CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211950Orig1s000

<u>SUMMARY REVIEW</u>

Division Director Review and Cross-Discipline Team Leader Review of NDA 211950 Amendment Review

Review Date	See DARRTS Stamp Date
From	Wiley A. Chambers, M.D. and William M. Boyd, M.D.
Subject	Division Director and Cross-Discipline Team Leader Review
NDA #	211950
Applicant	Clearside Biomedical, Inc.
Date of Amendment	October 22, 2021
Proprietary Name	XIPERE
Established or Proper Name	triamcinolone acetonide ophthalmic suspension
Dosage Form(s)	(b) (4) injection
Proposed Dosing Regimen(s)	single dose suprachoroidal injectable suspension
Regulatory Action	Approval
Proposed Indication	Treatment of macular edema associated with uveitis in adult patients

Labeling:

During review of the submitted labeling from October 15, 2021, it was noted that Sections 8 and 13 of the package insert did not match the public literature derived information, as noted in Pharmacology Toxicology review dated September 6, 2019.

The applicant agreed to revise these sections and submitted the revisions on October 22, 2021. In addition to revising Sections 8 and 13, the applicant proposed an additional revision to Section 16, removing the table format, but retaining the text. This additional revision is acceptable.

Following are the revsions to Sections 8 and 13 (in track changes) and Section 16 (clean).

(b) (4)

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

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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/

WILEY A CHAMBERS
10/22/2021 11:53:17 AM

WILLIAM M BOYD
10/22/2021 11:58:23 AM

Division Director Review and Cross-Discipline Team Leader Review of NDA 211950 – Resubmission

Review Date	See DARRTS Stamp Date
From	Wiley A. Chambers, M.D. and William M. Boyd, M.D.
Subject	Division Director and Cross-Discipline Team Leader Review
NDA #	211950
Applicant	Clearside Biomedical, Inc.
Date of Submission	April 30, 2021
PDUFA Goal Date	October 30, 2021
Proprietary Name	XIPERE
Established or Proper Name	triamcinolone acetonide ophthalmic suspension
Dosage Form(s)	(b) (4) injection
Proposed Dosing Regimen(s)	single dose suprachoroidal injectable suspension
Regulatory Action	Approval
Proposed Indication	Treatment of macular edema associated with uveitis in adult patients

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Michael Puglisi
Medical Officer Review	Jennifer Harris
Statistical Review	Abel Eshete
Pharmacology Toxicology Review	Erin Ruhland
OPQ Review	Chunchun Zhang, Ben Zhang, Yong Wang, Poonam Delvadia, Rose Xu
Microbiology Review	Eric Adeeku
Clinical Pharmacology Review	Kunyi Wu
OPDP	Carrie Newcomer
OSI	Roy Blay
CDTL Review	William M. Boyd
OSE/DMEPA	Nasim Roosta

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Summary

This is a 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. See the Complete Response letter dated October 18, 2019, and the CDTL/Deputy Division Director memo also dated October 18, 2019.

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/or 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.

XIPERE, aka CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL is a (b) (4) sterilized, aqueous suspension of the corticosteroid triamcinolone acetonide (TA) without an antimicrobial preservative for suprachoroidal (SC) injection. CLS-TA 40 mg/mL has been submitted 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.

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the “device” definition. FDA will be regulating these products, including this product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including this product.

This is a 505(b)(2) application which identifies the listed drug product as Kenalog (NDA 14901). The applicant conducted its own clinical trial to establish the safety and effectiveness of its proposed triamcinolone acetonide injectable suspension 40 mg/mL product for the treatment of macular edema associated with non-infectious uveitis via suprachoroidal administration. The applicant also conducted its own nonclinical studies to support ocular pharmacology, pharmacokinetics, and ocular toxicity.

The application will be approved now that all outstanding chemistry manufacturing, clinical, and 505(b)(2) regulatory issues have been resolved.

2. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

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 and efficacy 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	• Uveitis (inflammation) can lead to permanent vision loss	Inflammation can be treated with the use of anti-inflammatory agents.
Current Treatment Options	• Intravitreal steroids	CLS-TA provides an effective alternate route of administration negating the need for entering the vitreous.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Improvement in visual acuity • Reduction in central retinal thickness	Study CLSJOOJ-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. DESI review established the efficacy of triamcinolone for multiple ocular inflammatory diseases. There is at least a 50 year history of usage for this product administered via a wide variety of different routes.
Risk and Risk Management	• 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.	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.

3. Background

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 US in 2007 and European Union (EU) in 2011.

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.

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.

Current Treatment Options for a Closely Related Indication

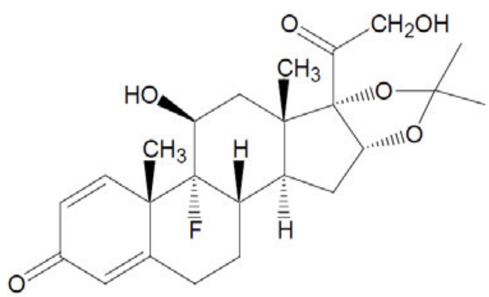
Drug	Endpoint	Treatment Effect	Intended Population
Adalimumab (Humira)	Time to treatment failure	5.6 months vs. 3 months (trial 1) > 18 months vs. 8.3 months (trial 2) > 18 months vs. 24.1 weeks (peds trial)	The treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric 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) (4) [redacted] and older, with chronic [redacted] (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 [redacted] (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

4. Product Quality

Triamcinolone acetonide (b) (4) is a white or almost white crystalline powder.

STRUCTURAL FORMULA



MOLECULAR FORMULA
$C_{24}H_{31}FO_6$

CHEMICAL NAME
• 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone
or
• 9-Fluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione
or
• Pregna-1,4-diene-3,20-dione,9-fluoro-11,21-dihydroxy-16,17-[(1 methylethyllidene)bis(oxy)]-, (11β,16α)

DRUG SUBSTANCE

Table 1: Release Specifications for Triamcinolone Acetonide (b) (4)

Test	**Acceptance Criteria**	**Analytical Method**
Appearance	White or almost white crystalline powder	Visual Inspection

Test	**Acceptance Criteria**	**Analytical Method**
Identification		
Infrared absorption	The IR spectrum of the preparation of the sample exhibits maxima only at the same wavenumbers as that of the appropriately prepared corresponding USP Reference Standard	USP <197K>
UV Absorption	The UV spectrum of the preparation of the sample exhibits absorption maxima and minima only at the same wavelengths as those appropriately prepared corresponding USP Reference Standard, and that the absorptivities and/or absorbance rations are within the specified limits	USP <197U>
Specific Rotation	Between +118° to +130°	USP <781S>
Loss on Drying	It loses NMT 1.5% of its weight	USP <731>
Chromatographic Purity Individual impurity Total Impurities	NMT 0.3% of any individual impurity is found NMT 0.8% of total impurities is found	USP <621> TP78807
Assay	NLT 97.0% and NMT 102.0% of $C_{24}H_{31}FO_6$, calculated on the dried basis	USP <621> TP78800
Bacterial Endotoxin	≤ (b) (4) EU/mg	USP <85> TP78798
Bioburden Total Aerobic Microbial Count: Total Combined Mold and Yeast Count:	< (b) (4) CFU/g < (b) (4) CFU/g	USP <61> TP78795
Residual Solvents (b) (4)	NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm	TP78823
Particle Size < (b) (4) µm < (b) (4) µm	More than (b) (4) % of particles More than (b) (4) % of particles	TP78859

