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APPLICATION NUMBER:

211950Orig1s000

CLINICAL REVIEW(S)

Medical Officer's Review of NDA 211950
Class 2 Resubmission

NDA 211950

Submission Date: April 30, 2021
Reviewer Received Date: April 30, 2021
Review Date: August 2, 2021

Applicant:

Clearside Biomedical, Inc
900 North Point Parkway
Suite 200
Alpharetta, GA 30005

Drug:

Xipere (triamcinolone acetonide injectable suspension)

Pharmacologic Category:

corticosteroid

Dosage Form and

Route of Administration:

suprachoroidal injection

Proposed Indication:

Treatment of macular edema associated with uveitis in adult patients

Submitted:

Submitted is a Class 2 resubmission of NDA 211950, Xipere (triamcinolone acetonide injectable suspension). The original NDA was submitted on December 19, 2018, and received a Complete Response (CR) on October 18, 2019. The CR was based on CMC, clinical and 505(b)(2) issues. The following approvability issues were communicated in the CR and have been addressed in this submission:

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing and holding of the drug substance and the drug product must comply with the current good manufacturing practice (cGMP) regulations in 21 CFR 210 and 211. During the pre-approval inspection of (b) (4), manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved or alternative manufacturing facilities which are in compliance with cGMPs must be included in the application.
2. There is insufficient information about the drug product to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling. Clinical use data should be submitted to support the use of the final to-be-marketed SCS Microinjector Delivery System.

The final to-be-marketed configuration should be evaluated by at least three physicians and in at least 30 patients.

3. Please provide data generated from three new registration batches using the proposed commercial process to demonstrate process robustness and product meeting quality standards of efficacy, stability, and safety. Please provide at least one registration batch with 3 months stability data at long term storage and 3 months stability data at accelerated condition.
4. One or more amendments to your pending application does not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a “recertification” for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, you must verify that the proposed change described in the amendment is not one of the types of amendments described above.

Please provide a list of your amendments submitted to FDA on or after December 5, 2016, clearly referencing each amendment by submission date, and either:

1. state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or
2. verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

The cover letter for your Complete Response and all future amendments to your unapproved 505(b)(2) application should continue to address the requirements under 21 CFR 314.60(f).

Reviewer’s Comments:

Issues #1, #3 and #4

CMC and 505(b)(2) regulatory issues will be addressed in separate reviews. Clinical issue #2 will be addressed in this review.

Issue #2

Currently, over 1,000 SC injections of CLS-TA have been performed across multiple clinical studies and multiple diseases. Of these administrations, 225 injections were performed in 173 patients with the final to-be-marketed SCS Microinjector across 62 investigator sites. The kits for both the final to-be-marketed SCS Microinjector and the device used previously (known as the “SCS Injector”) that were provided to investigators all contained the syringe, a vial adapter, and 2 needles, one 900 micron and one 1100 micron in length. The components of the SCS Injector and the final to-be-marketed SCS Microinjector coming into direct contact with the drug, as well as the internal volumes, surface areas, lengths, and weights of all components (i.e., syringe and needles) were identical. The devices differed only in (b) (4)

(b) (4) To confirm that these changes (b) (4) (b) (4) had no significant effect on the safety or effectiveness of the device, routine device verification and validation activities were performed to existing performance specifications.

The experience with injections using the final to-be-marketed SCS Microinjector come from two studies:

Azalea (CLS1001-302) which was reviewed during the first cycle for non-infectious uveitis and contains 13 subjects at 8 investigative sites that received both the SCS Injector (first injection) and the final to-be-marketed SCS Microinjector (second injection).

Topaz (CLS1003-302), a phase 3 trial for retinal vein occlusion in which 212 suprachoroidal injections of CLS-TA via the final to-be-marketed SCS Microinjector were administered by 86 physicians across 56 investigator sites.

To evaluate the usability and adverse event profile of the final to-be-marketed microinjector, patients who received CLS-TA using final to-be-marketed SCS Microinjector were compared to patients who received the injection via the SCS Injector in the Azalea study. The patients in the Topaz study were compared to those in the Sapphire study (CLS1003-301), which was a companion phase 3 study to TOPAZ and used the SCS Injector for the administration of CLS-TA to subjects diagnosed with RVO.

Azalea Study

A user evaluation of both injectors was conducted in the AZALEA study using questionnaires. At each treatment visit, i.e., Day 0 and Week 12, the physician administering study treatment completed a questionnaire about his/her experience using the injector device. An observer of the procedure also completed a questionnaire about his/her observations. In the analysis of safety, subjects receiving CLS-TA via both injectors (SCS Injector on Day 0 and SCS Microinjector on Week 12; n=13 subjects) were counted in the SCS Microinjector group, whereas subjects only receiving CLS-TA via the SCS Injector were counted in the SCS Injector group (n=25 subjects).

Physician Questionnaire in Noninfectious Uveitis (Safety Population)

Question	SCS Microinjector (N=13 Injections/ 8 Invest.) n (%)	SCS Injector (N=60 Injections/ 11 Invest.) n (%)
Did you feel adequately prepared to give an injection based on the training that you received?		
Yes	13 (100)	60 (100)
No	0	0
Were the written instructions clear and easy to follow?		
Yes	13 (100)	60 (100)
No	0	0
How do you rate the ease of loading the syringe with the vial adaptor, compared to loading other syringes?		
More easy	5 (38.5)	25 (41.7)
Same	6 (46.2)	31 (51.7)
More difficult	2 (15.4)	4 (6.7)
Was the needle easy to attach to the syringe?		
Yes	13(100)	60 (100)
No	0	0
Was the force required for the needle to penetrate the eye appropriate?		
Yes	9 (69.2)	45 (75.0)
No	4 (30.8)	15 (25.0)
How do you rate the force necessary for the injection?		
Acceptable	12 (92.3)	56 (93.3)
Not acceptable	1 (7.7)	4 (6.7)
Did you change needles?		
Yes	5 (38.5)	24 (40.0)
No	8 (61.5)	36 (60.0)
If so, why?		
a. Was unable to inject with the 900 micron needle	3 (23.1)	21 (35.0)
b. Physical or mechanical problem with the 1st needle	0	1 (1.7)
c. Other	2 (15.4)	2 (3.3)

Question	SCS Microinjector (N=13 Injections/ 8 Invest.) n (%)	SCS Injector (N=60 Injections/ 11 Invest.) n (%)
In your experience, did the suprachoroidal injection procedure present any new challenges as compared to other types of injections?		
Yes	2 (15.4)	8 (13.3)
No	11 (84.6)	51 (85.0)
Did you have difficulty with any of the steps in the procedure?		
Yes	1 (7.7)	6 (10.0)
No	12 (92.3)	54 (90.0)
Were you able to inject all of the contents of the syringe?		
Yes	11 (84.6)	59 (98.3)
No	2 (15.4)	1 (1.7)
If not, estimate the volume injected:		
a. < 50%	2 (15.4)	1 (1.7)
b. Approximately 50%	0	0
c. > 50%	0	0

Note: All 11 investigators participating in AZALEA administered CLS-TA via the SCS Injector. Of these, 8 investigators administered CLS-TA via the SCS Microinjector.

Percentages are based on the total number of injections administered by each injector.

Source: Section 5, [Table 9](#).

Observer Questionnaire in Noninfectious Uveitis (Safety Population)

Question	SCS Microinjector (N=13 Injections/ 8 Invest.) n (%)	SCS Injector (N=60 Injections/ 11 Invest.) n (%)
Did the physician review injection instructions?		
Yes	13 (100)	59 (98.3)
No	0	1 (1.7)
Were there any issues opening and removing components from the packaging		
Yes	0	1 (1.7)
No	13 (100)	59 (98.3)
Was the physician able to fill the injector appropriately utilizing the vial adaptor?		
Yes	13 (100)	59 (98.3)
No	0	1 (1.7)

Question	SCS Microinjector (N=13 Injections/ 8 Invest.) n (%)	SCS Injector (N=60 Injections/ 11 Invest.) n (%)
Did the physician have difficulty attaching the microneedle to the syringe?		
Yes	0	0
No	13 (100)	60 (100)
Did the physician measure the distance from the limbus to the injection site?		
Yes	13 (100)	60 (100)
No	0	0
If Yes, what method		
Cap	12 (92.3)	47 (78.3)
Caliper	1 (7.7)	13 (21.7)
Other	0	0
Did the physician use the 900 µm needle first?		
Yes	12 (92.3)	60 (100)
No	1 (7.7)	0
Did the physician need to change needles?		
Yes	5 (38.5)	23 (38.3)
No	8 (61.5)	37 (61.7)
Did the physician appear to have difficulty with the injection?		
Yes	1 (7.7)	7 (11.7)
No	12 (92.3)	53 (88.3)

Percentages are based on the total number of injections administered by each injector.

Source: Section 5, [Table 10](#).

Note: Responses following the injection from the SCS Microinjector (n=13) are presented separately from responses from all injections using the SCS Injector (n=60). In total, questionnaires were completed for 38 subjects at the first injection (all injections with the SCS Injector) and 35 subjects at the second injection (22 injections with the SCS Injector and 13 with the SCS Microinjector).

Most Commonly Reported Treatment-Emergent Adverse Events in the Study Eye in Noninfectious Uveitis (Safety Population)

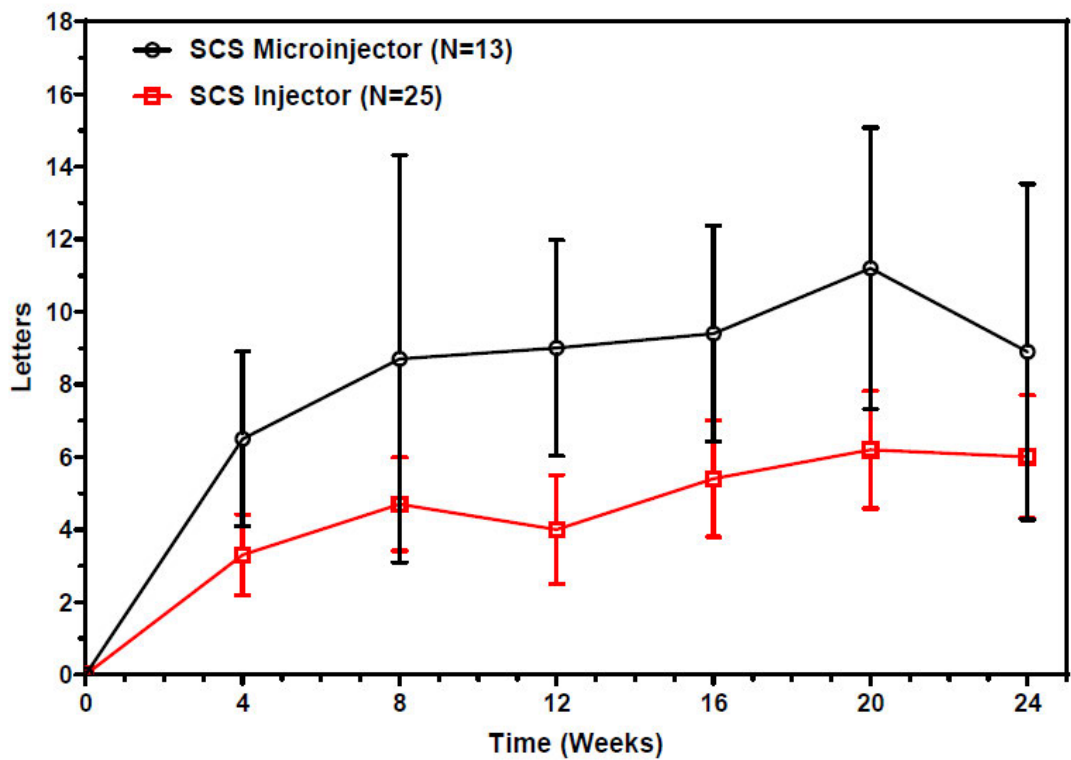
System Organ Class Preferred Term	SCS Microinjector (N=13 Subjects/ 8)	SCS Injector (N=25 Subjects/ 11 Invest.)
Any TEAE	9 (69.2)	10 (40.0)
Eye Disorders	8 (61.5)	8 (32.0)
Cataract Nuclear	0	2 (8.0)
Conjunctival hemorrhage	0	5 (20.0)
Eye inflammation	2 (15.4)	0
Eye pain	2 (15.4)	1 (4.0)

System Organ Class Preferred Term	SCS Microinjector (N=13 Subjects/ 8)	SCS Injector (N=25 Subjects/ 11 Invest.)
Injury, poisoning and procedural complications	2 (15.4)	1 (4.0)
Procedural headache	2 (15.4)	1 (4.0)
Investigations	2 (15.4)	2 (8.0)
Intraocular pressure increased	2 (15.4)	2 (8.0)

Source microinjector report p. 27

Note: In the analysis of safety, subjects receiving CLS-TA via both injectors (SCS Injector on Day 0 and SCS Microinjector on Week 12; n=13 subjects) were counted in the SCS Microinjector group, whereas subjects only receiving CLS-TA via the SCS Injector were counted in the SCS Injector group (n=25 subjects).

