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APPLICATION NUMBER:

211950Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	21-1950
Supporting document/s:	SDN001
Applicant's letter date:	12-19-2018
CDER stamp date:	12-19-2018
Product:	Xipere® (triamcinolone acetonide suprachoroidal injectable suspension; 40mg/mL)
Indication:	For the treatment of macular edema associated with uveitis
Applicant:	Clearside Biomedical Inc. (Alpharetta, GA)
Review Division:	Division of Transplant and Ophthalmology Products
Reviewer:	Erin Ruhland, PhD
Supervisor/Team Leader:	Lori Kotch, PhD, DABT
Division Director:	Ozlem Belen, MD
Project Manager:	Michael Puglisi

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1 Executive Summary

1.1 Introduction

The Applicant has submitted a 505(b)(2) NDA application for Xipere® (triamcinolone acetonide suprachoroidal injectable suspension; 40mg/mL) to treat macular edema associated with uveitis. Xipere® is administered via suprachoroidal injection with a proprietary microneedle. The Applicant references Kenalog (NDA 014901) for nonclinical systemic pharmacology and toxicology and has conducted original nonclinical studies to support ocular pharmacology, pharmacokinetics and ocular toxicity. A bridge to Kenalog (NDA 014901) is scientifically justified by a large difference in dose between that approved for Kenalog and the smaller dose proposed for Xipere®.

Triamcinolone acetonide is approved for multiple indications for systemic administration and as an intravitreal injection for treatment of macular edema associated with uveitis. This NDA represents a new formulation and route of administration compared to other formulations approved to date.

1.2 Brief Discussion of Nonclinical Findings

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 and details of the Pharmacology/Toxicology review (if conducted) were not found. Limited information is available in the Kenalog label regarding developmental and reproductive toxicity, genotoxicity and carcinogenesis. The information available was used in the proposed labeling. The labeling for Xipere should be updated as new information becomes available in the future.

1.3 Recommendations

1.3.1 Approvability

- The NDA is approvable from a Pharmacology/Toxicology perspective.

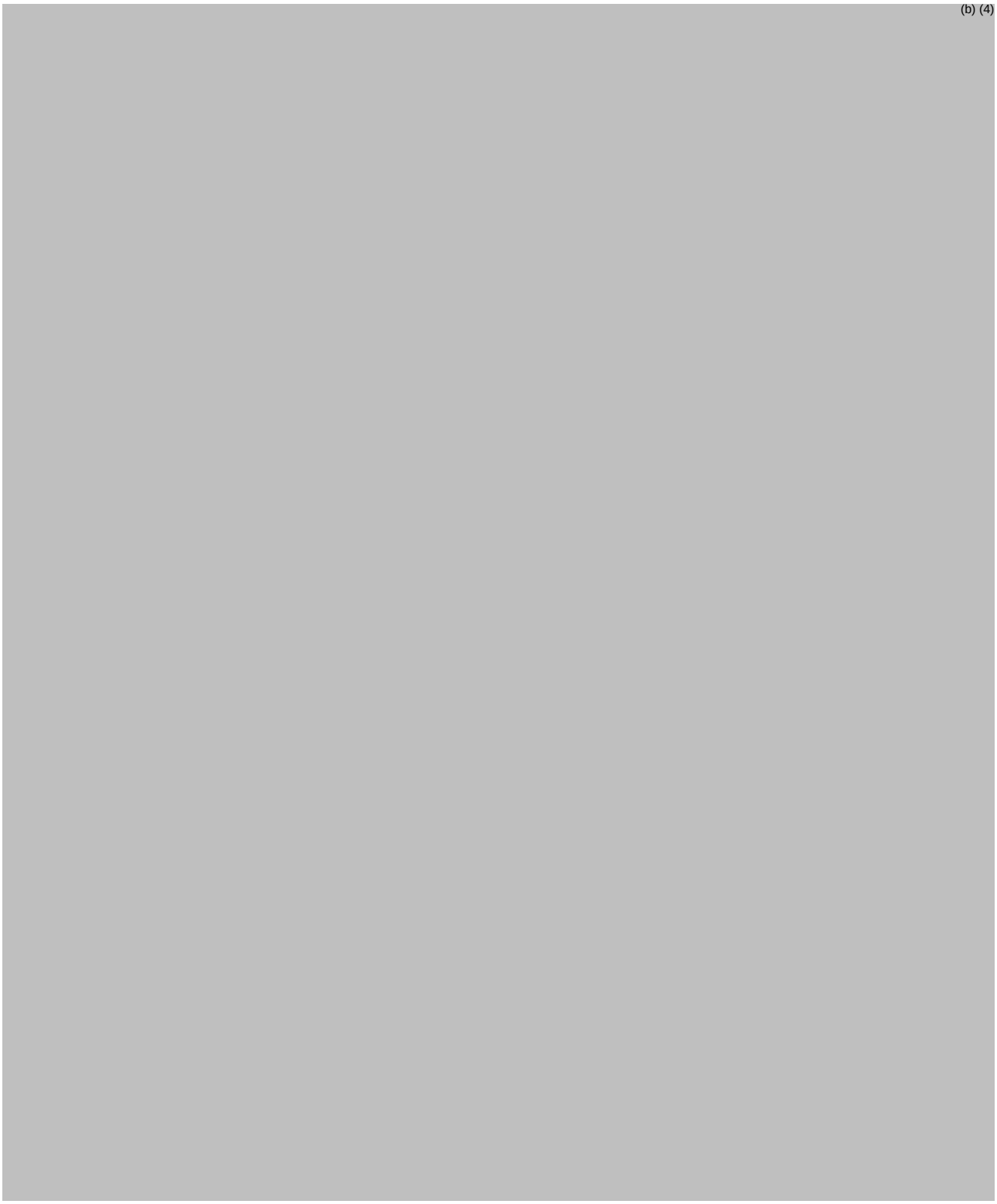
1.3.2 Additional Non Clinical Recommendations

