The etiologies for this treatment group were diabetic macular edema (24 eyes), retinal vascular occlusive disease (8 eyes), uveitis (5 eyes), and exudative age-related macular degeneration (5 eyes).

[b] Most subjects were diagnosed with idiopathic intermediate uveitis, with the exception that 2 eyes had Behcet's and Harada Disease associated with uveitis.

Source: Table 3 of the Applicant's summary

Table 12: Summary of Efficacy: Visual Acuity (Study CLS1001-304)

Publication	Treatment	N (eyes)	VA(mean±SD)				
			Snellen	LogMAR	ETDRS letters	Converted to ETDRS letters*	Change from BL in ETDRS letters
Randomized Controlled Trials							
Shin and Yu, 2015	4 mg IVTA	25			BL: 69.2±9.6 Did not improve significantly from BL throughout the follow-up period.	BL: 69.2±9.6 Did not improve significantly from BL throughout the follow-up period.	Did not improve significantly from BL throughout the follow-up period.
	Sham	25			BL: 69.6±9.0 Did not improve significantly from BL throughout the follow-up period.	BL: 69.6±9.0 Did not improve significantly from BL throughout the follow-up period.	Did not improve significantly from BL throughout the follow-up period.
Soheilian, 2010	1.25 mg IVB	15		0–12 w (improvement): −0.19±0.21** 0–24 w (improvement): −0.29±0.28** 0–36 w (improvement): −0.35±0.45*		0–12 w (improvement): 9.5±10.5** 0–24 w (improvement): 14.5±14** 0–36 w (improvement): 17.5±22.5*	12 w: +9.5 24 w: +14.5 36 w: +17.5
	2 mg IVTA	16		0–12 w (improvement): −0.14±0.30 0–24 w (improvement): −0.29±0.32** 0–36 w (improvement): −0.32±0.32**		0–12 w (improvement): 7±15 0–24 w (improvement): 14.5±16** 0–36 w (improvement): 16±16**	12 w: +7 24 w: +14.5 36 w: +16

Publication	Treatment	N (eyes)	VA(mean±SD)				
			Snellen	LogMAR	ETDRS letters	Converted to ETDRS letters*	Change from BL in ETDRS letters
Nonrandomized Prospective Studies							
Antcliff, 2001	2 mg IVTA	6		Mean improvement after 12 m: 0.27		Mean improvement after 12 m: 13.5	12 m: +13.5
Choudhry and Ghosh, 2007	4 mg IVTA in one eye	10		BL: 0.67±0.10 3 m: 0.22±0.15 6 m: 0.22±0.10		BL: 51.5±5 3 m: 74±7.5 6 m: 74±5	3 m: +22.5 6 m: +22.5
	20 mg PSTA in other eye	10		BL: 0.69±0.14 3 m: 0.28±0.21 6 m: 0.22±0.15		BL: 50.5±7 3 m: 71±10.5 6 m: 74±7.5	3 m: +20.5 6 m: +23.5
Goldstein, 2016	4 mg suprachoroidal TA	8	After a single suprachoroidal injection of TA, all 8 efficacy-evaluable subjects showed improvements in BCVA. Mean improvements ranged between 0.17 and 0.28 logMar (approximately 8 and 14 letters) sustained through the 26-w study period. Improvements in BCVA (a gain of ≥2 lines) were shown by 6 of 8 subjects (75%) at Week 8, and by all 4 subjects (100%) who needed no additional uveitis treatment through the 26-w posttreatment observation period of the study.				
Jennings, 1988	40 mg PS methylprednisone	10	BL: 20/134 1 w: 20/91 3-4 w: 20/115			BL: 44 1 w: 53 3-4 w: 47	1 w: +9 3-4 w: +3
	20 mg PSTA	2	BL: 20/115 1 w: 20/113 3-4 w: 20/50			BL: 47 1 w: 47 3-4 w: 65	1 w: +0 3-4 w: +18
Jovanović, 2017	40 mg PSTA	30		BL: 0.40±0.20 1 w: 0.20±0.10 12 w: 0.15±0.10		BL: 65±10 1 w: 75±5 12 w: 77.5±5	1 w: +10 12 w: +12.5
Munk, 2013	4 mg IVTA	29	BL: 20/63 1 d: 20/48 1 w: 20/36 1 m: 20/30 2 m: 20/30 3 m: 20/31		BL: 60.77±2.78 1 d: 66.04±3.18 1 w: 72.31±2.42 1 m: 76.3±3.06 2 m: 76.3±2.95 3 m: 75.76±3.41	BL: 60.77±2.78 1 d: 66.04±3.18 1 w: 72.31±2.42 1 m: 76.3±3.06 2 m: 76.3±2.95 3 m: 75.76±3.41	1 d: +5.27 1 w: +11.54 1 m: +15.53 2 m: +15.53 3 m: +14.99