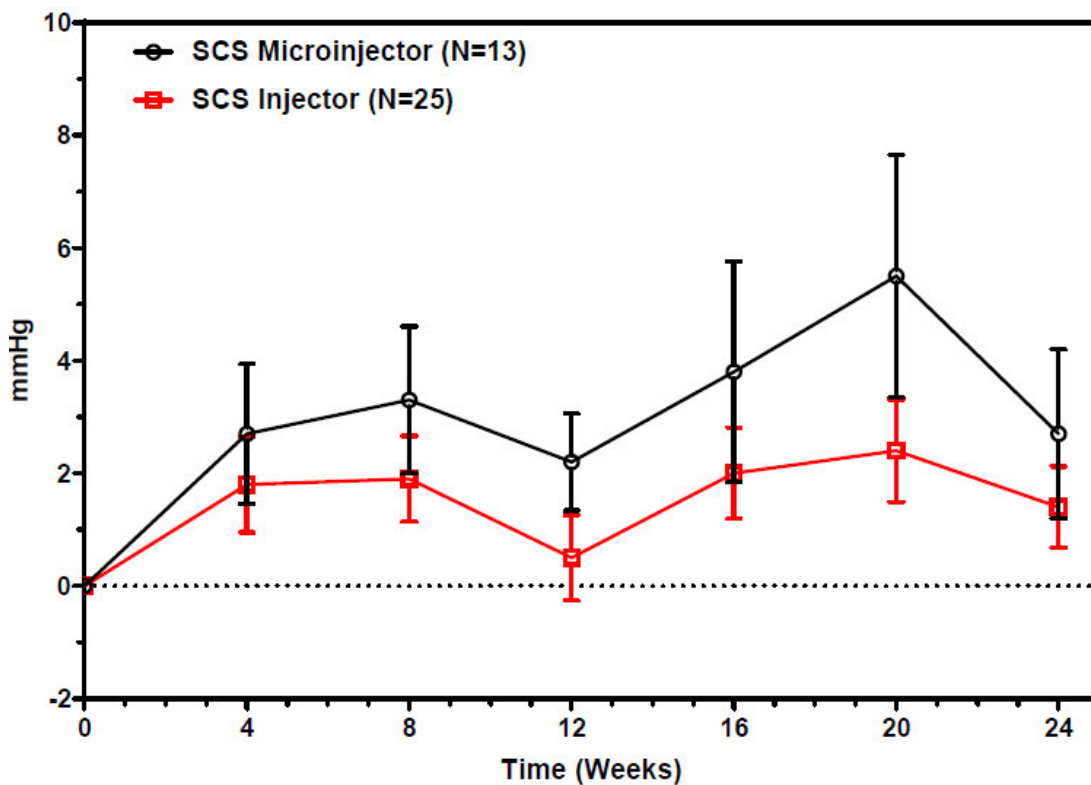
Mean ($\pm$ SEM) Change from Baseline in Best Corrected Visual Acuity Letter Score by Injector in Noninfectious Uveitis (Intent-to-Treat Population w/ LOCF)



Abbreviations: SEM = standard error of the mean; LOCF = last observation carried forward.
Source: Section 5, [Table 3](#).

Mean change from baseline in BCVA ranged from 6.5 letters to 11.2 letters in the SCS Microinjector group and from 3.3 letters to 6.2 letters in the SCS Injector group. While grouped together into a single arm, it should be noted that for the SCS Microinjector group, the mean changes from baseline from Week 4 through Week 12 actually reflect vision changes following the use of the SCS Injector, while changes after Week 12 reflect vision changes following the use of the SCS Microinjector.

Mean ($\pm$ SEM) Change from Baseline in Intraocular Pressure by Injector in Noninfectious Uveitis (Safety Population)



Week, n	0	4	8	12	16	20	24
SCS Microinjector	13	13	13	13	13	13	13
SCS Injector	25	25	25	24	23	23	25

Abbreviations: SEM = standard error of the mean
Source: Section 5, [Table 12](#).

Mean change from baseline in IOP ranged from 2.2 to 5.5 mmHg in the SCS Microinjector group and from 0.5 to 2.4 mmHg in the SCS Injector group. While grouped together into a single arm, it should be noted that for the SCS Microinjector group, the mean changes from baseline from Week 4 through Week 12 actually reflect intraocular pressure changes following the use of the SCS Injector, while changes after Week 12 reflect vision changes following the use of the SCS Microinjector.

During the course of the study, a total of 4 (30.8%) subjects experienced an increase from baseline in IOP >10 mmHg in the SCS Microinjector group compared to 2 (8.0%) subjects in the SCS Injector group. A total 2 (15.4%) subjects in the SCS Microinjector group experienced an IOP >30 mmHg, with the first event occurring at Week 8 (4 weeks before the second SC injection at Week 12 with the SCS Microinjector) and the second at Week 16.

Both subjects experienced an IOP >30 mmHg at Week 20. No subject in the SCS Injector group had an IOP >30 mmHg.

Results from TOPAZ (CLS1002-302) and SAPPHIRE (CLS1002- 301)

Analyses of subjects diagnosed with RVO compared data from subjects receiving SC CLS-TA via the final to-be-marketed SCS Microinjector (TOPAZ; n=160 subjects, 56 investigators) versus those receiving SC CLS-TA via the SCS Injector (SAPPHIRE; 231 subjects, 74 investigators).

Both RVO studies were terminated by the sponsor when SAPPHIRE failed to meet its primary efficacy endpoint. In TOPAZ, more than 70% of the subjects reached the primary timepoint (Week 8) and nearly half reached the Week 12 visit. At the time the study was terminated approximately 10% of the subjects had reached the Week 24 visit. In SAPPHIRE, 98% of the subjects reached the primary timepoint, over 90% reached the Week 24 visit, and over half of the subjects had completed the trial by study termination.

During the administration of SC CLS-TA via the SCS Microinjector in TOPAZ, a user evaluation was undertaken through the use of a questionnaire. At each treatment visit, the physician was asked to provide a response to questions regarding the use of the SCS microinjector delivery system. Responses from the SCS Microinjector (n=212 injections) from 86 treating physicians are presented.

Physician Questionnaire in Retinal Vein Occlusion (Safety Population)

Question	SCS Microinjector (TOPAZ)		
	First Injection (N=160 Injections) n (%)	Second Injection (N=47 Injections) n (%)	Third Injection (N=5 Injections) n (%)
CLS-TA Administered?			
CLS-TA	160 (100)	47 (100)	5 (100)
CLS-TA sham	0	0	0
If 1100 micron needle was used, was the 900 micron needle used first? ^a			
No	1/35 (2.9)	1/15 (6.7)	0
Yes	34/35 (97.1)	14/15 (93.3)	2/2 (100)
Did the SCS Microinjector and/or vial adapter operate as intended?			
No	3 (1.9)	2 (4.3)	0
Yes	157 (98.1)	45 (95.7)	5 (100)

^a During the first injection, a total of 35/160 injections were performed with the 1100 micron needle.

During the second injection, a total of 15/47 injections were performed with the 1100 micron needle.

During the third injection, a total of 2 injections were performed with the 1100 micron needle.

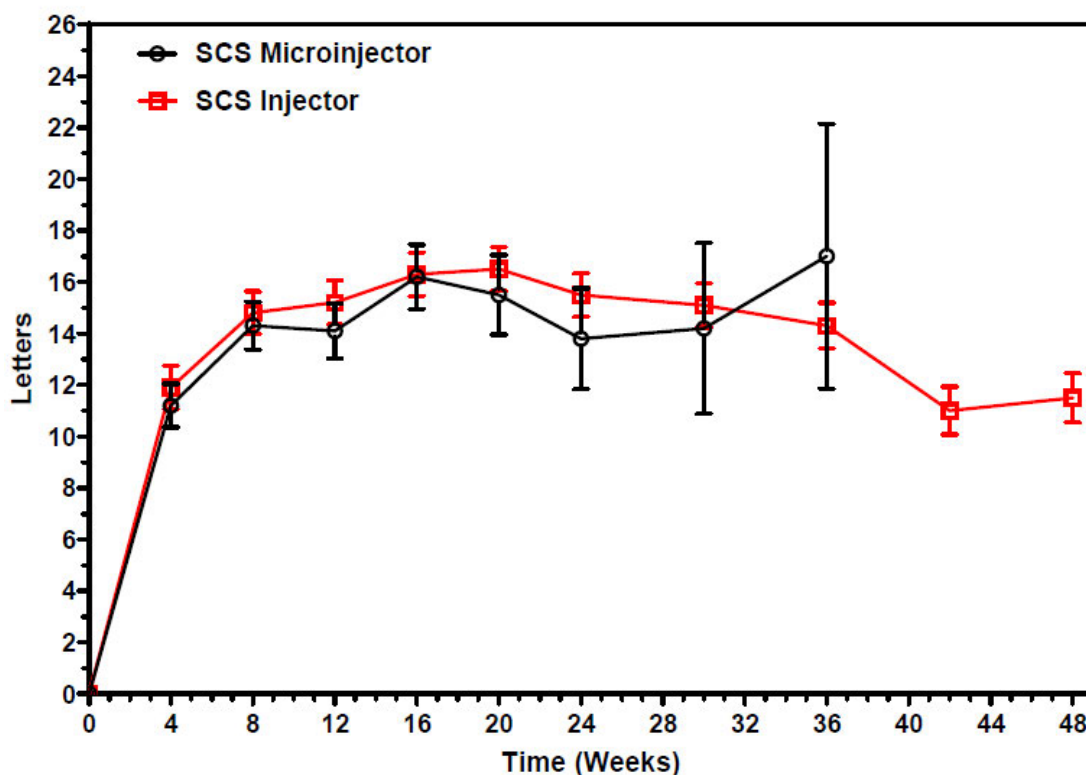
Source: TOPAZ CSR Table 14.2.2.4.5.

Most Commonly Reported Treatment-Emergent Adverse Events in the Study Eye in Retinal Vein Occlusion (Safety Population)

System Organ Class Preferred Term	SCS Microinjector (N=212 Injections) n (%)	SCS Injector (N=648 Injections) n (%)
Any TEAE	30 (14.2)	148 (22.8)
Eye Disorders	21 (9.9)	131 (20.2)
Cataract	1 (0.5)	20 (3.1)
Cataract subcapsular	0	19 (2.9)
Conjunctival hemorrhage	6 (2.8)	41 (6.3)
Conjunctival hyperemia	3 (1.4)	4 (0.6)
Eye pain	3 (1.4)	20 (3.1)
Retinal vascular disorder	3 (1.4)	1 (0.2)
Visual acuity reduced	2 (0.9)	17 (2.6)
Vitreous detachment	0	13 (2.0)

Investigations	11 (5.2)	36 (5.6)
Intraocular pressure increased	11 (5.2)	34 (5.2)

Mean ($\pm$ SEM) Change from Baseline in Best Corrected Visual Acuity Letter Score by Injector in Retinal Vein Occlusion (Intent-to-Treat Population)



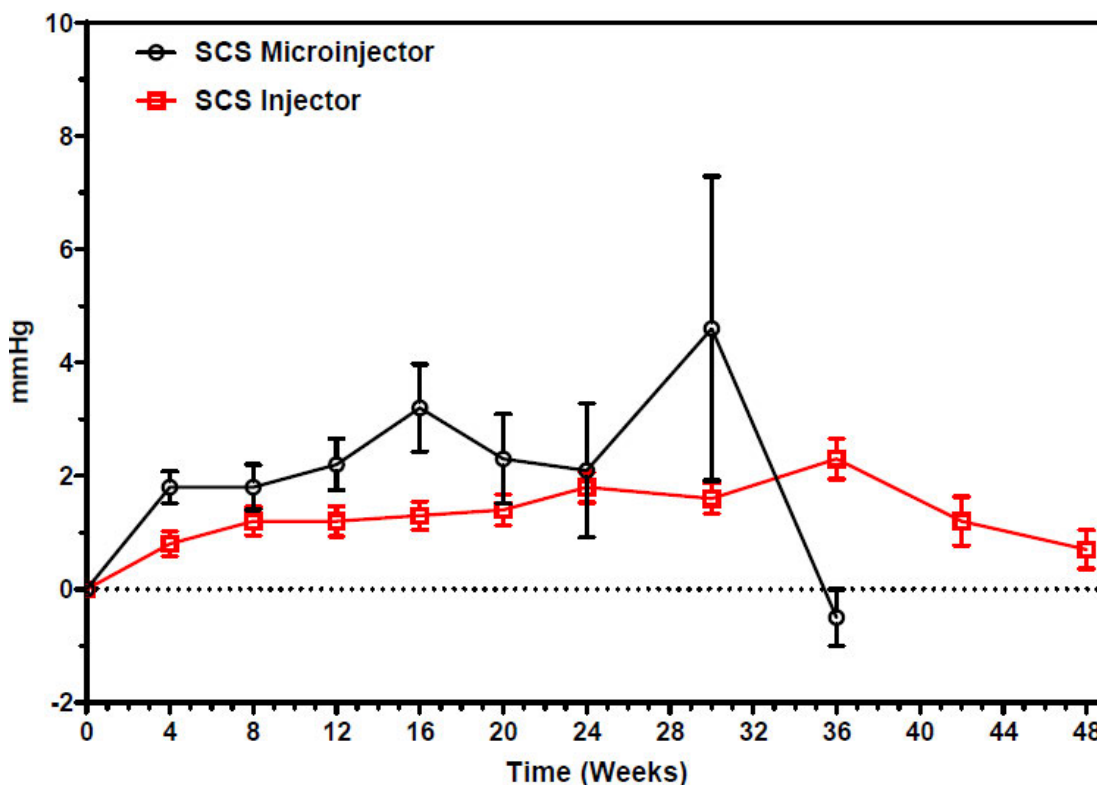
Week, n	0	4	8	12	16	20	24	30	36	42	48
SCS Microinjector	160	146	116	77	49	28	16	5	2	0	0
SCS Injector	229	228	225	219	219	216	216	206	172	140	121

Abbreviations: SEM = standard error of the mean

Source: SAPHIRE CSR [Table 14.2.2.1.1](#), TOPAZ CSR [Table 14.2.2.1.1](#).

Mean change from baseline in BCVA increased similarly in comparison to baseline at all post-baseline timepoints in both injection groups. Mean change from baseline in BCVA ranged from 11.2 letters to 17.0 letters in the SCS Microinjector group and from 11.9 letters to 16.5 letters in the SCS Injector group.

Mean ($\pm$ SEM) Change from Baseline in Intraocular Pressure by Injector in Retinal Vein Occlusion (Safety Population)



Week, n	0	4	8	12	16	20	24	30	36	42	48
SCS Microinjector	160	145	115	76	50	28	16	5	2	0	0
SCS Injector	229	228	225	223	220	216	214	205	172	140	121

Abbreviations: SEM = standard error of the mean

Source: SAPHIRE CSR [Table 14.3.4.4.1](#), TOPAZ CSR [Table 14.3.4.4.1](#).