Test	Acceptance Criteria	Analytical Method
Related Substances Impurity B	NMT [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) ([redacted] (b) (4) %)	Ph. Eur. TP78844
Impurity C	NMT [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) ([redacted] (b) (4) %)	
Unspecified Impurities	For each impurity, NMT [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) ([redacted] (b) (4) %)	
Total	NMT [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) ([redacted] (b) (4) %)	

Source: Module 3.2.S.4. Control of Drug Substance

DRUG PRODUCT

CLS-TA is a [redacted] (b) (4) sterilized aqueous suspension of triamcinolone acetonide (TA) without an antimicrobial preservative for ocular injection. The drug product is supplied as a 0.9 mL of CLS-TA suspension in a 2 mL / 13 mm glass vial with a rubber stopper and an aluminum seal for single use. The injection volume of the dose is 0.1 mL; therefore, the intended dose is 4 mg of TA per injection. CLS-TA is produced under cGMP conditions [redacted] (b) (4) [redacted] (b) (4).

The composition of CLS-TA is described in table on the next page.

Table 2: Formulation Composition of CLS-TA

Component	Function	Quality Reference	Concentration (% w/v or as noted)	Quantity / dose (0.1 mL injection, mg)	Quantity per vial (mg)[a]
Triamcinolone acetonide	Active	See Module 3.2.S.4.1	40 mg/mL		(b) (4)
Carboxymethylcellulose sodium	(b) (4)	USP-NF	0.5%		
Polysorbate 80	(b) (4)	USP-NF	0.02%		
Sodium chloride	Isotonicity agent	USP-NF	0.55%		
Potassium chloride	(b) (4)	USP-NF	(b) (4)%		
Calcium chloride dihydrate	(b) (4)	USP-NF	(b) (4)%		
Magnesium chloride hexahydrate	(b) (4)	USP-NF	(b) (4)%		
Sodium acetate trihydrate	(b) (4)	USP-NF	(b) (4)%		
Sodium citrate dihydrate	(b) (4)	USP-NF	(b) (4)%		
Hydrochloric acid	pH adjustment	USP-NF	as needed	NA	NA
Water for Injection	(b) (4)	USP-NF	q.s.	NA	NA

[a] Based on a fill of 0.9 mL per vial

Source: Module 3.2.P.1. Description and Composition of the Drug Product

Table 3: Quality Control Specifications (Drug Product)

Determination	Acceptance Criteria	Test Method	Purpose
Appearance	White to off-white suspension with no visible foreign particulate matter. The suspension is contained in a clear glass vial with a rubber stopper, an aluminum seal and a flip-top cap.	Visual Test Method M9362	Release and Stability
Resuspendability / Redispersibility	A homogenous suspension that is visually dispersed upon agitation and no aggregates are observed.	Visual Test Method M9362	Release and Stability
Primary Identification	The retention time of the sample matches the retention time of a similarly prepared USP reference standard.	High Performance Liquid Chromatography Test Method M9049	Release and Stability
Secondary Identification	The UV absorption scan of the sample matches the absorption scan of a similarly prepared USP reference standard over the same spectral range.	High Performance Liquid Chromatography – Diode Array Detection Test Method M9049	Release and Stability
Assay	(b) (4) % Label Claim ((b) (4) mg/mL) Label Claim: 40 mg/mL	High Performance Liquid Chromatography Test Method M9049	Release and Stability

Determination	Acceptance Criteria	Test Method	Purpose
Impurities Specified Identified Impurities:		High Performance Liquid Chromatography Test Method M9049	Release and Stability
Ph. Eur. Impurity A	NMT (b) (4)%		
Ph. Eur. Impurity B	NMT (b) (4)%		
Ph. Eur. Impurity C	NMT (b) (4)%		
Ph. Eur. Impurity D	NMT (b) (4)%		
Ph. Eur. Impurity E	NMT (b) (4)%		
Ph. Eur. Impurity F	NMT (b) (4)%		
Specified Unidentified Impurities: Unknown Impurity (b) (4) Unknown Impurity, (b) (4)	NMT (b) (4)% NMT (b) (4)%		
Unspecified Unidentified Impurities:	NMT (b) (4)%, each		
Total Impurities[a]:	NMT (b) (4)%		
pH	(b) (4)	Potentiometric USP <791>	Release and Stability
Particle Size Distribution D10: D50: D90:	 < (b) µm < (b) µm < (b) (4) µm	Laser Diffraction M11771	Release and Stability
Osmolality	(b) (4) mOsm/kg	Freezing Point Depression USP <785>	Release and Stability
Viscosity	(b) (4) (b) (4)	Rotational Viscometry Test Method M9088 USP <912> Method I	Release and Stability

Dispensability	[redacted] (b) (4)	Physical Test Method [redacted] (b) (4)	Release and Stability
Functionality	[redacted] (b) (4)	Physical Test Method [redacted] (b) (4)	Release and Stability
Bacterial Endotoxin	NMT [redacted] (b) (4) EU/mg of triamcinolone acetonide	Kinetic chromogenic TP79029 USP <85>	Release and Stability
Uniformity of Dosage Units	Meets the requirements	Acceptance Value Calculation USP <905>	Release and Stability
Sterility	Sterile	Direct Transfer TP79030 USP <71>	Release and Stability
Injection Volume in Container	[redacted] (b) (4)	Physical Test Method [redacted] (b) (4) USP <1>	Release and Stability
Container Closure Integrity Test	All test containers must show no evidence of microbial ingress	Microbial Ingress TP79520	Release and Stability
NMT= No more than; RRT=Relative retention time; mOsm=milliosmoles; cPs=centipoise; UV=ultraviolet; ID=Identification; USP=Unites States Pharmacopoeia; EU=Endotoxin units			

[a] All impurities reported above Limit of Quantitation [redacted] (b) (4) are summed together as total impurities.
Source: Module 3.2.P.5. Control of Drug Product

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CDRH CONSULT

See the CDRH review dated 10/18/2021.

CDRH completed a review dated 10/18/2021 and noted that the device constituent of the combination product is now approvable for the proposed indication. There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

CDRH reviewed materials in the resubmission that addressed the deficiencies cited in their original 8/1/2019 review. Specifically, the applicant adequately responded to items 1, 2 and 3.