- Labeling should be updated as new information becomes available.

1.3.3 Labeling

1.3.3.1 Applicant's version of the labeling (Sections 8.1, 8.2, 12.1, and 13 only)

(b) (4)



(b) (4)

1.3.3.2 FDA version of the labeling (Sections 8.1, 8.2, 12.1, and 13 only; ~~strikethough~~ font represents suggested deletions and red font represents suggested additions)

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with **XIPERE** in pregnant women to inform drug-associated risks. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids has been shown to produce teratogenicity at clinically relevant doses. ~~There is negligible systemic **XIPERE** exposure following suprachoroidal injection *[see Clinical Pharmacology (12.3)]*.~~

Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (b) (4)

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data

Animal reproduction studies using **XIPERE** have not been conducted. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids to pregnant mice and rabbits during organogenesis has been shown to produce cleft palate, embryofetal death, herniated abdominal viscera, hypoplastic kidneys and craniofacial malformations.

12.1 Mechanism of Action

Triamcinolone acetonide is a synthetic glucocorticoid (b) (4) with ~~immunosuppressive and~~ anti-inflammatory activity. (b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No information is available on the carcinogenic potential of triamcinolone acetonide.

(b) (4)

Mutagenesis

No information is available on the mutagenic potential of triamcinolone acetonide.

(b) (4)

Fertility

No information is available on the effect of triamcinolone acetonide on fertility.

(b) (4)

Reviewer's note: Language in Section 13 proposed by the Applicant contains information derived from (b) (4) The (b) (4) is NOT

referenced by the Applicant for this NDA. This information should be removed from the labeling.

2 Drug Information

2.1 Drug

CAS Registry Number: 76-25-5

Generic Name: triamcinolone acetonide suprachoroidal injectable suspension (40 mg/mL)

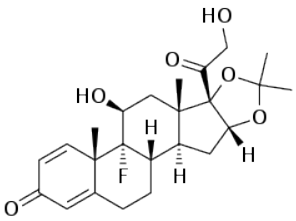
Code Names: CLS-TA, CLS1001

Proposed Brand Name: Xipere®

Chemical Name: 9-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-aceta with acetone.