Publication	Treatment	N (eyes)	VA(mean±SD)				
			Snellen	LogMAR	ETDRS letters	Converted to ETDRS letters*	Change from BL in ETDRS letters
Morrison, 2007	20 mg IVTA	8 (13 injections)		BL: 0.76 (0.07°) 1 w: 0.62 (0.09°) 1 m: 0.49 (0.09°) 3 m: 0.46 (0.08°)		BL: 47 (3.5°) 1 w: 54 (4.5°) 1 m: 60.5 (4.5°) 3 m: 62 (4°)	1 w: +7 1 m: +13.5 3 m: +15
Venkatesh, 2007	40 mg PSTA	11	Decimal fraction of Snellen VA: 0 d: 0.231±80.08 3 d: 0.3530±0.17 2 w: 0.4964±0.23 6 w: 0.6100±0.22* 12 w: 0.7110±0.23			0 d: 53±180 3 d: 62±47 2 w: 70±53 6 w: 74±52* 12 w: 78±53	3 d: +9 2 w: +17 6 w: +21 12 w: +25
	1 mg/kg oral prednisolone	22	Decimal fraction of Snellen VA: 0 d: 0.2986±0.12 3 d: 0.4150±0.14 2 w: 0.5805±0.22* 6 w: 0.7600±0.22 12 w: 0.6880±0.28			0 d: 59±39 3 d: 66±42 2 w: 73±52* 6 w: 79±52 12 w: 77±57	3 d: +7 2 w: +14 6 w: +20 12 w:+18
Young, 2001	4 mg IVTA	6	BL: 6/27 1 m: 6/11 3 m: 6/10 6 m: 6/16 12 m: 6/30			BL: 52 1 m: 72 3 m: 74 6 m: 64 12 m: 50	1 m: +20 3 m: +22 6 m: +12 12 m: -2
Retrospective Studies							
Androudi, 2005	4 mg IVTA	20		BL: 0.9±0.5 1 m: 0.8±0.6 LFU[b]: 0.8±0.6		BL: 40±25 1 m: 45±30 LFU[b]: 45±30	1 m: +5 LFU[b]: +5
Bae, 2011	1.25 mg IVB	10		BL: 0.73±0.41 1 m: 0.26±0.22*		BL: 48.5±20.5 1 m: 72±11*	1 m: +23.5
	4 mg IVTA	11		BL: 0.73±0.33 1 m: 0.35±0.19*		BL: 48.5±16.5 1 m: 67.5±9.5*	1 m: +19
	40 mg PSTA	10		BL: 0.71±0.23 1 m: 0.30±0.19*		BL: 49.5±11.5 1 m: 70±9.5*	1 m: +20.5

Publication	Treatment	N (eyes)	VA(mean±SD)				
			Snellen	LogMAR	ETDRS letters	Converted to ETDRS letters*	Change from BL in ETDRS letters
Das-Bhaumik and Jones, 2006	2 mg IVTA	33	Snellen VA improved by > 2 lines after 14 injections (38.9%) and by > 1 line in 22 eyes (61.1%). There was no change in 12 eyes (33.3%) and a deterioration in 2 eyes (both 6/24 to 6/60 with intractable CME). Of the eyes with a pre-injection acuity of 6/60 or better, 12/24 (50%) showed a > 2-line improvement. Of the eyes worse than 6/60, only 2/12 (16.6%) showed a > 2-line improvement, but 6 showed a ≥ 1-line improvement (in all of which, CMO was eliminated).				
Gutfleisch, 2007	4 mg IVTA	19		BL: 0.54±0.19 2 w: 0.64±0.31 6 w: 0.48±0.28 3 m: 0.46±0.3 6 m: 0.57±0.29 12 m: 0.57±0.31		BL: 58±9.5 2 w: 53±15.5 6 w: 61±14 3 m: 62±15 6 m: 56.5±14.5 12 m: 56.5±15.5	2 w: -5 6 w: +3 3 m: +4 6 m: -1.5 12 m: -1.5
Hogewind, 2008	~10mg IVTA	33	The BCVA after IVTA increased at 3m in both groups: 11 eyes (52%) with intermediate uveitis and 9 eyes (50%) with posterior uveitis responded with an improvement in vision of >2 lines. Twelve months after IVTA, 10 eyes (48%) with intermediate uveitis and 6 eyes (32%) with posterior uveitis responded with an improvement in vision of >2 lines. No significant differences were found (p >0.05).				
Jea, 2006	4 mg IVTA	42	Did not report VA				
	40 mg PSTA	43					
Kok, 2005	4 mg IVTA	65		BL: 0.65 Post-TA: 0.39 Mean improvement: 0.26		BL: 52.5 Post-TA: 65.5 Mean improvement: 13	Post-TA: +13
Lasave, 2009	2.5 mg IVB	16		BL: 1.2±0.4 1 m: 1.1±0.4* 3 m: 1±0.3* 6 m: 0.8±0.4*		BL: 25±20 1 m: 30±20* 3 m: 35±15* 6 m: 45±20*	1 m: +5 3 m: +10 6 m: +20
	4 mg IVTA	20		BL: 1.1±0.2 1 m: 0.8±0.4* 3 m: 0.7±0.4* 6 m: 0.7±0.3*		BL: 30±10 1 m: 45±20* 3 m: 50±20* 6 m: 50±15*	1 m: +15 3 m: +20 6 m: +20