(b) (4), (b) (5)

[redacted]

(b) (4), (b) (5)

[redacted]

FACILITIES

The drug product manufacturing site for the application was transferred to Alcami Corporation from [redacted] (b) (4) in the resubmission. All the manufacturing sites are currently acceptable. The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities with post-approval inspection recommendations for Alcami (FEI 1000110990) and [redacted] (b) (4) on [redacted] (b) (4)

The following commercial DS/DP Control Testing Laboratories have been proposed by the applicant to support external testing function of the pending drug product. The facilities proposed below, unless noted otherwise, are within compliance standards and have the ability to perform the function and responsibilities outline in the application following assessment:		
Facility Name/FEI	**Responsibilities**	**Previous OPMA evaluation**
[redacted] (b) (4)		Relevant and acceptable. Site is a contract [redacted] (b) (4) The 2014 inspection found the CRU profile acceptable.
		Relevant and acceptable.10/15/2018 evaluation approved the facility based on profile CTL
Alcami Carolinas Corporation/ 1942094	Analytical testing and stability testing (physical, chemical, and microbiological testing)	Relevant and acceptable.

OPQ RECOMMENDED ACTION

See the IQA Integrated review dated 10/18/2021.

All the manufacturing process deficiencies have been resolved with adequate in-process controls (IPCs) or appropriate justifications. Therefore, NDA 211950 is recommended approval from Product Quality perspective.

OPQ has one non-approvability comment to be included it as an "additional comment" from Biopharmaceutics in the action letter:

> We acknowledge your commitment to perform additional in vitro drug release studies post-approval. We recommend that you submit the following data/information in a

supplement when they are available: (1) data demonstrating the discriminating ability of the proposed in vitro drug release method (M20682) against smaller particle size distributions that is representative of meaningful changes; (2) multi-point drug release profiles (individual, mean, %RSD) for the clinical batches and registration stability batches.

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 9/6/2019:

The Applicant has conducted nonclinical studies which provide ocular distribution and ocular toxicology for the proposed formulation and route of administration. In those studies, following suprachoroidal injection, low systemic exposure and no adverse toxicity were associated with the test article.

For pharmacology, safety pharmacology, general toxicology, genotoxicity, developmental and reproductive toxicology, and carcinogenesis, the applicant references Kenalog (NDA 014901), an approved formulation of triamcinolone acetonide administered by systemic route (intramuscular, intra-articular). Across indications, the highest doses in the labeling are 100 mg per day or higher. These doses exceed the dose proposed for XIPERE (4mg) and therefore a scientific bridge is justified based on dose comparison.

Limited information is available in the Kenalog label regarding developmental and reproductive toxicity, genotoxicity and carcinogenesis. The information available was used in the proposed XIPERE labeling.

6. Clinical Pharmacology

From the original Clinical Pharmacology Review dated 8/27/2019:

The proposed dosage regimen and route of administration of XIPERE is 4 mg (0.1 mL of 40mg/mL CLS-TA) via suprachoroidal injection. Since XIPERE is proposed to be administered via suprachoroidal injection locally into the affected eye, efficacy is not related to systemic exposure of triamcinolone acetonide (TA).

Two Phase 3 studies, CLS1001-301 and CLS1001-302, were conducted and the PK exposure of TA following suprachoroidal repeat dose administration of 4 mg XIPERE was evaluated in a subset of 19 ME patients. In all 19 patients, the range of plasma TA concentrations was from <10 pg/mL (LLOQ of the assay) to 243.4 pg/mL, which occurred in only one patient. However, for all other patients, TA plasma concentrations were at or below 100 pg/mL at all timepoints in both studies.

7. Clinical Microbiology

Not applicable. This product is not an anti-infective.

8. Clinical/Statistical- Efficacy

MICROINJECTOR USABILITY STUDY

As part of the Complete Response Letter dated October 18, 2019, the following deficiency was cited:

> 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.

From the Medical Officer's Review of the Class 2 Resubmission dated 9/13/2021: Roughly one thousand 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. [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) To confirm that these changes [redacted] (b) (4) [redacted] (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.

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.

Compared to the Topaz study, the number of patients in the microinjector group in the Azalea study is relatively small and represents patients 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.

DRUG PRODUCT EFFICACY

From the original Medical Officer's Review dated 10/16/2019: 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 PEACHTREE study (CLS1O1-301) was a Phase 3, randomized, masked, sham-controlled, multicenter study to assess the efficacy and safety of suprachoroidally injected CLS-TA (4 mg) 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 (CLS1OO1-201) and a Phase 3 open-label study, AZALEA (CLS1O1-302). 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 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.

Efficacy Results - Primary Endpoint CLS1O1-301 PEACHTREE

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

Table 12: 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)	
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.

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

[b] The 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.

Source: Module 5.3.5.1 CSR for CLS1001-301

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.

Secondary Endpoint: Mean Change from Baseline in Central Subfield Retinal Thickness at Week 24

Table 13: Mean Change from Baseline in Central Subfield Retinal Thickness at Week 24, Study Eye (LOCF Method) (Intent-to-Treat Population)

	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)
Median	-125.00	0.00
Min, Max	-551, 191	-380, 298
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.
Notes: 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.
[a] Subjects who completed the assessment, but for whom a definitive post Baseline result was not available, were also not included in the imputation.
[b] The difference in means, CIs, and p-value were from an ANCOVA with factors for treatment group and country, and covariate Baseline CST.
Source: Post-text Table 14.2.5.1.

Source: Module 5.3.5.1 CSR for CLS1001-301

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.

Drug Efficacy Study Implementation (DESI)

The efficacy of corticosteroids including triamcinolone acetonide via multiple routes of administration was established in published clinical studies reviewed as part of the Drug Efficacy Study Implementation (DESI) review. Triamcinolone 40 mg was found to be efficacious/or 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. of the original Medical Officer review dated 10/16/2019.

Summary of Efficacy

The efficacy of triamcinolone acetonide via multiple routes of administration was established in adequate and well controlled studies published and reviewed as part of the Drug Efficacy Study Implementation (DESI) review. They have been used as anti-inflammatory agents for the treatment of various diseases in the US/or 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 literature findings and the long history of use of this product in ophthalmic inflammatory diseases; the efficacy in uveitis associated macula edema has been established.

9. Safety

From the original Medical Officer's Review dated 10/16/2019: 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 directly with the PEACHTREE study because:

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

The Medical Officer review concentrated 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 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.