Molecular Formula/Molecular Weight: $C_{24}H_{31}FO_6$ / 434.50 g/mol

Structure:



Pharmacologic Class: Glucocorticoid; corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 115,683
- DMF (b) (4)
- NDA 014901 [Kenalog; reference listed drug (RLD) for 505(b)2; approved 2-1-1965]

2.3 Drug Formulation

Component	Function	Concentration (% w/v or as noted)
Triamcinolone acetonide	Active ingredient	40 mg/mL
Carboxymethylcellulose sodium	(b) (4)	0.5%
Polysorbate 80		0.02%
Sodium chloride	Isotonicity agent	0.55%
Potassium chloride	(b) (4)	
Calcium chloride dihydrate		
Magnesium chloride hexahydrate		
Sodium acetate trihydrate		
Sodium citrate dihydrate		
(b) (4)		
Hydrochloric acid	pH adjustment	To pH 6.5
Water for injection	(b) (4)	q.s. to 0.9mL / vial

2.4 Comments on Novel Excipients

- None of the excipients are specifically qualified for suprachoroidal injection (since such a category does not exist in current database). The vehicle was not associated with any toxicity in the nonclinical studies.

2.5 Comments on Impurities/Degradants of Concern

- No issues have been identified by CMC.

2.6 Proposed Clinical Population and Dosing Regimen

Xipere® is indicated for the treatment of macular edema associated with uveitis and is administered by suprachoroidal injection using the SCS Microinjector. The recommended dose of Xipere is 4 mg (0.1 mL of 40 mg/mL triamcinolone acetonide suprachoroidal injectable suspension).

Repeat treatment is not discussed in the Dosage and Administration section of the labeling, however in the pivotal Phase 3 trial, Xipere was administered on Day 0 and then again at Week 12 (Clinical Study CLS1001-301).

2.7 Regulatory Background

- Pre-NDA meeting (IND 115,683; SDN099)
  - Scheduled with the Applicant on 8-7-2018
  - The Applicant found the Division of Transplant and Ophthalmology Product's response to be adequate and cancelled the meeting.
  - Nonclinical review:
    - Erin Ruhland, PhD, dated 8-16-2018

        - The Applicant asked whether the nonclinical studies as described are sufficient and adequate to support a 505(b)(2) NDA for CLS-TA for the stated indication.
            - The Agency agreed that the nonclinical data submitted to date appear to provide sufficient support for NDA submission.
            - At the time of the pre-NDA meeting, the Applicant proposed to rely on Triesence (NDA 22-048). NDA 22-048 was itself a 505(b)(2) NDA which referenced Kenalog® (NDA 014901) and (b) (4)
- NDA submission (12-19-2018)
    - At the time of filing this NDA, the Applicant was told to reference only Kenalog (NDA 014901) and the Applicant amended Form 356h.
    - Therefore, any information derived from the (b) (4) cannot be used for approval of Xipere since the Applicant did not reference that NDA in this application.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

- **Primary pharmacodynamics**
    - Study CLS1001-PD-001: Comparison of triamcinolone acetonide administered to the suprachoroidal space (SCS) via microneedles versus intravitreally (IV) in a porcine model of posterior uveitis
    - Study CLS1001-PD-002: Pharmacodynamic study of triamcinolone acetonide administered by microneedle injection into the suprachoroidal space or by intravitreal injection in a LPS-induced model of posterior segment uveitis in New Zealand White rabbits
    - Study CLS1001-PD-003: Pharmacodynamic study of suprachoroidal and intravitreal administration triamcinolone acetonide in a pigmented rabbits endotoxin-induced uveitis model (LPS model)
    - Study CLS1001-PD-004: A pharmacodynamic study of suprachoroidal and intravitreal triamcinolone acetonide in a rabbit model of retinal vascular hyperpermeability
    - Study CLS1001-PD-005: Evaluation of oral prednisone vs. suprachoroidal space (SCS) triamcinolone acetonide (CLS-TA) in a porcine model of posterior uveitis.