Publication	Treatment	N (eyes)	VA(mean±SD)				
			Snellen	LogMAR	ETDRS letters	Converted to ETDRS letters*	Change from BL in ETDRS letters
Lasave, 2017	1.25 mg IVB	20		BL: 1±0.4 1 m: 0.8±0.4* 24 m: 0.8±0.3*		BL: 35±20 1 m: 45±20* 24 m: 45±15*	1 m: +10 24 m: +10
	4 mg IVTA	24		BL: 1.1±0.2 1 m: 0.8±0.4* 24 m: 0.6±0.2*		BL: 30±10 1 m: 45±20* 24 m: 55±10*	1 m: +15 24 m: +25
Leder, 2011	TA (either PSTA or OFTA; dose of 40 mg or 20 mg [96% and 4% of injections, respectively])	156	Halving of the visual angle at 1 m: 52% (95% CI 48, 57) Halving of the visual angle 3 m: 57% (95% CI 51, 62) Median time to outcome: 8.1w				
Maca, 2009	4 mg IVTA	24 (1st injection)	**d-VA** Mean d-VA improved significantly from BL (0.25±0.17 dec) to Week 1 (0.38±0.23 dec, p<0.01), further until Week 4 (0.42±0.27 dec, p=0.29). Between Weeks 4 and 12 (0.40±0.30 dec) values did not change in a significant fashion (p=0.77). Again, values at Week 12 were significantly better than values obtained prior to IVTA treatment (p<0.01). **n-VA** Mean n-VA improved significantly from 0.84±0.27 logRAD at BL to 0.69±0.31 logRAD at Week 1 (p<0.01), and then tended to recover even more until Weeks 4 (0.65±0.36 logRAD, p=0.20) and 12 (0.59±0.37 logRAD, p=0.43).				
	4 mg IVTA	13 (2nd injection)	**d-VA** Following a similar pattern as was noted after the first injection, values improved from 0.27±0.13 dec at Week 12 to 0.38±0.24 dec at Week 13 (p=0.01) and to 0.44±0.27 dec at Week 16 (p=0.41). Thereafter d-VA did not change until Week 24 (0.40±0.27 dec, p=0.41). d-VA at Week 24 had not improved significantly as compared with Week 12 or BL (p=0.28 and p=0.07, respectively). **n-VA** Mean n-VA at the second injection time point (Week 12) was 0.56±0.4 logRAD. No significant changes were observed during the follow-up visits at Week 13 (0.63±0.4 logRAD, p=0.32), Week 16 (0.67±0.39 logRAD, p=0.52) and Week 24 (0.78±0.35 logRAD, p=0.19). Mean n-VA at Week 24 tended to be worse than at Week 12, albeit not at a significant level (p=0.07) and was unchanged to levels of Week 12 (p=0.49).				
	4 mg IVTA	4 (3rd injection)	This group was too small for reliable statistical analysis.				