Overall Exposure

Table 17: 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)
Reason for Rescue[a], n (%):		
Decrease of 10 or more ETDRS BCVA letters read from Baseline (Day 0)	3 (3.1)	14 (21.9)
Increase in CST ≥100 µm or 20% from Baseline	3 (3.1)	17 (26.6)
≥1.5 step increase from Baseline in level of inflammation	4 (4.2)	11 (17.2)
Medical judgment that uveitic complications have not improved	13 (13.5)	31 (48.4)
Time to First Rescue (Days)[b]		
N	96	64
Mean (SE)	143.4 (2.44)	91.5 (7.57)
Median	NE	84.0
25th - 75th Percentile	NE - NE	29.0 - NE
Min, Max	29, 217	7, 204
Duration of Treatment (Days)[c]		
N	96	64
Mean (STD)	159.9 (28.87)	123.6 (42.88)
Median	169.0	85.0
Min, Max	85, 197	85, 180

BCVA=best corrected visual acuity, CST=central subfield thickness, ETDRS=early treatment of diabetic retinopathy study, NE=not evaluable, SE=standard error, STD=standard deviation. Notes:

[a] Beginning at Week 4 (Visit 3), if any of the following criteria were met in the Study eye, the use of a treatment could be introduced: [1] the therapy implemented was left to the discretion of the Investigator, [2] a decrease of 10 or more ETDRS BCVA letters read from Baseline (Day 0), [3] an increase in CST of >100 µm or 20%, whichever was lower from Baseline (Day 0) based on the CST measurement at the clinical site, [4] a >1.5-step increase from Baseline (Day 0) in the level of inflammation (eg, AC cells or vitreous haze) or an increased from 3+ to 4+, [5] in the Investigators medical judgement, the uveitic complications in the Study eye did not improve and the condition had to be addressed.

[b] Summary of time to rescue was based on Kaplan-Meier estimates.

[c] For subjects with both injections/shams, Duration of Study Treatment was calculated as: Date of second injection/sham – Date of first injection/sham + 85 where 85 was 12 weeks + 1 day. For subjects with only the first injection/sham, Duration of Treatment was calculated as: 85 where 85 was 12 weeks + day of injection/sham.

Source: Module 5.3.5.1 CSR for CLS1001-301

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
	CLS-TA	Sialoadenitis	Recovered / Resolved	No
	CLS-TA	Lumbar vertebral fracture	Recovered / Resolved	No

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.

Treatment-Emergent Adverse Events

Table 28: 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 (%) E	Control (N=64) n (%) E	Overall (N=160) n (%) E
Intraocular pressure increased	17 (17.7) 21	4 (6.3) 4	21 (13.1) 25
Eye pain	14 (14.6) 18	0 0	14 (8.8) 18
Cataract subcapsular	7 (7.3) 7	3 (4.7) 4	10 (6.3) 11
Cystoid macular oedema	0 0	9 (14.1) 11	9 (5.6) 11
Uveitis	2 (2.1) 2	7 (10.9) 7	9 (5.6) 9
Ocular hypertension	2 (2.1) 3	5 (7.8) 5	7 (4.4) 8
Conjunctival haemorrhage	4 (4.2) 4	2 (3.1) 2	6 (3.8) 6
Injection site pain	4 (4.2) 4	2 (3.1) 2	6 (3.8) 6
Vitreous detachment	5 (5.2) 5	1 (1.6) 1	6 (3.8) 6
Visual acuity reduced	4 (4.2) 5	1 (1.6) 1	5 (3.1) 6

E = Number of total corresponding events; TEAE = Treatment-Emergent Adverse Event.
Note(s): Adverse Events were coded using MedDRA coding dictionary 18.1. TEAEs are defined as any event occurring post treatment (injection) or, if pre-existing, worsening after Day 1. If the subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE. Table presents number and percentage of subjects (n (%)) and number of events (E). Percentages are based on the number of subjects in the respective group.
Source: PEACHTREE CSR Post-text Table 14.3.2.21.

Source: Module 2.7.4 Summary of Clinical Safety

Summary 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.

10. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application. There were no issues that were thought to benefit from a discussion at an advisory committee meeting.

11. Pediatrics

This application did not trigger PREA (i.e., no new indication, no new dosage form, no new dosing regimen, no new route of administration, no new active ingredient) and thus was not presented at the Pediatric Review Committee (PeRC).

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 in doses greater than administered for this indication. 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.

12. Other Relevant Regulatory Issues

OSI

From the Office of Scientific Investigations (OSI) review dated 8/20/2019: 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.

The clinical sites of Drs. Rifkin and Wang were inspected in support of this NDA with regard to their conduct of Protocol CLS1001-301. Based on the results of these inspections, the study appears to have been conducted adequately at Dr. Wang's site. The data generated at this site appear acceptable in support of the respective indication. The inspection at Dr. Rifkin's site revealed that three subjects were randomized to the study despite failing to meet minor eligibility criteria.

Statistics
From the Office of Biostatistics review dated 9/13/2019: The primary evidence for the efficacy of CLS-TA comes from one Phase 3 study (Study CLS1001-301). The primary objective of this study was to evaluate the efficacy of CLS-TA in subjects with ME associated with non-infectious uveitis. The study enrolled 160 adult subjects in 53 sites located across three countries (80 subjects in the Unites States, 70 subjects in India, and 10 subjects in Israel). Eligible subjects were randomized in a 3:2 ratio to receive either 2 unilateral suprachoroidal injections of CLS-TA (96 subjects) or 2 unilateral suprachoroidal injections of a sham Control (64 subjects), administered to the study eye approximately 12 weeks apart. The total duration of the study was approximately 27 weeks.

The primary efficacy endpoint of the study was the proportion of subjects with 15 letters or more improvement from baseline at Week 24. The primary efficacy analysis was conducted using a Cochran-Mantel-Haenszel (CMH) test adjusting for a country subgroup (US+Israel vs. India). This study showed that the proportion of subjects with 15 letters or more improvement from baseline at Week 24 was significantly higher in the CLS-TA arm compared with the Control arm (45% vs 16%; diff (95% CI): 31 (15%, 46%]). In both arms, the main reason for administration of rescue medication was the investigators' judgment that uveitic complications have not improved.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, XIPERE, and granted conditional acceptance on 4/20/2019. They also completed a labeling review dated 4/1/2019. Labeling discussions with the applicant were deferred until the items cited in the Complete Response letter were addressed.

DMEPA finalized a Human Factors Study Report Review on 10/10/2019. Clearside Biomedical submitted a "SCS Microinjector Usability Study." DMEPA's review of the usability study results identified several missing elements from the human factors (HF) validation study report that impacted their ability to provide a full review.

They completed a second labeling review dated 9/28/2021. DO did not agree with the following labeling recommendations in that review:

Regarding the Package Insert and Carton /Container labels:

- Revise the statement, "[redacted] (b) (4) in the "Dosage Form and Strengths" section of the Highlights to the following: [redacted] (b) (6) (b) (6)

DO believes [redacted] (b) (4) (b) (4)

- [redacted] (b) (4)

DO disagreed. [redacted] (b) (4)

- [redacted] (b) (4)

DO disagreed. [redacted] (b) (4)

[redacted] (b) (4)

DO disagreed. [redacted] (b) (4)

- [redacted] (b) (4)

DO disagreed. [redacted] (b) (4)

OPDP
Office of Prescription Drug Promotion (OPDP) completed a labeling review dated 10/6/2021.

Financial Disclosures

Covered Clinical Studies:
Peachtree CLSlOOl-301
Azalea CLSlOOl-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
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: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study: 2 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)

13. Labeling

The labeling submitted by the applicant on 10/15/2021, is acceptable and is attached at the end of this review in an Appendix. The application for NDA 211950 XIPERE (triamcinolone acetonide ophthalmic suspension) for suprachoroidal injection for the treatment of macular edema associated with uveitis will be approved with the attached labeling.