Mean change from baseline in IOP increased in comparison to baseline at all post-baseline timepoints in both injection groups. Mean change from baseline in IOP ranged from 1.82 to 4.1 mmHg in the SCS Microinjector group and from 0.8 to 2.3 mmHg in the SCS Injector group.

A total 8 (5.0%) subjects in the SCS Microinjector group experienced an IOP ≥ 30 mmHg during the study, while 12 (5.2%) subjects in the SCS Injector group experience the same degree of IOP elevation

Reviewer's Comments:

The Applicant has adequately addressed the request for clinical use data with the final to-be-marketed configuration evaluated by at least three physicians and in at least 30 patients. There was no clinical difference in the ability to administer the drug product between the injector and microinjector based on physician and observer questionnaires in the Azalea and Topaz study.

The number of patients in the microinjector group in the Azalea study is small and represents patient who received injections via both the injector and microinjector; therefore, the safety, IOP and VA results from the Topaz study are more indicative of those events expected with the microinjector. There were no clinically significant changes in visual acuity or IOP between groups. The overall adverse events profile was similar. The clinical use data submitted, is adequate to support the safety of use of the microinjector for administration of triamcinolone acetonide injectable suspension.

In addition to addressing the clinical use data, the Applicant has also submitted a Safety Update to the NDA. Since the data cut for the initial NDA, an additional 609 subjects (including 287 new Sapphire and 322 new Topas subjects) have been added to the safety database. The updated safety profile for CLS-TA is consistent with the original NDA data. No new or unexpected adverse events have occurred.

Recommended Regulatory Action:

NDA 211950 is recommended for approval. See the CDTL memo for final labeling and the additional approvability issues that were communicated in the October 18, 2019, CR letter.

Jennifer D. Harris, M.D.
Medical Officer

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/s/

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09/13/2021 09:43:39 AM

Clinical Review
 {Jennifer Harris, M.D.}
 {NDA 211950}
 {triamcinolone acetonide injectable suspension}

CLINICAL REVIEW

Application Type	N
Application Number(s)	NDA 211950 IND 115683
Priority or Standard	Standard
Submit Date(s)	December 19, 2018
Received Date(s)	December 19, 2018
PDUFA Goal Date	October 19, 2019
Division/Office	OND
Reviewer Name(s)	Jennifer D Harris, MD
Review Completion Date	August 1, 2019
Established/Proper Name	triamcinolone acetonide ophthalmic suspension
(Proposed) Trade Name	Xipere
Applicant	Clearside Biomedical, Inc.
Dosage Form(s)	suspension
Applicant Proposed Dosing Regimen(s)	Single dose suprachoroidal injectable suspension
Applicant Proposed Indication(s)/Population(s)	treatment of macular edema associated with uveitis
Recommendation on Regulatory Action	Complete response due to issues with manufacturing facility
Recommended Indication(s)/Population(s) (if applicable)	Treatment of macular edema associated with uveitis in adult patients

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

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NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL is a preservative-free, (b) (4) sterilized, aqueous suspension of the corticosteroid triamcinolone acetonide (TA) formulated for suprachoroidal (SC) injection. CLS-TA 40 mg/mL has been developed for the treatment of macular edema (ME) associated with uveitis. In this injection procedure, drug is injected approximately 4 mm posterior to the limbus via the suprachoroidal space (SCS) Microinjector, an ophthalmic dispenser comprised of a proprietary manual piston syringe and needle assembly. After injection, the injectate moves posteriorly from the site of the injection, with the fluid being absorbed into the inner sclera, choroid, retinal pigment epithelial (RPE) cells, and retina.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 21950 CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL is recommended for approval for the treatment of macular edema associated with uveitis. The efficacy of triamcinolone acetonide via multiple routes of administration was established as part of the Drug Efficacy Study Implementation (DESI) review and has been used as an anti-inflammatory agent for the treatment of various diseases in the US for over 50 years. Triamcinolone 40 mg was found to be efficacious for the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. The data in this NDA demonstrates the efficacy of triamcinolone for macular edema associated with uveitis. CLS-TA is superior to placebo in the clinical improvement in visual acuity in patients with uveitis associated macula edema. Based on the results of this clinical trial, the DESI findings and the long history of use of this product in ophthalmic inflammatory diseases; the efficacy in uveitis associated macula edema has been established.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL is both statistically and clinically superior compared to placebo in the improvement in visual acuity in patients with macular edema associated with uveitis. The effectiveness of this treatment starts within 4 weeks after administration and is sustained throughout the study period. CLS-TA is also statistically superior compared to placebo in the mean reduction in central retinal thickness.

The safety of triamcinolone via routes other than suprachoroidal has been well established based on the long history of the use of this product and the extensive safety database. There were no new or unknown risks identified in this NDA review when this product is administered by this new route in uveitis patients with macula edema. The types of adverse events seen were the types of events expected as they are either related to the underlying disease process or known risks associated with intraocular steroid use.

The benefits in treatment of this sight threatening ocular inflammatory indication outweighs the risks associated with triamcinolone acetonide injectable suspension.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<i>Uveitis (inflammation) can lead to permanent vision loss</i>	<i>Inflammation can be treated with the use of anti-inflammatory agents</i>
Current Treatment Options	<i>Intraocular steroids</i>	<i>CLS-TA provides an effective alternate route of administration negating the need for entering the intraocular space</i>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• <i>Improvement in visual acuity</i> • <i>Reduction in central retinal thickness</i>	• <i>Study CLS1001-301 demonstrates a significant improvement in visual acuity and central retinal thickness within 4 weeks after administration of CLS-TA that is sustained throughout the 24 week study.</i> • <i>DESI review established the efficacy of triamcinolone for multiple ocular inflammatory diseases and provided for the existing 50 year history of usage for this product</i>
Risk and Risk Management	<i>There are several known ocular complications associated with the use of corticosteroids. These include but are not limited to increased intraocular pressure, posterior subcapsular cataract formation, secondary ocular infections, and corneal and scleral thinning.</i>	<i>There were no new or unknown risks identified in this NDA review when this product is administered in the suprachoroidal space. The types of adverse events seen were the types of events expected as they are either related to the underlying disease process or known risks associated with intraocular steroid use.</i>

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:		Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as	Sec 6.1 Additional endpoints
		☒ Patient reported outcome (PRO)	
		☐ Observer reported outcome (ObsRO)	
		☐ Clinician reported outcome (ClinRO)	
		☒ Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:		
		☐ Input informed from participation in meetings with patient stakeholders	
		☐ Patient-focused drug development or other stakeholder meeting summary reports	
		☐ Observational survey studies designed to capture patient experience data	
		☐ Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.		

2. Therapeutic Context

2.1. Analysis of Condition

Uveitis is a general term used to describe a set of ocular inflammatory diseases. The whole eye can be affected in uveitis or the inflammation may dominate in specific locations of the eye. Uveitis is classified by anatomic location within the eye as being anterior-, intermediate-, posterior- or pan-uveitis. It is also described by the course (acute, recurrent or chronic); and according to its etiology, in terms of being infectious or noninfectious.

Uveitis is a leading cause of visual loss in the developed world. Causes of vision loss associated with uveitis include macular edema, cataract formation, chorioretinal scarring, retinal detachment, and secondary glaucoma.

Macular edema is a major cause of visual loss in uveitis, is defined as abnormal thickening of the macula associated with the accumulation of fluid in the outer plexiform and the inner nuclear layers of the retina, and occasionally the intracellular spaces as a result of the breakdown of the blood-retinal barrier.

2.2. Analysis of Current Treatment Options

Drug	Endpoint	Treatment Effect	Intended Population
Adalimumab (Humira)	Time to treatment failure	5.6 months vs. 3 months (trial 1) > 18 months vs. 8.3 months (trial 2) > 18 months vs. 24.1 weeks (peds trial)	The treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.
fluocinolone acetonide implant (Retisert)	recurrence of uveitis (i.e. ≥ 2 step increase in cells or flare) in the study eye within 34 weeks following implantation	54% vs. 7% (trial 1) 40% vs. 14% (trial 2)	Patients, age ^(b) and older, with chronic ^{(b) (4)} non-infectious posterior uveitis
dexamethasone intravitreal implant (Ozurdex)	proportion of patients with vitreous haze score of 0 (no inflammation) at week 8	47% vs. 12%	Patients ≥ 18 y.o. with non-infectious ^{(b) (4)} or posterior uveitis

Triamcinolone	DESI		Inflammatory conditions of the eye
Prednisone	DESI		Inflammatory conditions of the eye
Dexamethasone	DESI		Inflammatory conditions of the eye

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Triamcinolone acetonide is a glucocorticosteroid that has been used as an anti-inflammatory agent for the treatment of various diseases in the US for over 50 years and was the subject of a Drug Efficacy Study Implementation (DESI) review. Triamcinolone 40 mg was found to be efficacious for the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

Triamcinolone acetonide is available in a range of different pharmaceutical forms including suspensions for injection. Triamcinolone acetonide injectable suspension was initially permitted by the US FDA in 1957 for intramuscular and intra-articular use (Kenalog). In the US, two suspensions for intravitreal (IVT) injection (Triesence; Trivaris) were approved in 2007 and 2008, respectively, for the indications of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. Triesence was also approved for visualization during vitrectomy in the EU in 2011.

Trivaris was discontinued in the US in 2011. Triesence continues to be available as a marketed product in the US. None of the TA-containing products have been withdrawn from the market or put on clinical hold for safety reasons. Triamcinolone acetonide is currently not approved in any country to be administered as a suprachoroidal injection for the treatment of any condition.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following were the key agreements reached for the NDA submission:

- o Safety population of 301 unique subjects exposed to suprachoroidally injected CLS-TA
- o One adequate and well-controlled Phase 3 study, CLS1001-301 (PEACHTREE), to support the safety and efficacy of CLS-TA for the treatment of subjects with macular

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- edema associated with uveitis
- o A comprehensive literature review on the use of TA for the treatment of subjects with ME associated with uveitis, may be included as a study report in lieu of a second Phase 3 trial

3.3. Foreign Regulatory Actions and Marketing History

Similar to the US marketing history, triamcinolone acetonide (TA) has been used for the treatment of various diseases across Europe, and in other territories across the world for over 50 years. In addition, Triesence was approved in 2011 for visualization during vitrectomy in the EU, Switzerland and Canada.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical inspections were conducted at two clinical sites. The sites chosen were based on the use of the OSI site selection tool. There was no specific efficacy/safety or scientific misconduct concerns.

Site 106 (Dr Rifkin) inspection was noted as VIA (Voluntary Action Indicated) for failure to adhere to the protocol. Three out of the four enrolled subjects did not meet the inclusion criteria. Three of the four enrollees had visual acuities outside of the enrollment criteria and one received topical steroids within the enrollment period.

Site 102 (Dr Wang) inspection result was determined to be NAI (No Action Indicated).

4.2. Product Quality

A 483 was issued for the drug product manufacturer on (b) (4). The following issues were raised and communicated with the manufacturer:

(b) (4)

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(b) (4)

Reviewer's Comments:

The issues identified are not expected to be resolved during this review cycle.

4.3. Clinical Microbiology

N/A

4.4. Nonclinical Pharmacology/Toxicology

Pharmacologic studies in animal models of endotoxin-induced uveitis with therapeutically relevant levels of TA administered suprachoroidally were conducted during drug development. See nonclinical review for details.

4.5. Clinical Pharmacology

Clinical pharmacology was evaluated in three trials to evaluate the systemic PK. The clinical PK studies demonstrated that systemic TA levels following suprachoroidal injection of CLS-TA

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were below the limits of quantification. And are below the levels of IVT injections. See PK review for details.

4.6. Devices and Companion Diagnostic Issues

A companion diagnostic is not included in the application. The microinjector syringe used to dispense the drug product will be co-packaged and labeled as part of the drug.

4.7. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table of Studies/Clinical Trials

Study No. Country Last Subject Completed or Date of Data Cut	Study Design and Population	Test Product Doses	Duration of Dosing Duration of Follow-up	Primary and Key Secondary Efficacy Endpoint(s) Efficacy Population	Key Demographic Characteristics
CLS1001-301 (PEACHTREE) US/Israel/India 18 JAN 2018	Phase 3, randomized, masked, sham-controlled, multicenter study evaluating safety and efficacy of 4 mg CLS-TA administered via SC injection in subjects with ME associated with NIU	4 mg CLS-TA or control Doses: 2	2 treatments (Day 0 and Week 12) Follow-up 24 weeks following Baseline	Percentage of subjects with a change from Baseline to Week 24 of ≥ 15 ETDRS letters read in BCVA Efficacy population – 160 subjects: 96 CLS-TA 64 control	Male: 45.0%; Female: 55.0% Median age: 51 years (Range 18 to 92 years) Race: Asian (45.0%), White (40.6%), Black/African American (13.8%)
CLS1001-201 (DOGWOOD) US 02 DEC 2015	Phase 2, randomized, masked, controlled, multicenter study evaluating safety & efficacy of CLS-TA in subjects with ME following uveitis	4 mg or 0.8 mg CLS-TA Doses: 1	1 treatment (Day 1) Follow-up 8 weeks after treatment	Mean change (SD) from Baseline in CST at 2 months Efficacy population – 22 subjects: 17 CLS-TA 4 mg 5 CLS-TA 0.8 mg	Male: 45.5%; Female: 54.5% Median age: 53.0 years (Range 20 to 83 years) Race: White (81.8%), Black/African American (18.2%)

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CLS1001-302 (AZALEA) US 24 JAN 2018	Phase 3, open-label, multicenter study to evaluate the safety of CLS-TA administered in subjects with NIU	4 mg CLS-TA Doses: 2	2 treatments (Day 0 and Week 12) Follow-up 12 weeks after treatment 2	Change in BCVA by ETDRS letters read^a Changes in CST from Baseline Improvement in signs of inflammation. Efficacy population – 38 subjects	Male: 34.2%; Female: 65.8% Mean age: 52.4 years (Range 22 to 77 years) Race: White (81.6%); Black/African American (18.4%)
--	--	------------------------------------	---	---	---

BCVA = best corrected visual acuity; CLS-TA = triamcinolone acetonide injectable suspension, 40 mg/mL; CST = central subfield thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; ME = macular edema; NIU = noninfectious uveitis; SC = suprachoroidal; SD = standard deviation; TA = triamcinolone acetonide; US = United States

^a Additional endpoints

5.2. Review Strategy

The primary support for evaluating the efficacy for this product was based on a single phase 3 trial, the literature reports used in the DESI review for triamcinolone acetonide suspension 40 mg/ml and the 50 year history of the use of this product. The pivotal study PEACHTREE (CLS1001-301) was a Phase 3, randomized, masked, sham-controlled, multicenter study to assess the efficacy and safety of suprachoroidally injected CLS-TA (4 mg) administered compared to control (sham procedure to mimic a suprachoroidal injection) in the treatment of subjects with macular edema (ME) associated with uveitis.