Pharmacokinetics

- Absorption
    - CLS1001-ADME-002: A 13-week ocular pharmacokinetic study of a single bilateral suprachoroidal injection of triamcinolone acetonide in rabbits

Toxicology

- Repeat dose toxicity
    - CLS1001-TOX-002: A single and repeat administration toxicity and toxicokinetics study of CLS1001 suprachoroidal injectable suspension in albino rabbits with a 28-day recovery period
- Combination toxicity
    - CLS1001-TOX-004: A single administration toxicity and toxicokinetics study of CLS1001 suprachoroidal injectable suspension and intravitreal Eylea in albino rabbits with a 28-day recovery period

Publications cited

- Abarca, E., *et al*., 2013, "Effect of choroidal perfusion on ocular tissue distribution after intravitreal or suprachoroidal injection in an arterially perfused *ex vivo* pig eye model", *J Ocul Pharmacol Ther*, 29(8): 715-722.
- Abdelkader, H., and R. Alany, 2012, "Controlled and continuous release ocular drug delivery systems: pros and cons", *Curr Drug Deliv*, 9(4): 421 – 430.
- Aref, A., *et al*., 2015, "Incidence, risk factors, and timing of elevated intraocular pressure after intravitreal triamcinolone acetonide injection for macular edema secondary to retinal vein occlusion", *JAMA Ophthalmol*, 133(9): 1022 - 1029.
- ARVO, 2018, "Statement for the use of animals in ophthalmic and vision research",

3.2 Studies Not Reviewed

Pharmacokinetics

- Absorption
    - CLS1001-ADME-001: A 13-week ocular pharmacokinetic study of triamcinolone acetonide administered into the suprachoroidal space of albino rabbits using a microneedle
- Analytical methods and validation reports
    - C93U26611: Triamcinolone acetonide. Validation of an RRLC-Ms/MS method in New Zealand rabbit plasma
    - C93U31711: Triamcinolone acetonide. Development of an HPLC-Ms/MS method (regression) in albino rabbit aqueous humor, lens, iris-ciliary body, vitreous humor, retina, and sclera-choroid

Single dose toxicity

- CLS1001-TOX-001: Acute and 13- and 17-week ocular tolerance and toxicokinetic study following a single bilateral injection of triamcinolone acetonide into the suprachoroidal space of albino rabbits using a microneedle

Reviewer's note: Study CLS1001-TOX-001 was performed with a formulation different from the final proposed clinical formulation.

4 Pharmacology

4.1 Primary Pharmacology

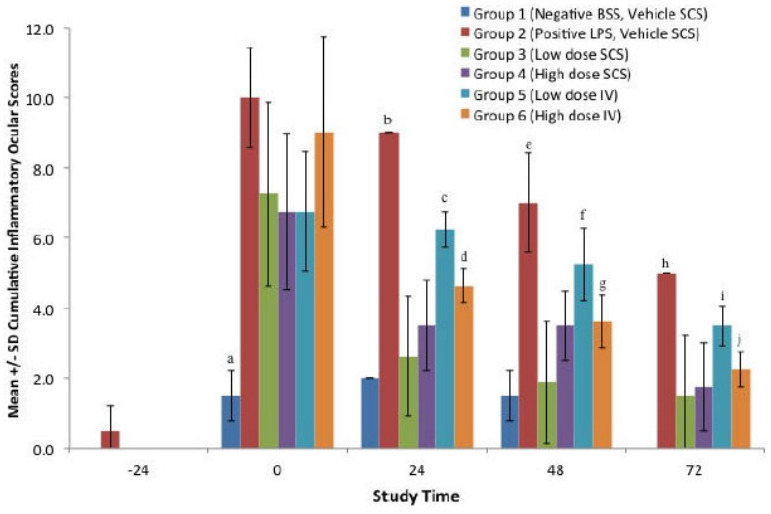
Mechanism of action: Triamcinolone acetonide is a corticosteroid with anti-inflammatory and immunomodulating properties. It binds to and activates the glucocorticoid receptor, leading to activation of anti-inflammatory transcription factors and prevents the synthesis of prostaglandins and leukotrienes.