14. 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	Original Medical Officer's review Section 6.1. 6.2 and 6.3
	□ Patient reported outcome (PRO)	
	■ Observer reported outcome (ObsRO)	Visual Acuity
	□ 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.	

15. Regulatory Action

NDA 211950 XIPERE (triamcinolone acetonide ophthalmic suspension) for suprachoroidal injection will be approved for the treatment of macular edema associated with uveitis. There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

The items cited in the October 18, 2019, Complete Response letter have all been adequately addressed. All amendments to the application comply with 21 CFR 314.60(f). Clinical, OPQ and CDRH now recommend approval of the application.

The following additional comments should be transmitted as an Information Request:

> We acknowledge your commitment to perform additional in vitro drug release studies post-approval. We recommend that you submit the following data/information in a supplement when they are available: (1) data demonstrating the discriminating ability of the proposed in vitro drug release method (M20682) against smaller particle size distributions that is representative of meaningful changes; (2) multi-point drug release profiles (individual, mean, %RSD) for the clinical batches and registration stability batches.

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

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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/

WILLIAM M BOYD
10/20/2021 09:36:52 AM

WILEY A CHAMBERS
10/20/2021 09:54:07 AM

Cross-Discipline Team Leader and Deputy Division Director Review of NDA 211950

Date	October 17, 2019
From	Wiley A. Chambers, M.D. and William M. Boyd, M.D.
Subject	Deputy Division Director and Cross-Discipline Team Leader Review
NDA #	211950
Applicant	Clearside Biomedical, Inc.
Date of Submission	December 19, 2018
PDUFA Goal Date	October 19, 2019
Proprietary Name	XIPERE
Established or Proper Name	triamcinolone acetonide ophthalmic suspension
Dosage Form(s)	[redacted] (b) (4) injection
Proposed Dosing Regimen(s)	single dose suprachoroidal injectable suspension
Regulatory Action	Complete Response
Proposed Indication	Treatment of macular edema associated with uveitis in adult patients

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Michael Puglisi
Medical Officer Review	Jennifer Harris
Statistical Review	Abel Eshete
Pharmacology Toxicology Review	Erin Ruhland
OPQ Review	Chunchun Zhang, Ben Zhang, Yong Wang
Microbiology Review	Eric Adeeku
Clinical Pharmacology Review	Kunyi Wu
OPDP	N/A
OSI	Roy Blay
CDTL Review	William M. Boyd
OSE/DMEPA	Nasim Roosta
OSE/DRISK	N/A

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Summary

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.

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/or 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.

XIPERE, aka 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. This is not a combination product. Under CFR 21 200.50, this product and its dispenser, planned to be packaged together, is regulated as an ophthalmic drug.

This is a 505(b)(2) application which identifies the listed drug product as Kenalog (NDA 14901). The applicant conducted its own clinical trial to establish the safety and effectiveness of its proposed triamcinolone acetonide injectable suspension 40 mg/mL product for the treatment of macular edema associated with non-infectious uveitis via suprachoroidal administration. The applicant also conducted its own nonclinical studies to support ocular pharmacology, pharmacokinetics, and ocular toxicity.

2. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

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 and efficacy 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	• Uveitis (inflammation) can lead to permanent vision loss	Inflammation can be treated with the use of anti-inflammatory agents.
Current Treatment Options	• Intraocular steroids	CLS-TA provides an effective alternate route of administration negating the need for entering the intraocular space.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Improvement in visual acuity • Reduction in central retinal thickness	Study CLSJOOJ-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. DESI review established the efficacy of triamcinolone for multiple ocular inflammatory diseases. There is at least a 50 year history of usage for this product administered via a wide variety of different routes.
Risk and Risk Management	• 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.	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.

3. Background

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 US in 2007 and European Union (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.

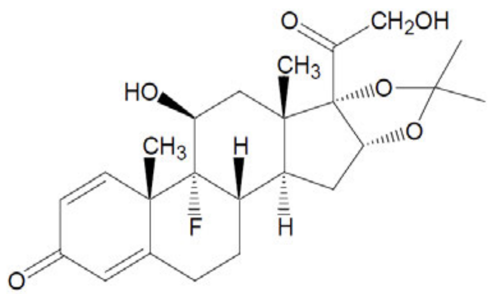
Current Treatment Options for a Closely Related Indication

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) (4) 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

4. Product Quality

Triamcinolone acetonide (b) (4) is a white or almost white crystalline powder.

STRUCTURAL FORMULA



MOLECULAR FORMULA
$C_{24}H_{31}FO_6$

CHEMICAL NAME
• 9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone
or
• 9-Fluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione
or
• Pregna-1,4-diene-3,20-dione,9-fluoro-11,21-dihydroxy-16,17-[(1 methylethyllidene)bis(oxy)]-, (11β,16α)

DRUG SUBSTANCE

Table 1: Release Specifications for Triamcinolone Acetonide (b) (4)

Test	**Acceptance Criteria**	**Analytical Method**
Appearance	White or almost white crystalline powder	Visual
Identification		
Infrared absorption	Meets the requirements	USP <197K>
UV Absorption	Meets the requirements	USP <197U>
Specific Rotation	Between +118° to +130°	USP <781S>
Loss on Drying	NMT 1.5%	USP <731>
Chromatographic Purity		Triamcinolone acetonide USP Monograph
Individual impurity	NMT 0.3%	
Total Impurities	NMT 0.8%	

Test	Acceptance Criteria	Analytical Method
Assay	97.0 – 102.0% (dried basis)	Triamcinolone acetonide USP Monograph
Bacterial Endotoxin	NMT [redacted] EU/mg	USP <85>
Bioburden	TAMC: < [redacted] CFU/g TYMC: < [redacted] CFU/g	USP <61>
Residual Solvents [redacted]	NMT [redacted] ppm NMT [redacted] ppm NMT [redacted] ppm	CON-IM-1051
Particle Size < [redacted] µm < [redacted] µm	[redacted] % of particles [redacted] % of particles	Accepted on Certificate of Analysis - [redacted]

Source: Module 3.2.S.4. Control of Drug Substance

DRUG PRODUCT

CLS-TA is a preservative-free, [redacted] sterilized aqueous suspension of triamcinolone acetonide (TA) formulated for ocular injection. The drug product is supplied as a 0.9 mL of CLS-TA suspension in a 2 mL / 13 mm glass vial with a rubber stopper and an aluminum seal for single use. The injection volume of the dose is 0.1 mL; therefore, the intended dose is 4 mg of TA per injection. CLS-TA is produced under cGMP conditions [redacted]

The composition of CLS-TA is described in table on the next page.