Two additional studies conducted were a Phase 2 randomized, masked, sham-controlled, multicenter study, DOGWOOD (CLS1001-201) and a Phase 3 open-label study, AZALEA (CLS1001-302). The DOGWOOD trial primary efficacy assessment was change in retinal thickness from Baseline in central subfield thickness (CST), as measured by spectral-domain optical coherence tomography (SD-OCT) at 2 months which is not considered an acceptable endpoint for macular edema associated uveitis trials. The trial enrolled 22 subjects in a 4:1 randomization. Based on the size and design of this trial, the results were only viewed as informative for the design of the definitive phase 3 trial.

The AZALEA study was used primarily as supportive information for the safety evaluation of the product due to the small number of subjects enrolled and the open-label design.

Based on the DESI review and the Agency's findings, ophthalmic steroids have been determined to be efficacious for eye disorders and diseases such as sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory condition unresponsive to topical corticosteroids. See section 13.1 for references.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. [PEACHTREE (CLS1001-301)]

6.1.1. Study Design

Overview and Objective

The purpose of this study was to evaluate the safety and efficacy of suprachoroidally administered CLS-TA, triamcinolone acetonide injectable suspension, for the treatment of macular edema associated with non-infectious uveitis.

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Objectives:

Primary

The primary objective of the study is to demonstrate the efficacy of CLS-TA as shown by the change from baseline in best corrected visual acuity (BCVA) in subjects with macular edema associated with non-infectious uveitis

Secondary

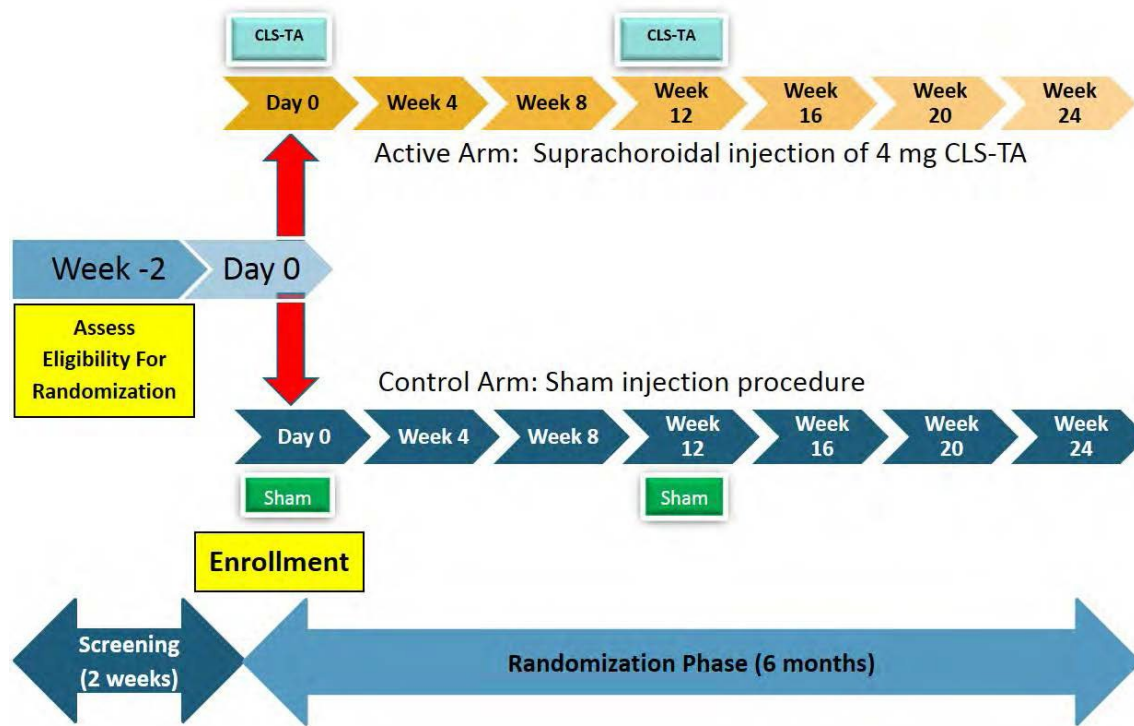
To determine mean change from baseline in central subfield thickness

Trial Design

PEACHTREE was a Phase 3, randomized, masked, controlled multicenter study to assess the safety and efficacy of suprachoroidally injected CLS-TA for the treatment of subjects with uveitis. A total of 160 subjects were randomly assigned 3:2 to a CLS-TA arm (N=96) or to a sham arm (N=64) in this study.

Eligible subjects had a diagnosis of macular edema associated with noninfectious uveitis (NIU) of any etiology/disease diagnosis and could have uveitis with any anatomic location including anterior, intermediate, posterior, or panuveitis. All eligible subjects were required to have macular edema with a measurement of >300 microns in the central subfield (CST) measured by spectral domain (SD) optical coherence tomography (OCT) and reading between 5 and 70 early treatment of diabetic retinopathy study (ETDRS) letters in best corrected visual acuity (BCVA) at baseline.

During the study, subjects received either suprachoroidally injected CLS-TA 4 mg or underwent a sham suprachoroidal procedure at Baseline and at Week 12. Evaluations were every 4 weeks with the primary outcome at 24 weeks after randomization. The study design included 8 clinic visits over a maximum of 29 weeks.



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Rescue Criteria

Beginning at Week 4 (Visit 3), if any of the following criteria were met in the study eye, rescue treatment was introduced.

1. A decrease of 10 or more Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA letters read from baseline (Day 0)
2. An increase in CST of ≥ 100 microns or 20%, whichever is lower, from baseline (Day 0) based on the CST measurement at the clinical site
3. A ≥ 1.5 -step increase from baseline (Day 0) in the level of inflammation (e.g., anterior chamber cells or vitreous haze) or an increase from 3+ to 4+
4. In the investigator's medical judgement, the uveitic complications in the study eye have not improved and the condition needs to be addressed

Inclusion Criteria

1. A diagnosis of non-infectious uveitis of any etiology and from among those with anterior-, intermediate-, posterior- or pan-uveitis
2. Macular edema associated with non-infectious uveitis defined by:

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- a. A retinal thickness of ≥ 300 microns in the central subfield, with fluid as measured by SD-OCT (using the Heidelberg Spectralis or Zeiss Cirrus) and confirmed by the Central Reading Center
3. ETDRS BCVA score of ≥ 5 letters read (20/800 Snellen equivalent) and ≤ 70 letters read (20/40 Snellen equivalent) in the study eye
4. Understands the language of the informed consent; willing and able to provide written informed consent prior to any study procedures; willing to comply with the instructions and attend all scheduled study visits
5. At least 18 years of age

Exclusion Criteria

Ophthalmic Exclusion:

Subjects were ineligible for participation in this study if s/he meets any of the following criteria:

1. Has significant media opacity in the study eye precluding evaluation of the retina and vitreous
2. Has macular edema with etiology other than uveitis
3. Any active ocular disease or infection in the study eye other than uveitis
4. Intraocular pressure > 22 mmHg or uncontrolled glaucoma (open angle or angle closure) in the study eye at Visit 1; subjects are not excluded if IOP is ≤ 22 mmHg in the study eye with no more than 2 IOP lowering medications
5. History of any vitreoretinal surgery (examples include but are not limited to scleral buckle, retrieval of a dropped nucleus or intraocular lens) in the study eye; prior photocoagulation and IVT injections are acceptable; prior cataract extraction, Yttrium-Aluminum-Garnet laser capsulotomy, and pars plana vitrectomy is allowed, but must have been performed at least 3 months prior to Visit 2
6. Has had cyclodestructive procedures or filtration surgeries in the study eye in the 3 months prior to Visit 2
7. Has high myopia in the study eye defined as a spherical equivalent > -6 diopters or an axial length ≥ 26 mm
8. Has had photocoagulation or cryotherapy in the study eye within the 6 months prior to Visit 2
9. Has had any intravitreal injection of anti-VEGF treatment (bevacizumab, aflibercept, pegaptanib or ranibizumab) in the study eye in the 30 days prior to Visit 2

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10. In the study eye, any topical ocular corticosteroid in the 10 days prior to Visit 2; intraocular and periocular corticosteroid injection in the 2 months prior to Visit 2; an Ozurdex implant in the 6 months prior to Visit 2; Retisert or Iluvien implant in the 3 years prior to Visit 2

General Exclusion:

1. Female subjects who are pregnant, lactating or planning a pregnancy. Females of childbearing potential must agree to submit to a pregnancy test at screening and agree to use an acceptable method of contraception throughout participation in the study.
 - a. Acceptable methods of contraception include double barrier methods (condom with spermicide or diaphragm with spermicide), hormonal methods (oral contraceptives, implantable, transdermal, or injectable contraceptives), or an intrauterine contraceptive device with a documented failure rate of less than 1% per year. Abstinence may be considered an acceptable method of contraception at the discretion of the Investigator, but the subject must agree to use one of the acceptable birth control methods if she becomes sexually active.
2. Any uncontrolled systemic disease that, in the opinion of the Investigator, would preclude participation in the study (e.g., unstable medical status including uncontrolled elevated blood pressure, cardiovascular disease, and glycemic control) or put the subject at risk due to study treatment or procedures
3. Likely need for hospitalization or surgery within the study period, including planned elective surgery or hospitalization that cannot be deferred
4. Hypersensitivity to any component of the CLS-TA, fluorescein or to topical anesthetics
5. Is currently enrolled in an investigational drug or device study or has used an investigational drug or device within 30 days of Visit 2
6. Has used acetazolamide (Diamox) 1 week prior to Visit 2
7. Has taken systemic corticosteroids at doses greater than 20 mg per day for oral prednisone (or equivalent for other corticosteroids) in the 2 weeks prior to Visit 2; subjects on 20 mg or less per day can be enrolled if no increase in dosing is anticipated for the duration of the study; decreases and termination of dose are allowable during the study
8. Is currently using prescribed nonsteroidal anti-inflammatory drugs (excluding over-the-counter use) unless the dose has been stable for at least 2 weeks prior to Visit 2, and no increase in dosing is anticipated for the study duration; decreases and termination of dose are allowable during the study
9. Is currently using prescribed immunomodulatory therapies, unless the dose has been stable for at least 2 weeks prior to Visit 2, and no increase in dosing is anticipated for the study duration; decreases and termination of dose are allowable during the study

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10. Has taken any fingolimod or any other drug in the 6 weeks prior to Visit 2, where the drug is known to induce macular edema

Country Specific Criteria

Inclusion Criterion #1 (for subjects in Israel)

- A diagnosis of non-infectious uveitis of any etiology and from among those with anterior-, intermediate-, posterior- or pan-uveitis and who:
 - Were on an allowed maintenance therapy for their uveitis as specified in the protocol, and
 - In the opinion of the Investigator, failed previous uveitis treatment.

Exclusion Criterion #4 (for subjects in India)

- Intraocular pressure > 22 mmHg in the Study eye at Visit 1 or diagnosed glaucoma.

Study Schedule

Visit #	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5		Visit 6	Visit 7	Visit 8
Visit Type	Screening	Randomization /Treatment #1		Follow-Up		Treatment #2		Follow-Up		End Of Study
Visit Window	Day -14 to -1	Day 0		Month 1 Week 4 Day 28 ± 5	Month 2 Week 8 Day 56 ± 5	Month 3 Week 12 Day 84 ± 5		Month 4 Week 16 Day 112 ± 5	Month 5 Week 20 Day 140 ± 5	Month 6 Week 24 Day 168 ± 5
Assessments		Pre-dose	Post-dose			Pre-dose	Post-dose			
Informed Consent	√									
Assign Subject Number	√									
Demographics, Medical & Ocular Hx	√									
Eligibility Criteria	√	√								
Assess AEs		√	√	√	√	√	√	√	√	√
Con Med Review	√	√	√	√	√	√	√	√	√	√
Resting HR & BP	√	√				√				√
Central Lab Tests ^a	√									√
Review of Systems	√									√
BCVA ^b	√	√		√	√	√		√	√	√
Slit lamp Biomicroscopy ^{b,c}	√	√	√	√	√	√	√	√	√	√
IOP ^d	√	√	√	√	√	√	√	√	√	√
Dilated Indirect Ophthalmoscopy ^b	√	√	√	√	√	√	√	√	√	√

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Visit #	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5		Visit 6	Visit 7	Visit 8
Visit Type	Screening	Randomization /Treatment #1		Follow-Up		Treatment #2		Follow-Up		End Of Study
Visit Window	Day -14 to -1	Day 0		Month 1 Week 4 Day 28 ± 5	Month 2 Week 8 Day 56 ± 5	Month 3 Week 12 Day 84 ± 5		Month 4 Week 16 Day 112 ± 5	Month 5 Week 20 Day 140 ± 5	Month 6 Week 24 Day 168 ± 5
Assessments		Pre-dose	Post-dose			Pre-dose	Post-dose			
SD-OCT ^b	√	√		√	√	√		√	√	√
VFQ-25 & EQ-5D		√								√
PK Blood Draw (optional)		√		√		√				√
Select Study Eye/Confirm Study Eye	√					√				
Fluorescein Angiogram ^b	√									√
Fundus Photos ^b	√									√
IWRS/Randomize		√				√				
Study Drug Treatment ^a		INJECT				INJECT				

^a Central lab test samples should be collected prior to FA being performed; central labs include a serum pregnancy test for females of child bearing potential

^b Completed for both eyes at Visit 1 and Visit 8; study eye only for all other visits

^c Any finding of cataract should be graded

^d IOP collected for both eyes, except post-injection when data is collected for study eye only

^e Injection should be administered the same day as the pre-injection assessments at Visit 2 and at Visit 5

Source: Appendix 16.1.1, [Appendix A](#), Time and Events Schedule, CLS1001-301 Protocol Version 4, dated 12 Apr 2017.