Publication	Treatment	N (eyes)	VA(mean±SD)				
			Snellen	LogMAR	ETDRS letters	Converted to ETDRS letters*	Change from BL in ETDRS letters
Radwan, 2013	Br BID	34		BL: 0.39±0.28 1 m: 0.37±0.29 3 m: 0.31±0.27		BL: 65.5±14 1 m: 66.5±14.5 3 m: 69.5±13.5	1 m: +1.5 3 m: +4
	25 mg/mL IVB/ Br BID	21		BL: 0.55±0.24 1 m: 0.43±0.29 3 m: 0.35±0.23**		BL: 57.5±12 1 m: 63.5±14.5 3 m: 67.5±11.5**	1 m: +6 3 m: +10
	4 mg IVTA/ Br BID	12		BL: 0.52±0.50 1 m: 0.37±0.53 3 m: 0.33±0.55*		BL: 59±25 1 m: 66.5±26.5 3 m: 68.5±27.5*	1 m: +7.5 3 m: +9.5
Roesel, 2009	4 mg IVTA	48		BL: 0.61±0.35 1 m: 0.51±0.34* 3 m: 0.47±0.31* 6 m: 0.62±0.33 12 m: 0.67±0.33		BL: 54.5±17.5 1 m: 59.5±17* 3 m: 61.5±15.5* 6 m: 54±16.5 12 m: 51.5±16.5	1 m: +5 3 m: +7 6 m: -0.5 12 m: -3
	40 mg OFTA	49		BL: 0.58±0.39 1 m: 0.50±0.41* 3 m: 0.46±0.38* 6 m: 0.47±0.38 12 m: 0.44±0.31		BL: 56±19.5 1 m: 60±20.5* 3 m: 62±19* 6 m: 61.5±19 12 m: 63±15.5	1 m: +4 3 m: +6 6 m: +5.5 12 m: +7
Sallam, 2012	4 mg IVTA	41		Mean improvement[δ]: 1 injection: 0.34 2 injections: 0.24 3 injections: 0.42 4+ injections: 0.30		Mean improvement[δ]: 1 injection: 17 2 injections: 12 3 injections: 21 4+ injections: 15	1 injection: +17 2 injections: +12 3 injections: +21 4+ injections: +15

Publication	Treatment	N (eyes)	VA(mean±SD)				
			Snellen	LogMAR	ETDRS letters	Converted to ETDRS letters[a]	Change from BL in ETDRS letters
Sreekantam, 2017	40 mg Sub-tenon TA	22	Treatment with STA was associated with significant improvement in VA (p=0.0001). The number of subjects with a VA >6/12 increased from 1 (4.5%) to 17 (77.3%) with a corresponding reduction in those with 6/12 or worse from 19 (86.4%) to 5 (22.7%) (Fisher exact test, p=0.0001). Grouping visual outcome by timing of follow-up showed that those with follow-up at 4–8w comprised 14 subjects with a VA >6/12 and 3 with 6/12 or worse, whereas those with follow-up at later time points (9–19w) comprised 3 subjects with a VA >6/12 and 2 with 6/12 or worse.				
Steeples, 2017	IVTA	44 (66 injections)		BL: 0.62 2-4 w: 0.46±0.3 6-8 w: 0.40±0.3 12 w: 0.42±0.2 24 w: 0.41±0.3		BL: 54 2-4 w: 62±15 6-8 w: 65±15 12 w: 64±10 24 w: 64.5±15	2-4 w: +8 6-8 w: +11 12 w: +10 24 w: +10.5

Abbreviations: BCVA = Best-corrected VA; BID = twice a day; BL = baseline; Br = bromfenac drops; CI = confidence interval; d = day; dec = decimal visual acuity; d-VA = distance visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; IVB = intravitreal bevacizumab; IVTA = intravitreal TA; LFU = last follow-up; logMAR = logarithm of minimum angle of resolution; logRAD = logarithm of reading acuity determination; m = month(s); N = number; n-VA = near visual acuity; OFTA = orbital floor TA; PS = posterior sub-tenon; PSTA = posterior sub-tenon TA; SD = standard deviation; SE = standard error; STA = sub-tenon TA; TA = triamcinolone acetonide; VA = visual acuity; w = week(s).

[a] Conversion of Snellen to ETDRS letters was calculated using the following formula: 85 + 50 × log (Snellen fraction) (Gregori, 2010), which was rounded to the nearest letter. Conversion of logMAR to ETDRS letters was calculated using the conversion table in Beck, 2003 for the mean, and for converting SD and improvement each letter corresponded to 0.02 logMAR unit, per Ferris, 1982.

[b] Mean LFU was 34±9.5 weeks (range: 19-56 weeks).

[c] SE reported instead of SD.

[d] Values were estimated from Figure 1A as they were not reported numerically in the reference.