Formulation Composition of CLS-TA

Component	Function	Quality Reference	Concentration (% w/v or as noted)	Quantity / dose (0.1 mL injection, mg)	Quantity per vial (mg)[a]
Triamcinolone acetonide	Active	See Section 3.2.S.4.1	40 mg/mL		(b) (4)
Carboxymethylcellulose sodium	(b) (4)	USP-NF	0.5%		
Polysorbate 80	(b) (4)	USP-NF	0.02%		
Sodium chloride	Isotonicity agent	USP-NF	0.55%		
Potassium chloride	(b) (4)	USP-NF	(b) (4) %		
Calcium chloride dihydrate	(b) (4)	USP-NF	(b) (4) %		
Magnesium chloride hexahydrate	(b) (4)	USP-NF	(b) (4) %		
Sodium acetate trihydrate	(b) (4)	USP-NF	(b) (4) %		
Sodium citrate dihydrate	(b) (4)	USP-NF	(b) (4) %		
(b) (4)	(b) (4)	USP-NF	(b) (4)	NA	NA
Hydrochloric acid	pH adjustment	USP-NF	as needed	NA	NA
Water for Injection	(b) (4)	USP-NF	q.s.	NA	NA

[a] Based on a fill of 0.9 mL per vial

Source: Module 3.2.P.1. Description and Composition of the Drug Product

Quality Control Specifications (Drug Product)

Determination	Acceptance Criteria	Test Method	Sample Quantity (Release)	Sample Quantity (Stability)
Appearance	White to off-white suspension with no visible foreign particulate matter. The suspension is contained in a clear glass vial with a rubber stopper, an aluminum seal and a flip-top cap.	Visual Test Method M9362	1	1
Resuspendability / Redispersibility	A homogenous suspension that is visually dispersed upon agitation and no aggregates are observed.	Visual Test Method M9362	1	1
Primary Identification[a]	The retention time of the sample matches the retention time of a similarly prepared USP reference standard.	High Performance Liquid Chromatography Test Method M9049	(b) (4)	Not Performed
Secondary Identification[a]	The UV absorption scan of the sample matches the absorption scan of a similarly prepared USP reference standard over the same spectral range.	High Performance Liquid Chromatography – Diode Array Detection Test Method M9049		Not Performed
Assay	(b) (4) % Label Claim (b) (4) mg/mL) Label Claim: 40 mg/mL	High Performance Liquid Chromatography Test Method M9049		3

Determination	Acceptance Criteria	Test Method	Sample Quantity (Release)	Sample Quantity (Stability)
Impurities		High Performance Liquid Chromatography Test Method M9049	3 (b) (4)	3
Specified Identified Impurities:				
Ph. Eur. Impurity A	NMT (b) (4)%			
Ph. Eur. Impurity B	NMT (b) (4)%			
Ph. Eur. Impurity C	NMT (b) (4)%			
Ph. Eur. Impurity D	NMT (b) (4)%			
Ph. Eur. Impurity E	NMT (b) (4)%			
Ph. Eur. Impurity F	NMT (b) (4)%			
Specified Unidentified Impurities:				
Unknown Impurity, (b) (4) Unknown Impurity, (b) (4)	NMT (b) (4)% NMT (b) (4)%			
Unspecified Unidentified Impurities:	NMT (b) (4)%, each			
Total Impurities[b]:	NMT (b) (4)%			
pH	(b) (4)	Potentiometric USP <791>	(b) (4)	1
Particle Size Distribution D10: D50: D90:	 < (b) µm < (b) µm < (b) (4) µm	Laser Diffraction Test Method M11771		1
Osmolality	(b) (4) mOsm/kg	Freezing Point Depression USP <785>		1
Viscosity	(b) (4) (b) (4)	Rotational Viscometry Test Method M9088 USP <912> Method I		10

Syringeability[a]	(b) (4) [redacted]	Physical Test Method (b) (4) [redacted]	(b) (4) [redacted]	Functionality is performed during stability
Functionality	[redacted]	Physical Test Method (b) (4) [redacted]	[redacted]	3
Bacterial Endotoxin	NMT (b) (4) [redacted] EU/mg of triamcinolone	Kinetic chromogenic USP	[redacted]	1
Uniformity of Dosage Units[a]	Meets the requirements	Acceptance Value Calculation USP <905>	[redacted]	Not Performed
Sterility[d]	Sterile	Direct Transfer USP <71>	[redacted]	40
Injection Volume in Container[a]	(b) (4) [redacted]	Physical Test Method (b) (4) [redacted] USP <697>		Not Performed
Visual Inspection for Particulate[a]	Essentially free of visible particulates	Visual CON-IM-1075	AQL 0.65	Not Performed
NMT = No more than; RRT = Relative retention time; mOsm = milliosmoles; cPs = centipoise; UV = ultraviolet; ID = Identification; USP = Unites States Pharmacopoeia; EU = Endotoxin units				

(b) (4) [redacted]

Source: Module 3.2.P.5. Control of Drug Product

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CDRH CONSULT

CDRH review team was consulted by OPQ to review the SCS Microinjector. At filing, it was discussed at length with OPQ that this product is not a combination product under 21 CRF 200.50. XIPERE (triamcinolone acetonide ophthalmic suspension) for surprachoidal injection is copackaged with a microinjector delivery system and regulated as a drug. CDRH completed a review dated 8/12/2019 and located in Panorama. Their Complete Response deficiencies are located in Section 2.2 of their review; these deficiencies are also located in the original OPQ review (Executive Summary) dated 9/10/2019 and located in Panorama.

OPQ is aware that this product is not a combination product. Per their review dated 9/10/2019:

> CDRH was consulted to review the SCS microinjector and has identified several major deficiencies. Those deficiencies had been discussed with the clinical division on 7/22/2019. The clinical division indicated that the deficiencies are not needed to assess the potential safety and efficacy of the drug product since this is not a combination product. See the attached consult memo from CDRH for the detailed discussion. However, we recommend communicate these deficiencies as CR comments to the applicant from the product quality perspective.

The cited CDRH deficiencies are requests for additional information and fall into two categories. Some are not clinically relevant and some are redundant to other controls already included in the application. These requests will not be cited in the Complete Response letter. The microinjector delivery system has been used in a subset of subjects in the clinical trials used to establish efficacy and safety of the product. There will be a request within the Complete Response letter for clinical use information for the final to-be-marketed microinjector delivery system.

FACILITIES

The compliance status of the drug product manufacturing facility, [redacted] (b) (4) Inc. (FEI [redacted] (b) (4) was determined unacceptable based on the most recent inspection performed ending [redacted] (b) (4). Therefore, OPF has issued an overall recommendation of "Withhold" on [redacted] (b) (4)

Facility name and address	FEI	Responsibilities and profile code(s)	Status
[redacted]	(b) (4) [redacted]	(b) (4) [redacted]	Approve - Based on Previous History
			Approve - Based on Previous History
			Withhold - Based on PAI
			Approve - Based on Previous History
			No Evaluation Necessary
			No Evaluation Necessary

OPQ ACTION LETTER LANGUAGE

From the original OPQ review dated 9/10/2019:

Complete Response Issue:

1. During the pre-approval inspection of [redacted] (b) (4) Inc. [FEI [redacted] (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.