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Study Endpoints

Primary

The proportion of subjects with a change from Baseline of ≥ 15 letters in ETDRS letters read in BCVA at Visit 8 (24 weeks), subsequent to suprachoroidal injections of CLS-TA or sham injection procedures, in subjects with macular edema associated with non-infectious uveitis.

Secondary

Mean change from Baseline in CST as measured by SD-OCT at 24 weeks (Visit 8).

Additional

- o Triamcinolone acetonide systemic blood concentrations prior to each dose (Visits 2 and 5), 4 weeks following the first dose (Visit 3) and at 24 weeks (Visit 8) were used to estimate standard population PK parameters.
- o Change from Baseline in subject reported outcomes as measured by the Visual Function Questionnaire (VFQ-25) and the European Quality of Life 5-Dimensions (EQ-5D) questionnaire at Visit 8 (24 weeks).
- o Changes from the Baseline in CST measured by SD-OCT at each visit.
- o Changes from Baseline in BCVA at each visit as measured by ETDRS letters read.
- o Changes from Baseline in signs of uveitis, that is, AC cells, AC flare, and vitreous haze by visit.

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Safety Endpoints

- Incidence of TEAEs and SAEs, grouped by organ system, relatedness to study treatment, and severity.
- Percentage of subjects whose IOP increases were >10 mmHg from their own Baseline measurement at each follow-up visit (except Visits 2 and 5 [post-dose]).
- Percentage of subjects whose IOP increases were to a reading >30 mmHg at each follow-up visit (except Visits 2 and 5 [post-dose]).
- Percentage of subjects who required 1 or more additional IOP lowering medications at any follow-up visit (except Visits 2 and 5 [post-dose]).
- Changes in cataract grading.

Statistical Analysis Plan

Primary Endpoint

Since there was only one primary endpoint, no multiplicity adjustments were required for the primary analysis.

A count and proportion of subjects showing 15 or more ETDRS letters improvement in the BCVA at each visit was presented. A Cochran-Mantel-Haenszel (CMH) test was used to test differences in the proportion of subjects in the two treatment groups who showed 15 or more ETDRS letter improvement in BCVA at the Week 24 visit after adjusting for country effects.

The odds ratio (OR) estimate was presented along with a 95% confidence interval (CI) and the p-value from the CMH OR test. The Breslow Day (BD) test with Tarone's adjustment p-value was presented to confirm homogeneity of the OR between country and the suitability of using the CMH weighted OR to test for overall association.

Missing data imputed by LOCF in the ITT population were used for the primary efficacy analysis. For LOCF imputation, any subject who missed the scheduled assessment or received a rescue therapy had their data imputed by LOCF. When a subject was rescued, the data were imputed using LOCF using the last data prior to when additional treatment was provided. The PP population was used as a sensitivity analysis for the primary endpoint. Missing data in the PP population were not imputed and were treated as missing at any time point where data were not available. Following rescue therapy, data were not imputed in the PP analyses.

Secondary Endpoint

The difference in mean change from Baseline between the treatment groups at Week 24 were analyzed using an Analysis of Covariance (ANCOVA) model with factors for treatment group

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and country and covariate Baseline CST. This analysis was performed for the ITT population using LOCF and the PP population using observed data.

The CST was presented by treatment group and scheduled study visit up to Week 24. The summary statistics included their corresponding changes from Baseline. This summary was performed for the ITT population using observed data and LOCF.

Protocol Amendments

N/A – There were no major protocol amendments that affected the interpretation of the trial results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good clinical Practice.

Financial Disclosure

Details of the disclosable financial arrangements for the clinical investigators who participated in the development program are summarized in the following table.

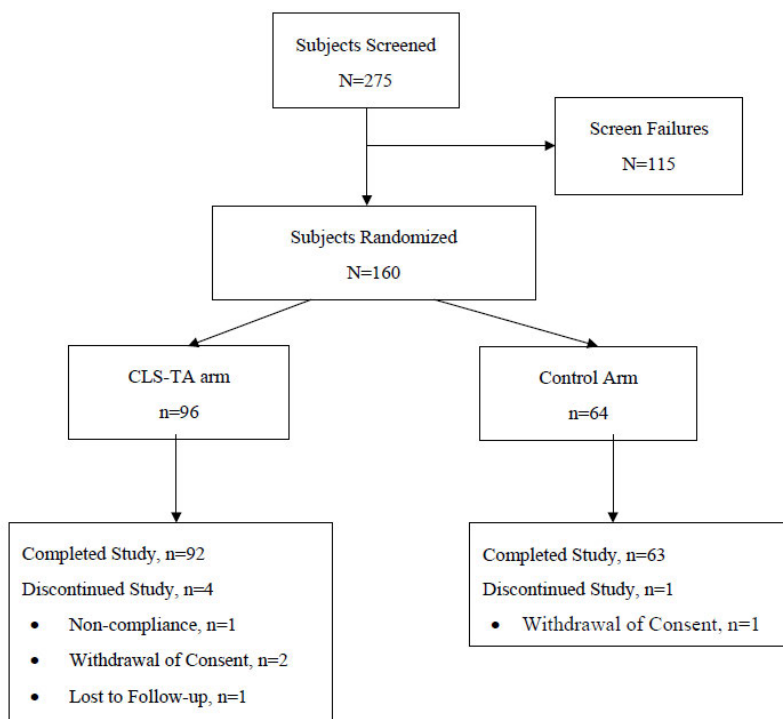
Investigator	Site	Disclosure	Number of Subjects		
			Peachtree	Dogwood	Azalea
(b) (6)	(b) (6)	Payments $\geq$ \$25,000	(b) (6)		
		Payments $\geq$ \$25,000			
		Equity interest $\geq$ \$50,000			
		Equity interest $\geq$ \$50,000			
		Payments $\geq$ \$25,000			

Clearside Biomedical has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for triamcinolone acetonide injectable suspension. There were five (5) investigators who disclosed financial ties to the

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sponsor. A review of these arrangements does not raise questions about the integrity of the results.

Patient Disposition



CSR Figure 2 page 60

Discontinued Subjects

Treatment Arm	Subject Number / Country	Age / Sex	Study Eye	Reason for Discontinuation
CLS-TA	(b) (6) / USA	22 / F	OD	Non-compliance
	(b) (6) / USA	67 / M	OD	Withdrawal by Subject
	(b) (6) / IND	49 / F	OS	Lost to Follow-up
	(b) (6) / IND	68 / F	OS	Withdrawal by Subject
Control	(b) (6) / IND	50 / F	OS	Withdrawal by Subject

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F=female, M=male, OD=Right eye, OS=Left eye, IND=India, USA=United States of America.

Source: Appendix 16.1.7, [Listing 16.1.7](#), Appendix 16.2.1, [Listing 16.2.1.1](#), Appendix 16.2.4, [Listing 16.2.4.1](#).

Ref: CSR Table 7 page 59

Reviewer's Comments: *The subjects that withdrew early from the study were not due to adverse events. See section 8.4.3 for adverse events leading to study **treatment** discontinuation.*

Protocol Violations/Deviations

Major Protocol Deviations (Intent-to-Treat)

	CLS-TA (N=96)	Control (N=64)
	n (%)	n (%)
Subjects with at least one major deviation	30 (31.3)	12 (18.8)
Protocol Deviation Category		
Non-compliance with exclusion criteria	6 (6.3)	4 (6.3)
Non-compliance with inclusion criteria	3 (3.1)	2 (3.1)
Non-compliance with study treatment	2 (2.1)	1 (1.6)
Non-compliant with masking	7 (7.3)	1 (1.6)
Non-compliant with obtaining ICF	4 (4.2)	1 (1.6)
Not performing Week 24 assessment	1 (1.0)	1 (1.6)
Prohibited concomitant therapy	9 (9.4)	2 (3.1)
Other	1 (1.0)	0

ICF=informed consent form.

Note(s): Percentages were based on the number of subjects in the respective group. If a subject reported more than one major protocol deviation in different categories, then that subject was counted once in each category.

CSR Table 8 page 65

Overall, 42/160 subjects (26.3%) had at least 1 major deviation, with more subjects experiencing major deviations in the CLS-TA arm (30/96 subjects [31.3%]) than in the Control arm (12/64 subjects [18.8%]). Most of the deviations were due to the use of prohibited medications (exclusive of rescue medications) (11/160 subjects [6.9%] overall) and non-compliance with exclusion criteria (10/160 subjects [6.3%] overall).

Reviewer's Comments:

The types of protocol violations due not raise concerns about the integrity of the outcome of the

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study.

Table of Demographic Characteristics

Subject Demographics

	CLS-TA (N=96)	Control (N=64)
Gender, n (%)		
Male	42 (43.8)	30 (46.9)
Female	54 (56.3)	34 (53.1)
Age (years)		
n	96	64
Mean (STD)	50.40 (14.180)	50.00 (15.083)
Median	52.00	49.50
Min, Max	18.0, 92.0	22.0, 85.0
Race, n (%)		
American Indian/Alaska Native	0	0
Asian	44 (45.8)	28 (43.8)
Black/African American	11 (11.5)	11 (17.2)
Native Hawaiian/Other Pacific Islander	0	0
White	40 (41.7)	25 (39.1)
Other	1 (1.0)	0
Ethnicity, n (%)		
Hispanic or Latino	10 (10.4)	6 (9.4)
Not Hispanic or Latino	86 (89.6)	58 (90.6)
Smoking History, n (%)		

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None	73 (76.0)	44 (68.8)
Former Smoker	13 (13.5)	15 (23.4)
Current Smoker	10 (10.4)	5 (7.8)
Not Captured	0	0

STD=standard deviation.

Note(s): Percentages were based on the number of subjects in the respective group.

CSR Table 10 page 68

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Ocular Baseline Characteristics, Uveitis Classification and Description, and Macular Edema, Study Eye (Intent - to-Treat Population)

	CLS-TA (N=96)	Control (N=64)
Ocular Baseline Characteristics^a		
BCVA Total Letter Score, Study Eye		
Mean (STD)	54.7 (13.92)	53.5 (12.91)
CST (µm), Study Eye		
Mean (STD)	480.9 (153.24)	525.4 (158.14)
Lens Status at Baseline, Study Eye, n (%):		
Abnormal	80 (83.3)	51 (79.7)
Uveitis Classification, Description and Etiology		
Time Since Uveitis Diagnosis (Weeks)		
Mean (STD)	177.4 (235.91)	107.1 (134.70)
Presence of, n (%):		
Anterior Uveitis (Anterior Chamber)	27 (28.1)	14 (21.9)
Intermediate Uveitis (Vitreous)	34 (35.4)	23 (35.9)
Posterior Uveitis (Retina or Choroid)	22 (22.9)	13 (20.3)
Panuveitis	28 (29.2)	24 (37.5)
Duration, n (%):		
Limited, ≤3 months	18 (18.8)	9 (14.1)

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Persistent, >3 months	78 (81.3)	55 (85.9)
Course of Uveitis ^b , n (%):		
Acute	5 (5.2)	6 (9.4)
Recurrent	31 (32.3)	17 (26.6)
Chronic	60 (62.5)	41 (64.1)
Etiology of Uveitis, n (%)		
Idiopathic	69 (71.9)	44 (68.8)
Pars Planitis	7 (7.3)	4 (6.3)
Sarcoidosis	4 (4.2)	5 (7.8)
Baseline Macular Edema		
Time Since Macular Edema Diagnosis (Weeks)		

	CLS-TA (N=96)	Control (N=64)
Mean (STD)	71.1 (212.80)	67.8 (113.91)
Presence of, n (%):		
Macular Edema	96 (100.0)	64 (100.0)
Foveal Reflex	15 (15.6)	9 (14.1)
Cysts	76 (79.2)	55 (85.9)
Intra-retinal Fluid	77 (80.2)	49 (76.6)
Sub-retinal Fluid	27 (28.1)	15 (23.4)
Fibrosis	3 (3.1)	3 (4.7)

BCVA=best corrected visual acuity, STD=standard deviation

^aPercentages were based on the number of subjects in the respective group.

^bUveitis course could be Acute=an episode of sudden onset and limited duration; Recurrent=repeated episodes separated by periods of inactivity without treatment ≥ 3 months duration; Chronic=persistent uveitis with relapse in <3 months after discontinuing treatment.

Ref: CST table 11 page 71

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Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No study drug was dispensed to subjects and all study treatments were administered by the investigator; therefore, subject treatment compliance was not applicable.

Summary of Rescue Medication Use

	CLS-TA (N=96)	Control (N=64)
Ever Received Rescue, n (%)	13 (13.5)	46 (71.9)
Received Rescue Prior to 2nd Injection, n (%)	5 (5.2)	32 (50.0)
Time to First Rescue (Days) ^b		
Mean (SE)	143.4 (2.44)	91.5 (7.57)

CSR, Table 17, page 117

Reviewer's Comments: *Subjects in the control groups received rescue medication at approximately five times the rate as those in the treatment group. In addition, the mean time to requiring rescue therapy was significantly longer in the treatment group versus control group, 143 days vs. 92 days. Both of these factors are supportive of the efficacy of the product for the proposed indication.*

Efficacy Results – Primary Endpoint

Primary endpoint: Proportion of Subjects Gaining ≥ 15 ETDRS letters in BCVA from Baseline at week 24 (Visit 8)

Best Corrected Visual Acuity at Week 24, Study Eye (LOCF Method) (Intent-to-Treat Population)

	CLS-TA (N=96)	Control (N=64)
Subjects Who Gained ≥ 15 Letters from Baseline at Week 24		
n	45	10
Proportion, n/N as %	46.9	15.6
Difference (CLS-TA – Control)	31.25	
Exact 95% CI for Difference	(15.5,45.9)	

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Relative Risk (95% CI)	2.94 (1.6, 5.3)	
Odds Ratio Adjusting for Country Group	4.97	
95% CI for Odds Ratio	(2.2, 11.2)	
CMH p-value ^a	<0.001	
Breslow-Day test with Tarone's adjustment p-value ^b	0.094	

BD=Breslow Day, CI=confidence interval, CMH=Cochran-Mantel-Haenzel, LOCF=last observation carried forward.