*p < 0.05, **p ≤ 0.01

Source: Table 4 of the Applicant's summary

Table 13: Summary of Efficacy: Macular Edema (Study CLS1001-304)

Publication	Treatment	N (eyes)	Method and Instrument Used to Measure ME	Central Subfield[a] Thickness (µm) (mean±SD)	Change from BL
Randomized Controlled Trials					
Shin and Yu, 2015	4 mg IVTA	25	SD-OCT; instrument NR	In the TA group, the thickness of the central foveal area decreased significantly beginning 1m after injection (p=0.013), while in the sham group, it significantly decreased from Month 3 (p=0.020). There were no significant differences between the 2 groups during the follow-up period. The parafoveal area thickness significantly decreased compared to BL in both groups beginning at 1m (p=0.001 in the TA group; p=0.004 in the sham group). The thickness decreased more in the TA group than in the sham group at Months 2 and 3 (p=0.030 and 0.014, respectively). The difference between the 2 groups was not significant after Month 4. Similar findings were observed in the thicknesses of the total foveal and parafoveal area.	
	Sham	25			
Soheilian, 2010	1.25 mg IVB	15	OCT; instrument NR		Change in central macular thickness: 12 w: −56.7±111.4 µm (−11%) 24 w: 0.8±133.9 µm (3%) 36 w: −42.0±171.1 µm (−2%)
	2 mg IVTA	16			Change in central macular thickness: 12 w: −55.8±75.9 µm (−14%)* 24 w: −68.6±85.8 µm (−17%)* 36 w: −74.6±108.0 µm (−19%)*
Nonrandomized Prospective Studies					
Antcliff, 2001	2 mg IVTA	6	NA	There was complete anatomic resolution of CME in 5 of the 6 cases within 1 week of injection, with the CME decreasing after 24 hours. CME began to return between 6 weeks and 3 months after injection. Three of the 6 subjects responded to subsequent 40-mg OFTA and maintained resolution. Two of those subjects continued to maintain resolution during longer term follow-up and had no CME 1 year later, whereas the last subject defaulted after 3 months. One subject had raised IOP develop, requiring a trabeculectomy, and did not respond to subsequent OFTA administered in the presence of a functioning filtration bleb. The sixth subject was aphakic with such massive CME that it measured 1365 µm in height. It decreased slightly but did not resolve	

Publication	Treatment	N (eyes)	Method and Instrument Used to Measure ME	Central Subfield* Thickness (µm) (mean±SD)	Change from BL
Choudhry and Ghosh, 2007	4 mg IVTA in 1 eye	10	FFA; instrument NR	At 3m, an angiographic anatomic success of resolution of ME was achieved in 77.8% (7/9) eyes that received IVTA compared with 55.6% (5/9) eyes that received PSTA in the fellow eye (p=0.32). The remaining 4 eyes in the PSTA group showed a partial resolution of anatomic success based on FFA. At 6m, complete resolution of CME achieved between the 2 groups was comparable (88.9% vs. 77.8% who received IVTA and PSTA, respectively, p=0.53). Although a favorable trend towards a speedier anatomic resolution of CME was observed in the IVTA group at 3m, the difference was statistically not significant. Recurrence of the disease process was seen in 1 and 2 eyes in the IVTA and PSTA eyes at the 6-m follow-up visit, respectively. OCT performed in 1 case had complete resolution of CME in both eyes at 6m.	
	20 mg PSTA in other eye	10			
Goldstein, 2016	4 mg suprachoroidal TA	7[b]	SD-OCT; instrument NR	BL: 547 (range: 364 to 825)	8 w: −154 µm 26 w: −107 µm
Jennings, 1988	40 mg PS methylprednisone	10	NA	Did not report ME results	
	20 mg PSTA	2			
Jovanović, 2017	40 mg PSTA	30	OCT; Cirrus SD-OCT device model 5000 (Carl Zeiss Meditec)	BL: 345±50 12 w: 219±35	12 w: −126 µm
Munk, 2013	4 mg IVTA	29	Central line scan; Spectralis SD-OCT (Software 1.6.5.4, Heidelberg Engineering)	BL: 552.7±24.7 1 d: 429.5±26.1 1 w: 346.2±12.4 1 m: 326.8±12.4 2 m: 359.9±19.7 3 m: 345.6±17.8	1 d: −123.2 µm 1 w: −206.5 µm 1 m: −225.9 µm 2 m: −192.8 µm 3 m: −207.1 µm
Morrison, 2007	20 mg IVTA	8 (13 injections)	OCT; Stratus 3000 OCT model (Carl Zeiss)	BL: 341 (28[d]) 1 w: 227 (32[d])* 1 m: 246 (33[d])* 3 m: 213 (35[d])**	1 w: −114 µm 1 m: −95 µm 3 m: −128 µm