Additional Comments for the letter:

1. The drug product is an ophthalmic suspension. Therefore, FDA recommends that for quality control purposes, you develop an in vitro drug release method and include the dissolution test in the specifications of the product. We have the following comments and request for information for the in vitro drug release test:

a. Submit the development and validation report for the proposed in vitro drug release method. Include justifications and enough data supporting the selection of the dissolution testing conditions (equipment/apparatus, in vitro drug release media, agitation/rotation speed, pH, sink conditions, use of surfactant if applicable, etc.). Provide data/information supporting the discriminating ability of the method with respect to the most relevant critical material attributes (CMAs, e.g., PSD), critical formulation variables, and critical process parameters (CPPs).

b. Collect and submit in vitro drug release profile data for the clinical batches and upcoming stability time points of the registration batches using the proposed drug release method. Based on the collected data, provide your proposal for the in vitro drug release acceptance criterion/criteria of the proposed drug product.

2. Update manufacturing process flow diagram to include all individual process step enhancements and all applicable recommendations noted in this Information Request.

3. We recommend you 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. Provide one registration batch with 3 months stability data at long term storage and 3 months stability data at accelerated condition.

(b) (4)

[redacted]

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(b) (4)

[redacted]

2. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 9/6/2019:

The Applicant has conducted nonclinical studies which provide ocular distribution and ocular toxicology for the proposed formulation and route of administration. In those studies, following suprachoroidal injection, low systemic exposure and no adverse toxicity were associated with the test article.

For pharmacology, safety pharmacology, general toxicology, genotoxicity, developmental and reproductive toxicology, and carcinogenesis, the applicant references Kenalog (NDA 014901), an approved formulation of triamcinolone acetonide administered by systemic route (intramuscular, intra-articular). Across indications, the highest doses in the labeling are 100 mg per day or higher. These doses exceed the dose proposed for Xipere (4mg) and therefore a scientific bridge is justified based on dose comparison.

Kenalog was approved in 1965. Limited information is available in the Kenalog label regarding developmental and reproductive toxicity, genotoxicity and carcinogenesis. The information available was used in the proposed XIPERE labeling.

3. Clinical Pharmacology

From the original Clinical Pharmacology Review dated 8/27/2019:

The proposed dosage regimen and route of administration of XIPERE is 4 mg (0.1 mL of 40mg/mL CLS-TA) via suprachoroidal injection. Since XIPERE is proposed to be administered via suprachoroidal injection locally into the affected eye, efficacy is not related to systemic exposure of triamcinolone acetonide (TA). This review only focuses on evaluating systemic TA concentrations/exposure to support the systemic safety of XIPERE.

Two Phase 3 studies, CLS1001-301 and CLS1001-302, were conducted and the PK exposure of TA following suprachoroidal repeat dose administration of 4 mg XIPERE was evaluated in a subset of 19 ME patients. In all 19 patients, the range of plasma TA concentrations was from <10 pg/mL (LLOQ of the assay) to 243.4 pg/mL, which occurred in only one patient. However, for all other patients, TA plasma concentrations were at or below 100 pg/mL at all timepoints in both studies.

4. Clinical Microbiology

Not applicable. This product is not an anti-infective.

5. Clinical/Statistical- Efficacy

From the original Medical Officer's Review dated 10/16/2019:

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 PEACHTREE study (CLS1O1-301) was a Phase 3, randomized, masked, sham-controlled, multicenter study to assess the efficacy and safety of suprachoroidally injected CLS-TA (4 mg) 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 (CLS1OO1-201) and a Phase 3 open-label study, AZALEA (CLS1O1-302). 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 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.

Efficacy Results - Primary Endpoint CLS1O1-301 PEACHTREE

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

Table 12: 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)	
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.

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

[b] The 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.

Source: Module 5.3.5.1 CSR for CLS1001-301

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.

Secondary Endpoint: Mean Change from Baseline in Central Subfield Retinal Thickness at Week 24

Table 13: Mean Change from Baseline in Central Subfield Retinal Thickness at Week 24, Study Eye (LOCF Method) (Intent-to-Treat Population)

	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)
Median	-125.00	0.00
Min, Max	-551, 191	-380, 298
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.
Notes: 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.
[a] Subjects who completed the assessment, but for whom a definitive post Baseline result was not available, were also not included in the imputation.
[b] The difference in means, CIs, and p-value were from an ANCOVA with factors for treatment group and country, and covariate Baseline CST.
Source: Post-text Table 14.2.5.1.

Source: Module 5.3.5.1 CSR for CLS1001-301

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.

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. Triamcinolone 40 mg was found to be efficacious/or 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. of the original Medical Officer review dated 10/16/2019.

Summary of Efficacy

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/or 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.

6. Safety

From the original Medical Officer's Review dated 10/16/2019:

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 directly with the PEACHTREE study because:

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

The Medical Officer review concentrated 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 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.

Overall Exposure

Table 17: 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)
Reason for Rescue[a], n (%):		
Decrease of 10 or more ETDRS BCVA letters read from Baseline (Day 0)	3 (3.1)	14 (21.9)
Increase in CST ≥100 µm or 20% from Baseline	3 (3.1)	17 (26.6)
≥1.5 step increase from Baseline in level of inflammation	4 (4.2)	11 (17.2)
Medical judgment that uveitic complications have not improved	13 (13.5)	31 (48.4)
Time to First Rescue (Days)[b]		
N	96	64
Mean (SE)	143.4 (2.44)	91.5 (7.57)
Median	NE	84.0
25th - 75th Percentile	NE - NE	29.0 - NE
Min, Max	29, 217	7, 204
Duration of Treatment (Days)[c]		
N	96	64
Mean (STD)	159.9 (28.87)	123.6 (42.88)
Median	169.0	85.0
Min, Max	85, 197	85, 180

BCVA=best corrected visual acuity, CST=central subfield thickness, ETDRS=early treatment of diabetic retinopathy study, NE=not evaluable, SE=standard error, STD=standard deviation. Notes:

[a] Beginning at Week 4 (Visit 3), if any of the following criteria were met in the Study eye, the use of a treatment could be introduced: [1] the therapy implemented was left to the discretion of the Investigator, [2] a decrease of 10 or more ETDRS BCVA letters read from Baseline (Day 0), [3] an increase in CST of >100 µm or 20%, whichever was lower from Baseline (Day 0) based on the CST measurement at the clinical site, [4] a >1.5-step increase from Baseline (Day 0) in the level of inflammation (eg, AC cells or vitreous haze) or an increased from 3+ to 4+, [5] in the Investigators medical judgement, the uveitic complications in the Study eye did not improve and the condition had to be addressed.

[b] Summary of time to rescue was based on Kaplan-Meier estimates.

[c] For subjects with both injections/shams, Duration of Study Treatment was calculated as: Date of second injection/sham – Date of first injection/sham + 85 where 85 was 12 weeks + 1 day. For subjects with only the first injection/sham, Duration of Treatment was calculated as: 85 where 85 was 12 weeks + day of injection/sham.