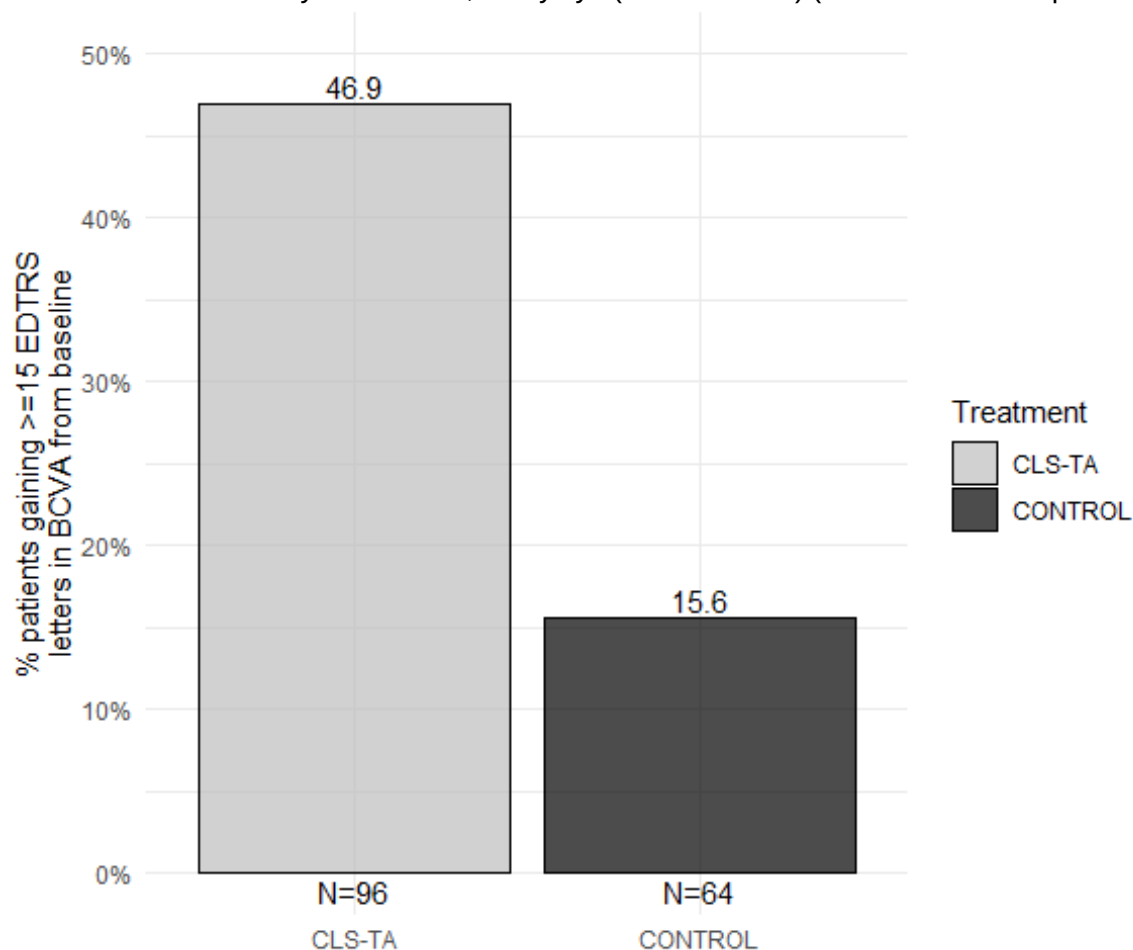
Note(s): Any subject who missed the scheduled assessment or received a rescue therapy had their data imputed by LOCF. When a subject was rescued, the data was imputed using LOCF from the last data prior to when additional treatment was provided. CMH stratification was based on country group with Israel subjects combined with USA subjects in order to include their data in the CMH analysis.

^aThe p-value was based on a CMH test for general association between treatment and response with stratification by country group.

^bThe p-value was based on the BD test with Tarone's adjustment to confirm homogeneity of the ORs between country groups and the suitability of using the CMH weighted OR to test for overall association.

Source: Post-text [Table 14.2.1.1](#).

Best Corrected Visual Acuity at Week 24, Study Eye (LOCF Method) (Intent-to-Treat Population)



p<0.001

CSR Figure 3, page78

Reviewer's Comment:

The study met its primary efficacy endpoint. Subjects in the CLS-TA group had both a statistically and clinically significant improvement compared to placebo in the improvement in visual acuity. In addition, the sensitivity analyses performed with the worst case and best-case imputation methods showed similar results.

The protocol for study CLS1001-301 did not prespecify examination of subgroups. A post-hoc analysis of the following subgroups was analyzed for the primary and secondary endpoints:

- Country (India; USA and Israel together) with several AE summaries.*
- Excluding all subjects with major protocol deviations.*

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- *Location of uveitis.*

The results of the analysis of each of the subgroups was consistent with the overall efficacy results.

Data Quality and Integrity

Refer to section 4.1 for details of the OSI audits conducted. After review of the deficiencies noted for site #106, it has been determined that including or excluding these patients in the data analysis would not have an effect on the efficacy demonstrated in the study under question.

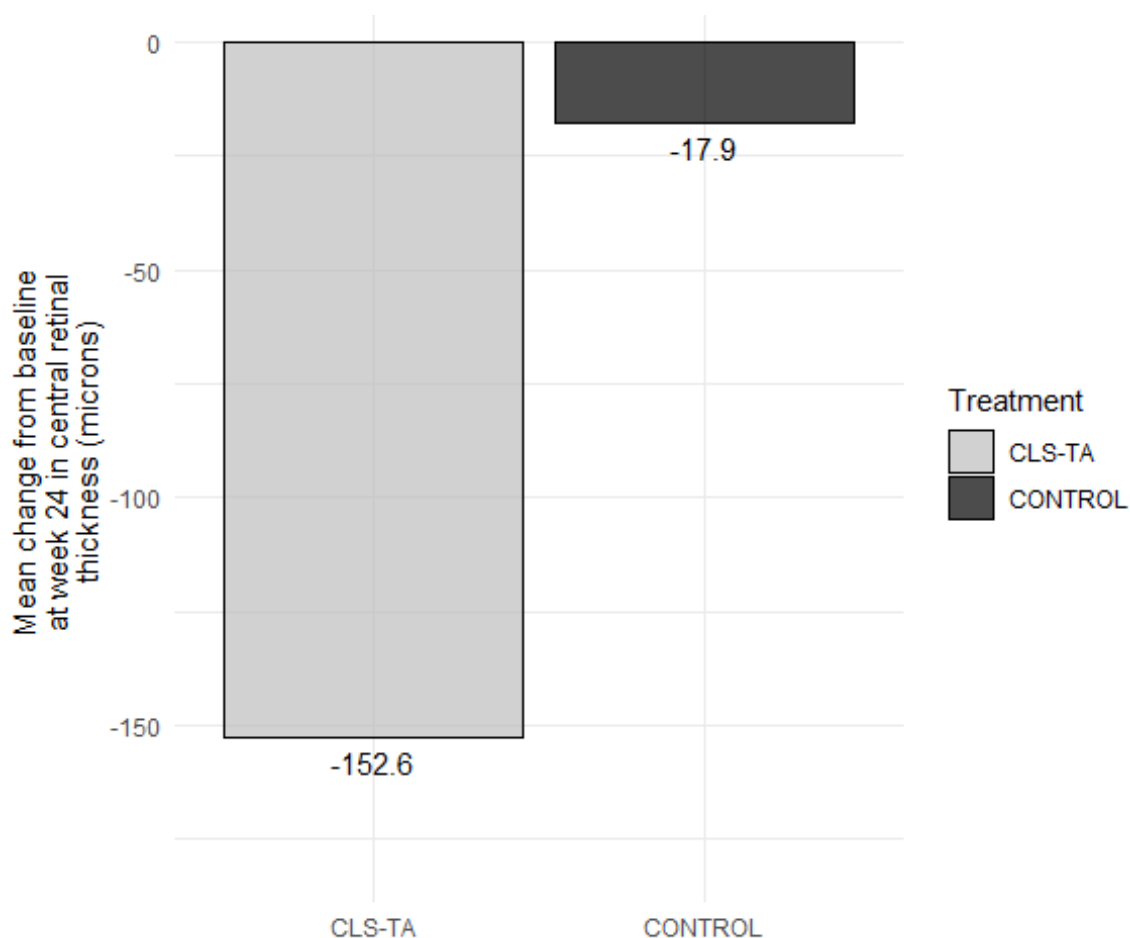
Efficacy Results – Secondary and other relevant endpoints

Secondary endpoint: Mean change from Baseline in CST as Measured by SD-OCT at 24 weeks (Visit 8).

	CLS-TA (N=96)	Control (N=64)
CST Change from Baseline at Week 24		
n	93 ^a	61 ^a
Mean (STD)	-152.6 (159.14)	-17.9 (150.98)
Difference in Means ^b	-157.71	
95% CI for Difference ^b	(-198.86, -116.57)	
p-value ^b	<0.001	

CI=confidence interval, CST=central subfield retinal thickness, LOCF=last observation carried forward, SD-OCT=spectral-domain optical coherence tomography, STD=standard deviation.
CSR Table 13 page81

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p<0.001
CST = central subfield retinal thickness., ITT=intent-to-treat.
CSR figure 5 page82

Reviewer's Comments:

The mean reduction in central retinal thickness for the treatment arm versus placebo was statistically significant. This is consistent with the primary efficacy endpoint which demonstrated a clinically significant improvement in visual acuity.

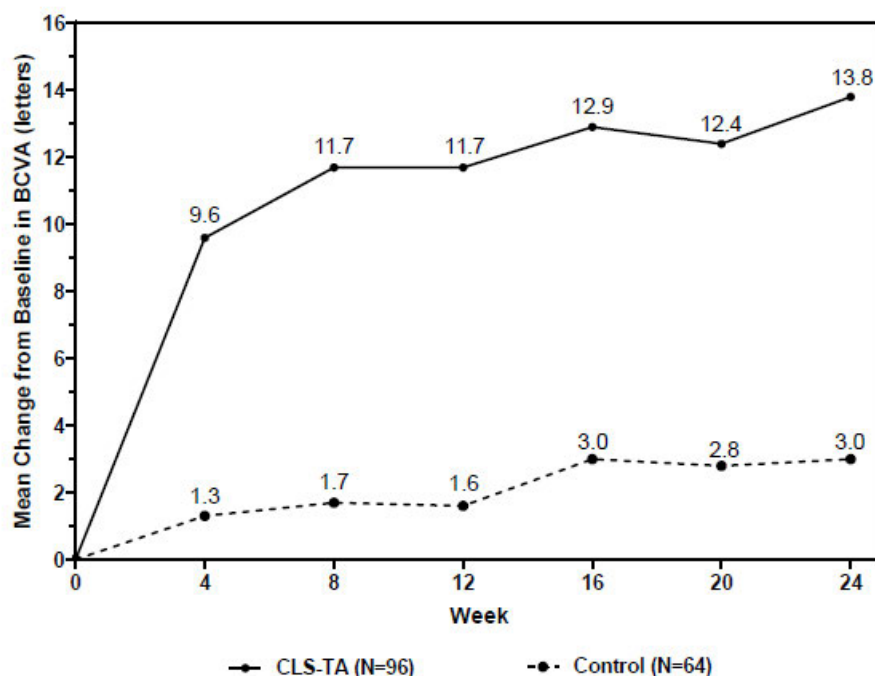
Dose/Dose Response

The dose chosen for this study was based on the marketed triamcinolone acetonide suspension which is approved for several indications. Dose ranging was not performed as part of this development program.

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Durability of Response

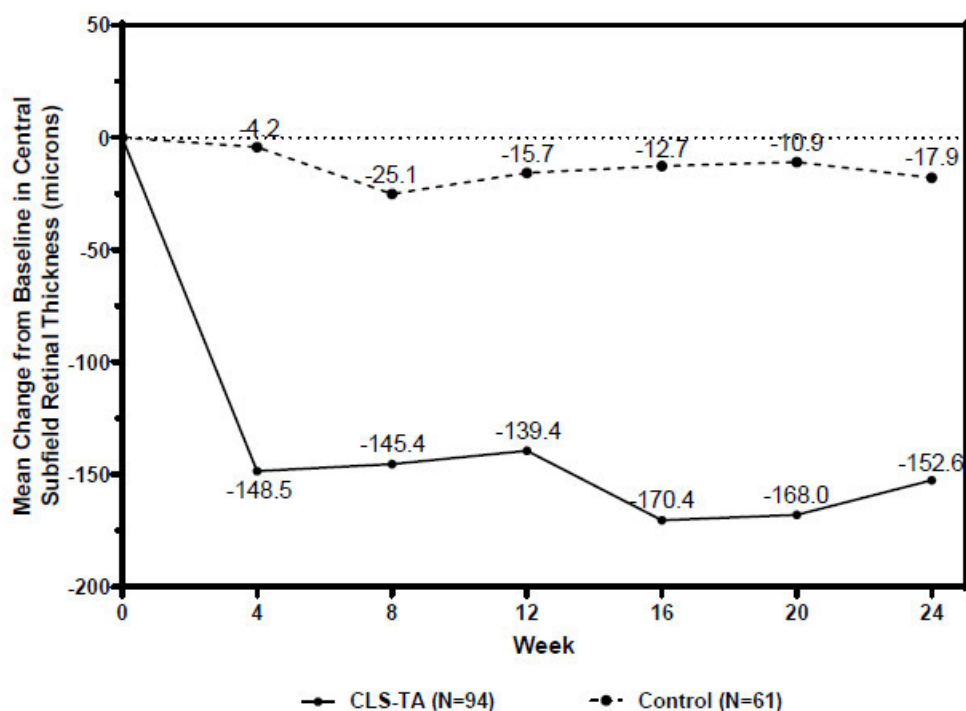
Post-hoc Endpoint: Mean Change from Baseline in BCVA in ETDRS Letters at Each Visit (LOCF Method) (Intent-to-Treat Population)



BCVA = best corrected visual acuity; CLS-TA = triamcinolone acetonide injectable suspension, 40 mg/mL;
ETDRS = Early Treatment of Diabetic Retinopathy Study; ITT = intent-to-treat; LOCF = last observation carried forward

Summary of Clinical Efficacy 2.7.3 Fig 3 page 21

Mean Change in CST by Visit Week, Study Eye (LOCF Method), ITT Population



CLS-TA = triamcinolone acetonide injectable suspension, 40 mg/mL; CST = central subfield thickness;
ITT = intent-to-treat; LOCF = last observation carried forward

Summary of Clinical Efficacy 2.7.3 Fig 4 page 22

Reviewer's Comments:

The mean change in visual acuity and the mean change from baseline in central retinal thickness both show significant improvement within 4 weeks after administration of CLS-TA and is sustained throughout the 24 week study.