Publication	Treatment	N (eyes)	Method and Instrument Used to Measure ME	Central Subfield* Thickness (µm) (mean±SD)	Change from BL
Venkatesh, 2007	40 mg PSTA	11	OCT; Optical Coherence Tomographer 3 model 3000 (Humphrey-Zeiss Medical System)	0 d: 417.09±124.65 3 d: 423.64±202.17 2 w: 323.55±121.43* 6 w: 247.09±64.29 12 w: 252.00±92.77	3 d: +6.55 µm 2 w: −93.52 µm 6 w: −170 µm 12 w: −165.09 µm
	1 mg/kg oral prednisolone	22		0 d: 401.29±158.79 3 d: 288.38±104.08 2 w: 236.62±28.02* 6 w: 222.81±42.28 12 w: 240.38±96.46	3 d: −112.91 µm 2 w: −164.67 µm 6 w: −178.48 µm 12 w: −160.91 µm
Young, 2001	4 mg IVTA	6	FA; instrument NR	Two subjects had no ME at 6m. In the 4 whose ME recurred, median duration of effect was 8w (range 6–10w).	
Retrospective Studies					
Androudi, 2005	4 mg IVTA	20	OCT and/or FA; instruments NR	CME improved but relapsed in the follow-up period in 5 cases and showed improvement but did not resolve completely in 4 cases. At last follow-up[b], CME was present in 10 of the cases (50%). In the remaining cases, CME resolved without evidence of recurrence during the follow-up time (median time of follow-up: 32w and 32.5w for the groups of subjects with persistent and resolved CME, respectively).	
Bae, 2011	1.25 mg IVB	10	OCT; Stratus OCT (Zeiss-Humphrey)	BL: 537±214 4 w: 293±234** 12 w: NR	4 w: −244 µm 12 w: −167±154 µm
	4 mg IVTA	11		BL: 594±151 1 m: 230±99** 12 w: NR	4 w: −364 µm 12 w: −328±233 µm
	40 mg PSTA	10		BL: 582±146 1 m: 273±102** 12 w: NR	4 w: −309 µm 12 w: −166±227 µm
Das-Bhaumik and Jones, 2006	2 mg IVTA	33	Slit-lamp biomicroscopy; instrument NR	Complete clinical resolution of CME was observed in 24/30 eyes (80%) and partial resolution in a further 3. There was no clinical change in 3 eyes.	

Publication	Treatment	N (eyes)	Method and Instrument Used to Measure ME	Central Subfield[a] Thickness (µm) (mean±SD)			Change from BL	
Gutfleisch, 2007	4 mg IVTA	19	FA; instrument NR	CME	2w	6w to 3m	6m	12m
				Less	6/12 (50%)	6/13 (46%)	6/13 (46%)	7/16 (44%)
				Unchanged	5/12 (42%)	6/13 (46%)	3/13 (23%)	7/16 (44%)
				More	1/12 (8%)	1/13 (8%)	4/13 (31%)	2/16 (12%)
Hogewind, 2008	~10mg IVTA	33	FA; instrument NR	CME	3m Intermediate/ Posterior	6m Intermediate/ Posterior	12m Intermediate/ Posterior	
				None	7/2	6/4	4/4	
				Reduction	11/13	9/7	5/3	
				Stable	2/2	4/7	4/4	
				Increase	1/0	1/1	5/6	
				Not examined	0/2	1/0	0/0	
				Dropout	0/0	0/0	3/2	
Jea, 2006	4 mg IVTA	42	NA	Did not report ME results				
	40 mg PSTA	43						
Kok, 2005	4 mg IVTA	65	NA	Did not report ME results				
Lasave, 2009	2.5 mg IVB	16	OCT; Stratus OCT (Carl Zeiss)	BL: 400.9±141.5 1 m: 332.1±120.7* 3 m: 323.4±108.1* 6 m: 344.7±135			1 m: −68.8 µm 3 m: −77.5 µm 6 m: −56.2 µm	
	4 mg IVTA	20		BL: 454.8±238.9 1 m: 303.3±164* 3 m: 289.4±141.2* 6 m: 296±134.4*			1 m: −151.5 µm 3 m: −165.4 µm 6 m: −158.8 µm	