Study CLS1001-PD-001: Comparison of triamcinolone acetonide administered to the suprachoroidal space (SCS) via microneedles versus intravitreally (IV) in a porcine model of posterior uveitis

This study compared the effects of triamcinolone acetonide (TA; 0.2 or 2 mg in 0.1mL) administered by either suprachoroidal space (SCS) injection or intravitreous injection in a porcine model of acute posterior uveitis (SCS). Weanling pigs were treated in the left eye with LPS twenty-four hours prior to SCS or IV injection of TA or vehicle.

Parameters evaluated included clinical observations (daily); slit lamp biomicroscopy, ocular coherence tomography, electroretinography, wide-field digital fundus photography, and intraocular pressure (IOP). Following sacrifice (72 hours after treatment), the eyes were removed, aqueous and vitreous humor collected and eyes processed for histopathology.

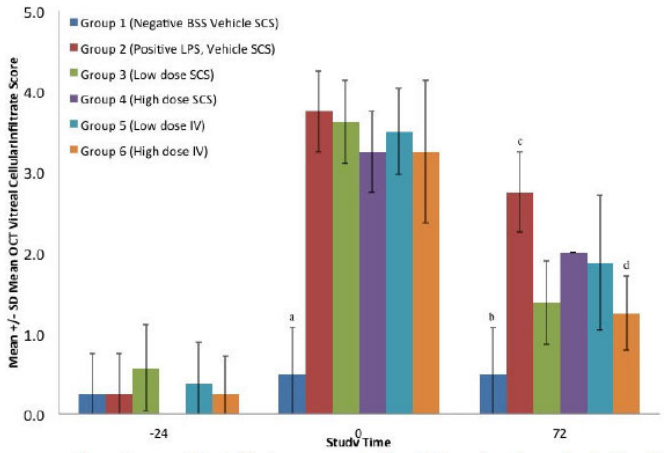
Following intravitreal injection of LPS, mean cumulative inflammatory scores in all eyes elevated. Treatment 24 hours later with TA caused a decrease in inflammatory scores with SCS injection showing a trend towards greater relief of inflammation than intravitreal injection.



Fundus photography revealed substantial cloudiness of the ocular posterior segment 24 hours after LPS injection and attributed to a cellular infiltrate into the vitreous humor and possible changes to the retina. In vehicle treated eyes, the cloudiness appeared to

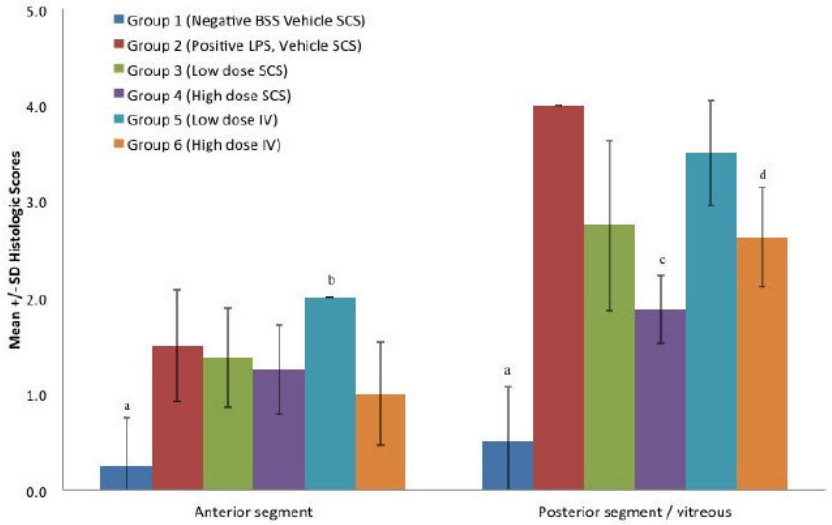
worsen from the 24 to 72 hours. Treatment with 0.2 and 2.0 mg TA into the SCS and 2.0 mg TA IV resulted in fundus images near pre-treatment appearance. However, treatment with 0.2 mg TA IV resulted in images only slightly improved over vehicle treated eyes.

Mean vitreal inflammatory scores increased following LPS injection. Eyes treated with 2.0 mg TA IV had significantly lower mean vitreal inflammatory scores than eyes receiving 2.0 mg TA SCS, but were not different than eyes receiving 0.2 mg TA SCS. Due to a technical error, OCT data from 2 pigs in Group 4 (High Dose, 2.0 mg SCS) was lost and therefore was not included in these results.