Persistence of Effect

Persistence of clinical effect was not evaluated in this development program.

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Additional Analyses Conducted on the Individual Trial

N/A

6.2. Drug Efficacy Study Implementation (DESI)

The efficacy of triamcinolone acetonide via multiple routes of administration was established as part of the Drug Efficacy Study Implementation (DESI) review and has been used as an anti-inflammatory agent for the treatment of various diseases in the US for over 50 years. Triamcinolone 40 mg was found to be efficacious for the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. The literature references used to originally establish efficacy for triamcinolone is listed in section 13.1.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to this review. The review of this product is supported by a single clinical trial and literature reports that resulted in the DESI determination for triamcinolone acetonide suspension 40mg/ml.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no anticipated differences expected in the way CLS-TA was studied and how it will be used in the postmarket setting that would affect labeling or the recommended regulatory action.

7.2.2. Other Relevant Benefits

N/A

7.3. Integrated Assessment of Effectiveness

The efficacy of triamcinolone acetonide via multiple routes of administration was established as part of the Drug Efficacy Study Implementation (DESI) review and has been used as an anti-inflammatory agent for the treatment of various diseases in the US for over 50 years. Triamcinolone 40 mg was found to be efficacious for the following ophthalmic diseases:

sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. The study contained in this NDA demonstrates the efficacy of triamcinolone for macular edema associated with uveitis. CLA-TS is superior to placebo in the clinical improvement in visual acuity in patients with uveitis associated macula edema. The effectiveness of this treatment started within 4 weeks after administration and continued for the duration of the trial. Based on the results of this clinical trial, the DESI findings and the long history of use of this product in ophthalmic inflammatory diseases; the efficacy in uveitis associated macula edema has been established.

8. Review of Safety

8.1. Safety Review Approach

The Applicant submitted safety data from seven (7) clinical studies to support the safety of CLS-TA. While approximately 300 subjects were contained in the safety database, most of the trials submitted were not able to be pooled with the PEACHTREE study and will be used as supportive evidence due to either:

- Patients receiving intravitreal injections (different route)*
- Patients receiving fewer doses than proposed for treatment*
- Intravitreal injections given in combination with VEGF inhibitors*
- CLS-TA injections given at a fraction of the dose proposed for marketing.*

This review will concentrate on the 96 subjects from the Peachtree trial that received multiple suprachoroidal injections of the test drug at the to be marketed concentration. Throughout the review, safety results from the Magnolia trial may be pooled where appropriate as this was an observational extension study of subjects who completed the Peachtree trial. Although patients in the Azalea study received two doses of 4mg of CLS-TA, the patients will not be pooled with Peachtree since this was an open label trial and patients were included that did not have macular edema.

The safety of triamcinolone via routes other than suprachoroidal has been well established based on the long history of the use of this product and the extensive safety database. This review will concentrate on evaluating any potential increased or unknown risk associated with this product administered by this new route in uveitis patients with macula edema.

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Clinical Trials Conducted during Development

Study No. Country Last Subject Completed or Date of Data Cut	Study Design and Population	Test Product and Comparator Doses of 4 mg CLS-TA	Duration of Dosing Duration of Follow-up	Safety Assessments Safety Population	Key Demographic Characteristics
Masked and Controlled Studies in Subjects with ME due to Uveitis (Group 1 and Group 2A studies)					
CLS1001-301 (PEACHTREE) US/Israel/India 18 JAN 2018	Phase 3, randomized, masked, sham-controlled, multicenter study evaluating safety and efficacy of 4 mg CLS-TA administered via SC injection in subjects with ME associated with NIU	4 mg CLS-TA or control Doses: 2	2 treatments (Day 0 and Week 12) Follow-up 24 weeks following Baseline	Monitoring of AEs, IOP, slit-lamp biomicroscopy, dilated ophthalmoscopy, fluorescein angiogram, fundus photographs, vitals, clinical laboratory tests, brief physical exam Safety population – 160 subjects: 96 CLS-TA 64 control	Male: 45.0%; Female: 55.0% Median age: 51 years (Range 18 to 92 years) Race: Asian (45.0%), White (40.6%), Black/African American (13.8%)
CLS1001-201 (DOGWOOD) US 02 DEC 2015	Phase 2, randomized, masked, controlled, multicenter study evaluating safety & efficacy of SC CLS-TA in subjects with ME following uveitis	4 mg or 0.8 mg CLS-TA Doses: 1	1 treatment (Day 1) Follow-up 8 weeks after treatment	Monitoring of AEs, IOP, slit-lamp biomicroscopy, indirect ophthalmoscopy, fluorescein angiogram, fundus photographs, vitreous haze, vitals ^a , clinical laboratory tests ^a , brief physical exam ^a Safety population – 22 subjects: 17 CLS-TA 4 mg 5 CLS-TA 0.8 mg	Male: 45.5%; Female: 54.5% Median age: 53.0 years (Range 20 to 83 years) Race: White (81.8%), Black/African American (18.2%)

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Study No. Country Last Subject Completed or Date of Data Cut	Study Design and Population	Test Product and Comparator Doses of 4 mg CLS-TA	Duration of Dosing Duration of Follow-up	Safety Assessments Safety Population	Key Demographic Characteristics
Studies Contributing to Longer-term Safety in Subjects with ME Due to Uveitis (Contributing to Group 2B and Group 3)					
CLS1001-302 (AZALEA) US 24 JAN 2018	Phase 3, open-label, multicenter study to evaluate the safety of SC CLS-TA administered in subjects with NIU	4 mg CLS-TA Doses: 2	2 treatments (Day 0 and Week 12) Follow-up 12 weeks after treatment 2	Monitoring of AEs, IOP, slit-lamp biomicroscopy, indirect ophthalmoscopy, cataract lens grading, AC cells, AC flare, fluorescein angiogram, fundus photographs, vitreous haze, vitals, clinical laboratory tests, brief physical exam Safety population – 38 subjects	Male: 34.2%; Female: 65.8% Mean age: 52.4 years (Range 22 to 77 years) Race: White (81.6%); Black/African American (18.4%)
CLS1001-303 (MAGNOLIA) US/India 17 APR 2018 (date of data cut for NDA) 22 MAY 2018	Phase 3, noninterventional, prospective, observational multicenter extension study of subjects with ME associated with NIU for subjects completing CLS1001-301 without receiving rescue medication	N/A; this study is prospective and observational with subjects extended from the PEACHTREE study	N/A Follow-up for up to 24 weeks after exit of PEACHTREE	Monitoring of AEs, IOP, slit-lamp biomicroscopy, cataract lens grading, AC cells, AC flare, dilated ophthalmoscopy, vitreous haze Safety population – 33 subjects 28 CLS-TA 5 control	Males: 54.5%; Females: 45.5% Median age: 50.0 years (Range 19 to 78 years) Race: Asian (66.7%), White (27.3%), Black/African American (6.1%)

Study No. Country Last Subject Completed or Date of Data Cut	Study Design and Population	Test Product and Comparator Doses of 4 mg CLS-TA	Duration of Dosing Duration of Follow-up	Safety Assessments Safety Population	Key Demographic Characteristics
Studies with CLS-TA in Additional Indications (Contributing to Group 4)					
Studies in RVO					
CLS1003-201 (TANZANITE) US 01 MAR 2016	Phase 2 randomized, masked, active-controlled, multicenter study evaluating the safety and efficacy of SC CLS-TA with IVT aflibercept in treatment naïve RVO subjects	4 mg CLS-TA + 2 mg IVT aflibercept or 2 mg IVT aflibercept + control Doses: 1	1 treatment (Day 0) Follow-up 3 months after treatment	Monitoring of AEs, IOP, slit-lamp biomicroscopy, dilated indirect ophthalmoscopy, fluorescein angiogram, fundus photographs, vitals, clinical laboratory tests, brief physical exam Safety population – 46 subjects 23 CLS-TA 4 mg + IVT aflibercept 23 IVT aflibercept + control procedure	Male: 50.0%; Female: 50.0% Median age: 68.00 years (Range 37 to 91 years) Race: White (82.6%), Black/African American (15.2%), American Indian or Alaska Native (2.2%)

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Study No. Country Last Subject Completed or Date of Data Cut	Study Design and Population	Test Product and Comparator Doses of 4 mg CLS-TA	Duration of Dosing Duration of Follow-up	Safety Assessments Safety Population	Key Demographic Characteristics
CLS1003-301 (SAPPHIRE) Global Ongoing at the time of cut for this NDA Clean data included through 01 OCT 2017 (data set dated 25 MAY 2018)	Phase 3 randomized, masked, active-controlled, multicenter study evaluating safety and efficacy of SC CLS- TA with IVT aflibercept in treatment naïve RVO subjects	4 mg CLS-TA + 2 mg IVT aflibercept or 2 mg IVT aflibercept only Doses: 3	3 treatments (Day 0, Week 12, Week 24) Follow-up: 24 weeks after treatment 3	Monitoring of AEs, IOP, slit-lamp biomicroscopy, indirect ophthalmoscopy, fluorescein angiogram, fundus photographs, vitals, clinical laboratory tests, brief physical exam Safety population – approximately 460 planned (1:1 randomization) 173 randomized, masked subjects receiving either CLS-TA 4 mg + IVT aflibercept or IVT aflibercept + control procedure	Males: 53.8%; Females: 46.2% Median age: 68.0 years Range (38 to 92 years) Race: White (87.9%), Asian (5.2%), Black/African American (5.2%), American Indian or Alaska Native, Other, and Unknown/Not Reported (0.6% each)

Study No. Country Last Subject Completed or Date of Data Cut	Study Design and Population	Test Product and Comparator Doses of 4 mg CLS-TA	Duration of Dosing Duration of Follow-up	Safety Assessments Safety Population	Key Demographic Characteristics
Studies in DME					
CLS1004-201 (TYBEE) US 17APR2018	Phase 2 randomized, masked, active-controlled, multicenter study evaluating the safety and efficacy of SC CLS-TA in treatment-naïve DME subjects	4 mg CLS-TA + 2 mg IVT aflibercept or 2 mg IVT aflibercept Doses: 2	2 treatments (Day 0, Week 12) Follow up 12 weeks after treatment 2	Monitoring of AEs, IOP, biomicroscopy, indirect ophthalmoscopy, cataract lens grading, fluorescein angiogram, fundus photographs, vitals, clinical laboratory tests, brief physical exam Safety population – 71 subjects 36 CLS-TA 4 mg + IVT aflibercept 35 IVT aflibercept only	Male: 70.4%; Female: 29.6% Median age: 60.0 yr (Range 19 to 83 years) Race: White (88.7%), Black/African American (7.0%), American Indian or Alaska Native, Other, and Not applicable (1.4% each)

AE = adverse event; DME = diabetic macular edema; IOP = intraocular pressure; IVT = intravitreal; CLS-TA = triamcinolone acetonide injectable suspension, 40 mg/mL; ME = macular edema; NIU = noninfectious uveitis; RVO = retinal vein occlusion; AMD = age-related macular degeneration; SC = suprachoroidal; TA = triamcinolone acetonide; US = United States

* Performed once at Screening.

Source: Clinical Study Reports; protocols

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Summary of Study Drug Administration and Rescue (Safety Population)

	CLS-TA (N=96)	Control (N=64)
Received Injection/Sham at Baseline, n (%)	96 (100.0)	64 (100.0)
Received Injection/Sham at Week 12, n (%)	84 (87.5)	29 (45.3)
Ever Received Rescue, n (%)	13 (13.5)	46 (71.9)
Received Rescue Prior to 2nd Injection, n (%)	5 (5.2)	32 (50.0)
Duration of Treatment (Days)^c		
Mean (STD)	159.9 (28.87)	123.6 (42.88)

Source: CSR Table 18 Page117

8.2.2. Relevant characteristics of the safety population:

The safety population evaluated during development sufficiently represents the expected target population for the product. The demographics and baseline characteristics of the population used to evaluate safety and efficacy were the same (see Section 6.1.2 Study Demographics).

8.2.3. Adequacy of the safety database:

The overall exposure to CLS-TA 4 mg during the development program was approximately 296 subjects. These include studies spanning various indications, and dose/dosing regimens. This database is adequate to evaluate safety due to the long history of use of triamcinolone.

There are several known ocular complications associated with the use of corticosteroids. These include but are not limited to increased intraocular pressure, posterior subcapsular cataract formation, secondary ocular infections, and corneal and scleral thinning. The clinical evaluations conducted during development adequately assessed these known adverse events.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This NDA submission was of sufficient quality to perform a substantive review of this product.