Source: Module 5.3.5.1 CSR for CLS1001-301

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) [redacted] 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) [redacted]	CLS-TA	Retinal Detachment	Recovered / Resolved	No
	CLS-TA	Sialoadenitis	Recovered / Resolved	No
	CLS-TA	Lumbar vertebral fracture	Recovered / Resolved	No

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) [redacted] and hepatorenal syndrome in Subject (b) (6) [redacted] Neither death is considered related to the study drug after review of the patient narratives.

Treatment-Emergent Adverse Events

Table 28: 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 (%) E	Control (N=64) n (%) E	Overall (N=160) n (%) E
Intraocular pressure increased	17 (17.7) 21	4 (6.3) 4	21 (13.1) 25
Eye pain	14 (14.6) 18	0 0	14 (8.8) 18
Cataract subcapsular	7 (7.3) 7	3 (4.7) 4	10 (6.3) 11
Cystoid macular oedema	0 0	9 (14.1) 11	9 (5.6) 11
Uveitis	2 (2.1) 2	7 (10.9) 7	9 (5.6) 9
Ocular hypertension	2 (2.1) 3	5 (7.8) 5	7 (4.4) 8
Conjunctival haemorrhage	4 (4.2) 4	2 (3.1) 2	6 (3.8) 6
Injection site pain	4 (4.2) 4	2 (3.1) 2	6 (3.8) 6
Vitreous detachment	5 (5.2) 5	1 (1.6) 1	6 (3.8) 6
Visual acuity reduced	4 (4.2) 5	1 (1.6) 1	5 (3.1) 6

E = Number of total corresponding events; TEAE = Treatment-Emergent Adverse Event.

Note(s): Adverse Events were coded using MedDRA coding dictionary 18.1. TEAEs are defined as any event occurring post treatment (injection) or, if pre-existing, worsening after Day 1. If the subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE. Table presents number and percentage of subjects (n (%)) and number of events (E). Percentages are based on the number of subjects in the respective group.

Source: PEACHTREE CSR Post-text Table 14.3.2.21.

Source: Module 2.7.4 Summary of Clinical Safety

Summary 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.

7. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application. There were no issues that were thought to benefit from a discussion at an advisory committee meeting.

8. Pediatrics

This application did not trigger PREA (i.e., no new indication, no new dosage form, no new dosing regimen, no new route of administration, no new active ingredient) and thus was not presented at the Pediatric Review Committee (PeRC).

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 in doses greater than administered for this indication. 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.

9. Other Relevant Regulatory Issues

OSI

From the Office of Scientific Investigations (OSI) review dated 8/20/2019:

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.

The clinical sites of Drs. Rifkin and Wang were inspected in support of this NDA with regard to their conduct of Protocol CLS1001-301. Based on the results of these inspections, the study appears to have been conducted adequately at Dr. Wang’s site. The data generated at this site appear acceptable in support of the respective indication. The inspection at Dr. Rifkin’s site revealed that three subjects were randomized to the study despite failing to meet minor eligibility criteria.

Statistics
From the Office of Biostatistics review dated 9/13/2019:

The primary evidence for the efficacy of CLS-TA comes from one Phase 3 study (Study CLS1001-301). The primary objective of this study was to evaluate the efficacy of CLS-TA in subjects with ME associated with non-infectious uveitis. The study enrolled 160 adult subjects in 53 sites located across three countries (80 subjects in the Unites States, 70 subjects in India, and 10 subjects in Israel). Eligible subjects were randomized in a 3:2 ratio to receive either 2 unilateral suprachoroidal injections of CLS-TA (96 subjects) or 2 unilateral suprachoroidal injections of a sham Control (64 subjects), administered to the study eye approximately 12 weeks apart. The total duration of the study was approximately 27 weeks.

The primary efficacy endpoint of the study was the proportion of subjects with 15 letters or more improvement from baseline at Week 24. The primary efficacy analysis was conducted using a Cochran-Mantel-Haenszel (CMH) test adjusting for a country subgroup (US+Israel vs. India). This study showed that the proportion of subjects with 15 letters or more improvement from baseline at Week 24 was significantly higher in the CLS-TA arm compared with the Control arm (45% vs 16%; diff (95% CI): 31 (15%, 46%]). In both arms, the main reason for administration of rescue medication was the investigators' judgment that uveitic complications have not improved.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, XIPERE, and granted conditional acceptance on 4/20/2019. They also completed a labeling review dated 4/1/2019.

Labeling discussions with the applicant are deferred until the items cited in the Complete Response letter are addressed.

DMEPA finalized a Human Factors Study Report Review on 10/10/2019. Clearside Biomedical submitted a "SCS Microinjector Usability Study." DMEPA's review of the usability study results identified several missing elements from the human factors (HF) validation study report that impacted their ability to provide a full review.

As noted previously this product is not a combination product under 21 CRF 200.50 - XIPERE (triamcinolone acetonide ophthalmic suspension) for surprachoidal injection with its copackaged microinjector delivery system is regulated as a drug. The Complete Response letter will be requesting actual clinical use data to support the use of the final to-be-marketed SCS Microinjector Delivery System. The configuration should be evaluated by at least three physicians and in at least 30 patients. This actual use clinical data supplants the need for a human factors study.

OPDP
Office of Prescription Drug Promotion (OPDP) did not review the labeling this review cycle. Labeling discussions with the applicant are deferred until the items cited in the Complete Response letter are addressed.

Financial Disclosures

Covered Clinical Studies:
Peachtree CLSlOOl-301
Azalea CLSlOOl-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
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: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study: 2 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)

10. Labeling

Labeling discussions with the applicant are deferred until the items cited in the Complete Response letter are addressed.

11. 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	Original Medical Officer's review Section 6.1. 6.2 and 6.3
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	■ Performance outcome (PerfO)	Visual Acuity
	□ 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	[e.g., Sec 2.1 Analysis of Condition]
	□ 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	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

12. Recommended Comments to the Applicant

The following Complete Response statements should be included in the CR letter:

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 [redacted] (b) (4) Inc. [FEI [redacted] (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::

i. state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

ii. 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).

The following additional comments should be transmitted as an Information Request:

5. The drug product is an ophthalmic suspension. We recommend that for quality control purposes, you develop an *in vitro* drug release method and include the dissolution test in the specifications of the product. We recommend that you submit the development and validation report for the proposed *in vitro* drug release method including justifications and enough data supporting the selection of the dissolution testing conditions (equipment/apparatus, in vitro drug release media, agitation/rotation speed, pH, sink conditions, use of surfactant if applicable, etc.). Please provide data/information supporting the discriminating ability of the method with respect to the most relevant critical material attributes (CMAs, e.g., PSD), critical formulation variables, and critical process parameters (CPPs).

6. Update manufacturing process flow diagram to include all individual process step enhancements described below

(b) (4)

[redacted]

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

WILLIAM M BOYD
10/18/2019 08:57:22 AM

WILEY A CHAMBERS
10/18/2019 02:04:13 PM