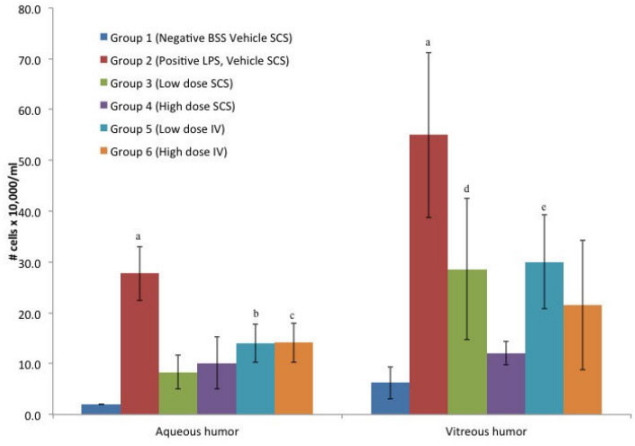
a. Group 1 mean cellular infiltrate scores are significantly lower than Groups 2 – 6 at time 0 (Wilcoxon; $P<0.006$).
b. Group 1 mean cellular infiltrate scores are significantly lower than Groups 2 – 6 at time 72 (Wilcoxon; $P<0.017$)
c. Group 2 mean cellular infiltrate scores are significantly higher than Groups 3, 4, 5, and 6 at time 72 (Wilcoxon; $P<0.034$).
d. Group 6 cellular infiltrate scores are significantly lower than Group 4 at time 72 (Wilcoxon; P-0.025).

No microscopic toxicological changes were attributed to TA treatment. However, all eyes treated with LPS had a cellular infiltrate composed primarily of neutrophils in the anterior uvea, vitreous, and retina. Vehicle SCS eyes had moderate to severe neutrophilic infiltrate in the iris, iris root and iridocorneal angles. Additionally, there was moderate to severe neutrophilic infiltrate in the vitreous body, inner retinal layers, and retinal perivascular cuffing of inflammatory cells. In low dose TA SCS (0.2mg), there was mild neutrophilic infiltrate in the iris, and moderate infiltrate of neutrophils in the inner retinal layers and vitreous. The anterior segment of eyes treated with high dose TA SCS (2mg) was normal, with only an occasional observed inflammation cell. The vitreous had very mild neutrophilic infiltration and very mild inner retinal cellular infiltrate. Upon scoring, TA SCS (2mg) had a significantly lower score than TA IV (2mg).



a. Group 1 mean histologic inflammatory scores are significantly lower than Groups 2 – 6 (Wilcoxon; $P<0.04$)
b. Group 5 mean histologic inflammatory scores are significantly higher than Groups 4 and 6 (Wilcoxon; $P<0.04$)
c. Group 4 mean histologic inflammatory scores are significantly lower than Groups 2, 5, and 6 (Wilcoxon; $P<0.04$)
d. Group 6 mean histologic inflammatory score are significantly lower than Group 2 (Wilcoxon; $P=0.018$)

Following LPS injection mean aqueous humor (AH) inflammatory cell counts increased. Treatment with TA decreased AH cell counts with no significant difference among the different treatment regimens. A similar effect was reported with vitreous cell counts, with high dose SCS injection (2mg) showed the lowest mean score 72 hours following treatment.



No changes in IOP, mean retinal thickness or ERG were attributed to the test article.

Study CLS1001-PD-002: Pharmacodynamic study of triamcinolone acetonide administered by microneedle injection into the suprachoroidal space or by intravitreal injection in a LPS-induced model of posterior segment uveitis in New Zealand White rabbits

This study evaluated the effects of triamcinolone acetonide administered by microneedle injection into the suprachoroidal space (SCS) or by intravitreal injection (IVT) in a LPS-induced model of posterior segment uveitis in New Zealand White rabbits. On Day 1, the right eye of each animal in received a 100 µL suprachoroidal (SCS) injection of the test or control article while another group received a single 100 µL intravitreal (IV) injection of the test article. On Day 6, the right eye of each animal received a subretinal injection of LPS.