8.3.2. Categorization of Adverse Events

The AEs were coded using the MedDRA coding dictionary. The treatment emergent adverse events (TEAE), were defined as any event occurring post treatment (injection) or, if pre-existing, worsening after Day 1. Only TEAEs (commencing after exposure to study treatment) were included in the AE and SAE summaries. The incidence of TEAEs were summarized by MedDRA system organ class (SOC) and preferred term (PT). The AEs related to IOP and cataract formation were summarized by treatment group.

8.3.3. Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns of intraocular administered products (i.e. biomicroscopy, fundoscopy, visual acuity, etc) were adequately addressed in the design and conduct of the trials for this product.

8.4. Safety Results

8.4.1. Deaths

No deaths were observed in subjects during the uveitis clinical program. Two (2) deaths were reported in the TYBEE study (Phase 2 DME) due to cardiac arrest in Subject (b) (6) and hepatorenal syndrome in Subject (b) (6). Neither death is considered related to the study drug after review of the patient narratives.

8.4.2. Serious Adverse Events

There were three SAEs (1 ocular, 2 non-ocular) experienced in subjects receiving CLS TA. The ocular SAE was a retinal detachment experienced by Subject (b) (6) and was considered unrelated to the study treatment

The two non-ocular SAEs (sialoadenitis and lumbar vertebral fracture) were not considered related to the study treatment

Subject Number	Study Arm	System Organ Class/Preferred Term/AE Verbatim Term	Outcome	Discontinued
(b) (6)	CLS-TA	Retinal Detachment	Recovered / Resolved	No
(b) (6)	CLS-TA	Sialoadenitis	Recovered / Resolved	No

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(b) (6)	CLS-TA	Lumbar vertebral fracture	Recovered / Resolved	No
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Reviewers Comment: Subject (b) (6) had a pre-existing vitreous detachment and underwent surgical correction for an inferior traction retinal detachment that was noted approximately 8 weeks following the second suprachoroidal administration of CLS-TA.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment

Subject Number	Treatment Arm	Preferred Term	Duration in Days	Outcome
(b) (6)	CLS-TA	Visual acuity reduced	15	Recovered / Resolved
	CLS-TA	Intraocular pressure increased	83	Recovered / Resolved
	CLS-TA	Vitreous hemorrhage	ongoing	Recovering / Resolving
	CLS-TA	Ocular hypertension	29	Recovered / Resolved
	CLS-TA	Uveitis	ongoing	Recovering / Resolving
	Control	Intraocular pressure increased	1	Recovered / Resolved
		Uveitis	162	Recovered / Resolved
	Control	Uveitis	92	Recovered / Resolved
	Control	Uveitis	33	Recovered / Resolved
	Control	Uveitis	64	Recovered / Resolved

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(b) (6)	Control	Iridocyclitis	21	Recovered / Resolved
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Treatment-emergent Adverse Events Leading to Study Withdrawal – Extension Study

Subject Number	Treatment Arm	Preferred Term	Duration in Days	Outcome
Study Eye				
MAGNOLIA (extension study)				
(b) (6)	CLS-TA	Post procedural inflammation	ongoing	Recovering / Resolving
	CLS-TA	Cataract	ongoing	Recovering / Resolving
	CLS-TA	Cystoid macular edema	ongoing	Recovering / Resolving

Reviewers Comments: *The number of subjects that discontinued study treatment during the clinical trial period was the same in the CLS-TA group and placebo group. The types of adverse events that lead to study treatment withdrawal during both the placebo-controlled trial and extension study were the types of events expected as they are either related to the underlying disease process or known risks associated with intraocular steroid use.*

8.4.4. Significant Adverse Events

See section 8.4.3 for significant events that lead to either study drug discontinuation or subject withdrawal from the study.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

	CLS-TA (N=96)	Control (N=64)
	n (%)	n (%)
Number of TEAEs	49 (51.0)	37 (57.8)
Eye disorders	41 (42.7)	34 (53.1)

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Anterior capsule contraction	2 (2.1)	0
Blepharitis	1 (1.0)	0
Cataract	0	1 (1.6)
Cataract cortical	1 (1.0)	0
Cataract subcapsular	7 (7.3)	3 (4.7)
Chalazion	2 (2.1)	0
Conjunctival disorder	1 (1.0)	0
Conjunctival hemorrhage	4 (4.2)	2 (3.1)
Conjunctival hyperemia	2 (2.1)	2 (3.1)
Conjunctival edema	2 (2.1)	0
Corneal epithelium defect	0	1 (1.6)
Cystoid macular edema	0	9 (14.1)
Detachment of retinal pigment	0	1 (1.6)
Dry eye	3 (3.1)	1 (1.6)
Eye irritation	2 (2.1)	0
Eye pain	14 (14.6)	0
Eye pruritus	2 (2.1)	0
Eyelid edema	1 (1.0)	0
Eyelid ptosis	2 (2.1)	0
Iridocyclitis	1 (1.0)	1 (1.6)
Macular degeneration	0	1 (1.6)
Macular fibrosis	0	1 (1.6)
Macular edema	0	2 (3.1)
Macular pseudohole	1 (1.0)	0
Meibomianitis	2 (2.1)	0

	CLS-TA (N=96)	Control (N=64)
	n (%)	n (%)
Night blindness	1 (1.0)	0
Ocular hyperemia	1 (1.0)	0
Ocular hypertension	2 (2.1)	5 (7.8)

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Open angle glaucoma	0	1 (1.6)
Papilledema	0	1 (1.6)
Photophobia	3 (3.1)	0
Photopsia	2 (2.1)	0
Posterior capsule opacification	1 (1.0)	0
Punctate keratitis	2 (2.1)	1 (1.6)
Retinal detachment	1 (1.0)	0
Retinal tear	1 (1.0)	0
Scleral hyperemia	1 (1.0)	0
Scleritis	0	1 (1.6)
Trichiasis	1 (1.0)	0
Uveitis	2 (2.1)	7 (10.9)
Vision blurred	2 (2.1)	0
Visual acuity reduced	4 (4.2)	1 (1.6)
Vitreous detachment	5 (5.2)	1 (1.6)
Vitreous floaters	3 (3.1)	0
Vitreous hemorrhage	1 (1.0)	0
Vitritis	1 (1.0)	0
General disorders and administration site conditions	6 (6.3)	3 (4.7)
Injection site discomfort	1 (1.0)	1 (1.6)
Injection site erythema	1 (1.0)	0
Injection site pain	4 (4.2)	2 (3.1)
	CLS-TA (N=96)	Control (N=64)
	n (%)	n (%)
Infections and infestations	0	1 (1.6)
Conjunctivitis	0	1 (1.6)
Injury, poisoning and procedural complications	1 (1.0)	0

Periorbital hemorrhage	1 (1.0)	0
Investigations	17 (17.7)	4 (6.3)
Intraocular pressure increased	17 (17.7)	4 (6.3)
Nervous system disorders	1 (1.0)	0
Visual field defect	1 (1.0)	0

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Treatment-Emergent Adverse Events Occurring in at Least 3% of the Subjects in Either Arm, Study Eye: Group 1 (Safety Population)

Preferred Term	CLS-TA (N=96) N (%)	Control (N=64) N (%)
Intraocular pressure increased	17 (17.7)	4 (6.3)
Eye pain	14 (14.6)	0
Cataract subcapsular	7 (7.3)	3 (4.7)
Cystoid macular edema	0	9 (14.1)
Uveitis	2 (2.1)	7 (10.9)
Ocular hypertension	2 (2.1)	5 (7.8)
Conjunctival hemorrhage	4 (4.2)	2 (3.1)
Injection site pain	4 (4.2)	2 (3.1)
Vitreous detachment	5 (5.2)	1 (1.6)
Visual acuity reduced	4 (4.2)	1 (1.6)

Module 2.7.4 Table 28

Reviewers Comment:

The types of adverse events identified during the study period are consistent with those historically seen with intraocular steroids. There are no new types of events or increase in the rate of events identified related to the injection into the suprachoroidal space.

8.4.6. Laboratory Findings

No relevant changes from Baseline in laboratory evaluations (hematology, biochemistry, and urinalysis parameters) or vital signs were observed for subjects in either treatment arm.

8.4.7. Vital Signs

No relevant changes from Baseline were observed for subjects in the CLS-TA or Control arms for systolic BP, diastolic BP, or heart rate.

8.4.8. Electrocardiograms (ECGs)

N/A - ECGs were not assessed as part of this development program.

8.4.9. QT

N/A – QT studies were not assessed as part of this development program.

8.4.10. Immunogenicity

Immunogenicity was not performed as part of this development program.

8.5. Analysis of Submission-Specific Safety Issues

There were no submission specific safety issues that arose during the development program that warranted a more thorough evaluation. The safety profile of triamcinolone is well characterized. Common adverse events associated with ocular steroids are increase intraocular pressure and development/worsening of cataracts which are analyzed in this subsection.

Summary of Elevated IOP - (Safety Population)

	CLS-TA (N = 96) n (%)	Control (N = 64) n (%)
IOP elevation $\geq$ 10 mmHg change from baseline at any post-baseline visit	15 (15.6)	11 (17.2)
IOP elevation $\geq$ 30 mmHg absolute reading at any post-baseline visit	6 (6.3)	5 (7.8)
Any IOP-lowering medication	7 (7.3)	6 (9.4)
Any surgical intervention for elevated IOP	1 (1.0)*	0

Summary of Clinical Safety table 52 page 120

IOP = intraocular pressure; mmHg = millimeters of mercury;

*Peripheral laser iridotomy performed for progression of pre-existing posterior synechiae leading to iris bombe and elevated IOP.

Reviewer's Comments:

The risk of IOP elevation with CLS-TA was similar to the control group in this study. There does not appear to be an increased risk in IOP elevation for this route of administration.

Cataract Grading ≥ 1 Increase at End of Study

Treatment Group	Cataract Location		
	Nuclear	Cortical	Posterior Subcapsular
CLS-TA (N=96)	3 (3.1%)	1 (1%)	5 (5.2%)
Control (N=64)	2 (3.1%)	0	3 (4.7%)

Source: table derived from CSR Table 14.3.6.2.3

The majority of subjects in both treatment arms had no change in their cataract grading at the end of the study. There does not appear to be an increase in risk of cataract development with this route of administration in this study of limited duration.

Two subjects (in the Control arm) underwent surgery to treat cataract in the Study eye, one at Week 16 and one at Week 24. No subjects in the CLS-TA arm underwent surgery to treat their cataract TEAEs.

8.6. Safety Analyses by Demographic Subgroups

The rate of adverse events was similar between age, gender, race groups. There were no clinically meaningful safety issues raised in the subgroup analysis.

8.7. Specific Safety Studies/Clinical Trials

N/A – there were no study specific safety concerns with this product.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Tumor development was not reported during this development program and is not a known safety risk related to corticosteroids.

8.8.2. Human Reproduction and Pregnancy

Pregnant and lactating women are excluded from all clinical studies of CLS-TA, and enrolled patients are instructed to use appropriate birth control methods. One patient had a positive serum pregnancy test after being exposed to SC administered TA in pregnancy. The pregnancy was terminated during the first trimester. Module 2.7.4 section 6.4

Labeled reproduction and pregnancy information for this class of drugs include information that corticosteroids may cause fetal harm when administered to a pregnant woman, particularly during the first trimester of pregnancy, and corticosteroids are secreted in human milk. The pharmacokinetic drug interaction profile of triamcinolone following absorption into the systemic circulation is expected to be similarly low whether administered by SC or IVT injection because systemic exposure via either route is minimal.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric patients were not included in this development program. Labeled pediatric information for this class of drugs include information that long-term use of corticosteroids can have negative effects on growth and development in children. Growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully monitored.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. The adverse effects of corticosteroids in pediatric patients are similar to those in adults.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

CLS-TA is administered by a physician into the suprachoroidal space. The potential for abuse of or dependence on TA administered via SC injection is limited.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Triamcinolone acetonide is a glucocorticosteroid that has been used as an anti-inflammatory agent for the treatment of various diseases in the US for over 50 years. Triamcinolone acetonide is available in a range of different pharmaceutical forms including suspensions for injection. None of the TA-containing products have been withdrawn from the market or put on clinical hold for safety reasons. *There are several complications associated with the use of topical and intraocular corticosteroids. These include but are not limited to increased intraocular pressure, posterior subcapsular cataract formation, secondary ocular infections, and corneal and scleral thinning. These are known labeled risk that are expected events in the postmarket setting. There*

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were no new risks identified with the formulation under study.

8.9.2. Expectations on Safety in the Postmarket Setting

See section 8.9.1

8.9.3. Additional Safety Issues From Other Disciplines

N/A – the safety profile of ocular corticosteroids is well established.

8.10. Integrated Assessment of Safety

The types of adverse events identified during the development program are consistent with those historically seen with intraocular steroids. The most frequently reported adverse events were increased intraocular pressure, eye pain and subcapsular cataract. There are no new types of events or increase in the rate of events identified related to the injection into the suprachoroidal space.

9. Advisory Committee Meeting and Other External Consultations

N/A -

10. Labeling Recommendations

10.1. Prescription Drug Labeling

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

10.2. Nonprescription Drug Labeling

11. Risk Evaluation and Mitigation Strategies (REMS)

N/A – There are no recommendations for this product.

12. Postmarketing Requirements and Commitments

N/A – There are no recommendations for this product.

13. Appendices

13.1. References

Articles cited in the DESI review for triamcinolone 40 mg/ml

1. Chavan, S.B., and E.J. Cummings. An initial evaluation of (aristocort) triamcinolone and its acetonide derivative in the therapy of ocular inflammation; Part II. Clinical studies. Amer. J. Ophthal. 49:516-530, (March) 1960.
2. Gordon, D.M. The treatment of chronic uveitis; preliminary comments on chronic degenerative diseases. Arch. Ophthal. (Chicago) 62:400-413, 1959.
3. Zavell, S., J.E. Blaydes, E.F. Anhalt, Jr., and G.B. Kara. Evaluation of kenacort (Triamcinolone) in the treatment of uveitis. Amer. J. Ophthal. 48:777-782 (December) 1959.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Peachtree CLS1001-301
Azalea CLS1001-302

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Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>5</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>3</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study: <u>2</u> Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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10/07/2019 03:18:44 PM

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