Publication	Treatment	N (eyes)	Method and Instrument Used to Measure ME	Central Subfield[a] Thickness (µm) (mean±SD)	Change from BL
Lasave, 2017	1.25 mg IVB	20	OCT; instrument NR	BL: 399.2±244.5 1 m: 360.9.1[st]140.7 24 m: 333.7±126	1 m: Could not be calculated[c] 24 m: −65.5 µm
	4 mg IVTA	24		BL: 464.4±226 1 m: 340.5±164 24 m: 316.5±246	1 m: −123.9 µm 24 m: −147.9 µm
Leder, 2011	TA (either PSTA or OFTA; dose of 40 mg or 20 mg [96% and 4% of injections, respectively])	156	OCT and/or FA; instrument(s) NR	53% (83/156) of eyes had clinically resolved CME at the 1-m visit following the first periocular corticosteroid injection, and 57% (89/156) of eyes had CME resolution by the 3-m visit following the first injection.	
Maca, 2009	4 mg IVTA	24 (1st injection)	Retinal Thickness Analyzer (Talia Technology Ltd.)	BL: 375±99 1 w: 235±80 4 w: 214±74 12 w: 265±100	1 w: −140 µm 4 w: −161 µm 12 w: −110 µm
	4 mg IVTA	13 (2nd injection)		12 w: 297±107 13w: 223±68 16 w: 188±65 24 w: 238±132	12 w: −78 µm 13w: −152 µm 16 w: −187 µm 24 w: −137 µm
	4 mg IVTA	4 (3rd injection)		This group was too small for reliable statistical analysis.	
Radwan, 2013	Br BID	34	OCT; instrument NR	BL: 353.97±96.91 1 m: 348.91±89.21 3 m: 301.82±63.19	1 m: −5.06 µm 3 m: −52.15 µm
	25 mg/mL IVB/ Br BID	21		BL: 459.14±154.86 1 m: 356.00±137.43** 3 m: 288.29±81.12**	1 m: −103.14 µm 3 m: −170.85 µm
	4 mg IVTA/ Br BID	12		BL: 422.58±175.03 1 m: 268.25±42.58* 3 m: 259.73±46.19**	1 m: −154.33 µm 3 m: −162.85 µm

Publication	Treatment	N (eyes)	Method and Instrument Used to Measure ME	Central Subfield[a] Thickness (µm) (mean±SD)			Change from BL	
Roesel, 2009	4 mg IVTA	48	FA; instrument NR	ME (FA)	After Treatment			
					1m	3m	6m	12m
				p-value	0.36	<0.01	0.1	0.56
				Comparison, % subjects				
				IVTA				
				Less	100	100	75	42
				Unchanged	0	0	0	29
				More	0	0	25	29
				OFTA				
				Less	76	20	20	20
				Unchanged	24	80	80	60
				More	0	0	0	20
	40 mg OFTA	49						
Sallam, 2012	4 mg IVTA	41	OCT or FA; instruments NR	Following the first IVTA injection, CME resolved in 36 of 41 eyes (88%) in a mean of 5w (range: 1–14w), but recurred in all eyes at a mean of 7m (range: 2-23m). After the second injection, CME improved in 31 of 41 eyes (76%), but recurred in 25 eyes at a mean of 5m (range: 1–13m).				
Sreekantam, 2017	40 mg Sub-tenon TA	22	OCT; Heidelberg Spectralis OCT (Heidelberg Engineering)	BL: 580.5±119.4 Post treatment: 332.7±95.4**			Post treatment: −247.7 µm	
Steeples, 2017	IVTA	44 (66 injections)	OCT; Spectralis (Heidelberg Engineering) or 3D-OCT 2000 (Topcon Corporation)	BL: 489±150 2-4 w: 309±111 6-8 w: 317±110 12 w: 322±116 24 w: 313±95			2-4 w: −180 µm 6-8 w: −172 µm 12 w: −167 µm 24 w: −176 µm	

Abbreviations: BID = twice a day; BL = baseline; Br = bromfenac drops; CME = cystoid ME; d = day; FA = fluorescein angiography; FFA = fundus fluorescein angiography; IV = intravitreal; IVB = intravitreal bevacizumab; IVTA = intravitreal TA; m = month(s); ME = macular edema; N = number; NA = not applicable; NR = not reported; OCT = optical coherence tomography; OFTA = orbital floor TA; PS =posterior sub-tenon; PSTA = posterior sub-tenon TA; SD = standard deviation; SE = standard error; TA = triamcinolone acetonide; w = week(s).