Twenty-four hours following LPS induction, all animals demonstrated signs of panuveitis, including fibrin plaque buildup in the anterior chamber and vitreous, retinal and choroidal inflammation, and vitritis. Fibrin plaque buildup in the anterior chamber was lessened in eyes treated with SCS TA compared with control and IV TA treated eyes. Vitritis, aqueous flare, and cellularity were substantially less severe in all TA treated groups compared to control eyes.

Iris vessel dilation and tortuosity was reduced in eyes treated with SCS TA and reduced to a lesser extent in eyes treated with IV TA when compared with the control group.

At the end of the study, fibrous strands, clumps, and plaques were present in the vitreous of all eyes in the control group; where none were observed in TA treated eyes (SCS and IV). Eyes treated with IV TA showed slightly less retinal and choroidal inflammation than eyes treated with SCS TA.

On Day 13, eyes treated with TA (SCS and IV) demonstrated only mild retinochoroiditis which was substantially less severe than in the control eyes.

Study CLS1001-PD-003: Pharmacodynamic study of suprachoroidal and intravitreal administration triamcinolone acetonide in a pigmented rabbits endotoxin-induced uveitis model (LPS model)

This study assessed the effects of suprachoroidal and intravitreal administration of triamcinolone acetonide in a model of endotoxin-induced uveitis in pigmented rabbits.

Triamcinolone acetonide (TA; 2 or 4 mg) was administered once into the right eyes on Day 0, either into the suprachoroidal space (SCS) using the Applicant's proprietary microneedles, or intravitreally (IV) using a standard needle. Vehicle was given by SCS injection. Methylprednisolone (Solumedrol®) was dosed by subconjunctival injection, and was used as a positive control group at the Day 1 time point. Uveitis was induced by an intravitreal administration of 100 ng lipopolysaccharide 1 day or 4 weeks after dose administration.

Pretreatment with 2 mg or 4 mg TA (SCS or IV) at 24 hours before induction of uveitis did not significantly decrease inflammation compared with vehicle as assessed by ocular exams, aqueous humor flare, or aqueous humor protein content. Cellular

infiltration scores in histopathology were reduced via both routes of TA; however, only TA IV was significantly different from control.

Administration of 4 mg TA (SCS or IV) 4 weeks before induction did not significantly decrease inflammation compared with vehicle as observed in ocular exams, aqueous humor flare, or aqueous humor protein content. Cellular infiltration observed by histopathology was reduced in both routes, but only reached statistical significance in the 4 mg TA IV group.

The relative effects of the treatments on the different inflammation endpoints, in comparison to the vehicle group, were graded as follows: -: no effect; +: slight reduction; ++: mild reduction; +++: significant reduction.

Treatment	Endpoints							
	Day 1				Week 4			
	Clinical inflammation scoring (slit lamp)	Aqueous humor flare	Aqueous humor protein content	Cellular infiltration scoring (histology)	Clinical inflammation scoring (slit lamp)	Aqueous humor flare	Aqueous humor protein content	Cellular infiltration scoring (histology)
4 mg/eye SCS TA	-	-	-	+	-	-	-	-
2 mg/eye SCS TA	-	-	-	+	NA	NA	NA	NA
4 mg/eye IVT TA	++	-	+	+++	-	-	-	+++
2 mg/eye IVT TA	+	+	++	+++	NA	NA	NA	NA
5 mg/eye subconjunctival Solumedrol®	+++	+	-	+++	NA	NA	NA	NA

Study CLS1001-PD-004: A pharmacodynamic study of suprachoroidal and intravitreal triamcinolone acetonide in a rabbit model of retinal vascular hyperpermeability

This study compared the effects of SCS TA and IV TA on retinal vascular leakage in a rabbit model of blood-retinal barrier (BRB) breakdown induced by intravitreal VEGF.