[a] Central subfield thickness includes measures of the terms central foveal, central retinal, and central macular thickness.

[b] Seven of 8 subjects in the per-protocol population qualified for the study based on meeting the requirement for ME associated with their uveitis, that is, a measurement of central subfield thickness greater than or equal to 310 µm by SD-OCT. One subject qualified for the study based upon haze alone, with no ME at enrollment.

[c] This is how the value was presented in the reference, therefore the change from baseline could not be calculated for this value.

[d] SE reported instead of SD.

*p < 0.05, **p ≤ 0.01

Source: Table 6 of the Applicant's summary

Reviewer's remark: During End-of-Phase 2 meeting, the Agency stated that a single Phase 3 pivotal clinical study in conjunction with comprehensive literature review of the use of TA for the treatment of macular edema will support a 505(b)(2) NDA for CLS-TA for the stated indication. In the NDA submission, the Applicant provided literature summary based on 27 publications and the results of their pivotal Phase 3 study. However, after the NDA for this product was submitted, it was noted that the Applicant was basing their submission on their own clinical data and the findings from the approval of Triesence (NDA 22048). The Agency informed the Applicant that since the approval of Triesence was based on the original DESI review for steroids, the review for CLS-TA will also be based on the single Phase 3 study and the Agency's finding of safety and efficacy in the DESI review, not Triesence. The Applicant's literature summary submitted to support efficacy and safety of CLS-TA presented above is thus considered as only supportive evidence as opposed to being considered in lieu of a second Phase 3 study as original intended (See meeting minutes).

6.2 Summary of Studies CLS1001-201 and CLS1001-302

In addition to the pivotal study and the literature summary, this NDA submission also included supporting efficacy data from two additional studies (CLS1001-201 and CLS1001-302). Study CLS1001-201 was a Phase 2, randomized, masked, multicenter study. The primary objective of this study was to determine the safety and efficacy of CLS-TA in subjects with macular edema (ME) following uveitis. The study enrolled a total of 22 subjects. Of these, 17 subjects received a single injection of CLS-TA at 4 mg while the remaining 5 subjects received a single injection

of CLS-TA at 0.8 mg. The primary efficacy endpoint was the change in central subfield retinal thickness (CST) from baseline at 2 months. The primary efficacy analysis was performed using a paired t-test to assess the statistical significance of a difference in means between baseline and Month 2 CST for the 4 mg treatment group. The corresponding 95% confidence interval and p-value from the paired t-test were also presented. The primary efficacy analysis was conducted on the ITT population which included all randomized subjects who received at least one dose of the study drug. The summary results show that the mean (SD) CST for the 4 mg arm was 526.29 (131.616) μm at baseline and 372.06 (175.444) μm at Month 2. The mean (SD) change from baseline in CST at 2 months after the treatment was statistically significant (change from Baseline: –164.44 [173.148], p=0.0017). With respect to safety, 19 (86.4%) subjects reported at least one adverse event [14 (82.4%) in the CLS-TA 4 mg treatment arm and 5 (100%) in the CLS-TA 0.8 mg treatment arm]. Per the safety summary, the majority of the reported adverse events were mild or moderate in severity. Ocular adverse events were reported in the study eye for 13 (59.1%) subjects 8 (47.1%) in the CLS-TA 4 mg treatment arm and 5 (100.0%) in the CLS-TA 0.8 mg treatment arm. The most commonly reported adverse events were macular edema, uveitis, conjunctival hemorrhage, eye pain, injection site pain, IOP increased, and hypertension.

Study CLS1001-302 was an open-label safety study designed to assess the safety of 4 mg of CLS-TA administered via Suprachoroidal (SC) injection for the treatment of subjects with non-infectious uveitis. Treatment consisted of 2 unilateral SC injections of 4 mg of CLS-TA in 0.1 mL, administered 12 weeks apart. This study enrolled 35 subjects diagnosed with non-infectious uveitis for which the administration of local corticosteroid medication was a viable treatment option. Based on the safety results, the Applicant concluded that suprachoroidal CLS-TA was safe and well tolerated over the 24-week study. There were no deaths, serious adverse events or adverse events that lead to subject discontinuation. The study reports that there was a slight numerical increase in pre-injection IOP in the study eye at post-baseline visits during the study. Mean IOP increased from 13.3 mmHg (SD 3.57) at baseline to 15.2 (SD 4.40) at Week 24 in the study eye.

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/s/

ABEL T ESHETE
09/13/2019 03:35:55 PM

YAN WANG
09/13/2019 03:41:28 PM
I concur.