Rabbits were treated of SCS TA (4 mg in 0.1mL) with Applicant's proprietary microneedle or IV TA (2 mg in 0.05mL) once into the right eye on Day 0. BRB breakdown was induced by an intravitreal injection of recombinant human vascular endothelial growth factor (rhVEGF) into the right eye at 1 month after dosing. Retinal vascular leakage was documented using a systemic fluorescein injection and retinal angiography at 47 hours following VEGF induction, and was quantified 48 hours after VEGF induction using ocular fluorophotometry. The same animals were rechallenged with VEGF at Month 2, and the same parameters were assessed.

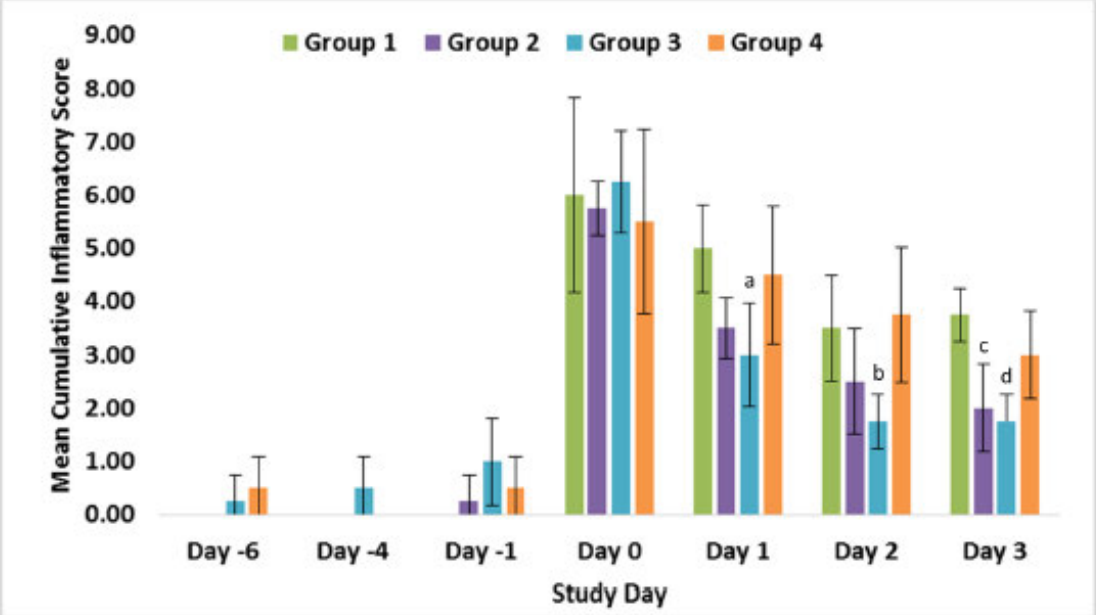
Following the Month 1 VEGF challenge, placebo animals displayed a marked level of retinal vascular leakage and fluorescein content in the vitreoretinal compartment. Animals that received suprachoroidal TA displayed a 60% reduction in vascular leakage when compared with placebo. Animals administered IV TA displayed an 87% reduction in vascular leakage when compared with placebo. Similar results were shown following the Month 2 VEGF rechallenge.

Study CLS1001-PD-005: Evaluation of oral prednisone vs. suprachoroidal space (SCS) triamcinolone acetonide (CLS-TA) in a porcine model of posterior uveitis.

This study compared the effects of SCS TA and oral prednisone in a porcine model of acute posterior uveitis.

Twenty-four hours after the induction of acute posterior uveitis by intravitreal lipopolysaccharide injection, pigs were treated with SCS TA (CLS1001 formulation 2mg) or oral prednisone (1 mg/kg/day or 0.1 mg/kg/day; repeated every 24 hours until euthanasia).

Following induction with LPS, mean inflammation scores for all groups were markedly increased compared with pretreatment scores. Thereafter, mean inflammation scores generally decreased in all groups over the following 3 days. On Days 1 and 2 (24 and 48 hours after initiation of treatment, respectively), only SCS-TA had mean cumulative inflammation scores significantly lower than placebo treated eyes. By 72 hours after initiation of treatment, animals treated with 1 mg/kg oral prednisone SCS-TA had significantly lower mean cumulative inflammation scores than placebo treated eyes.

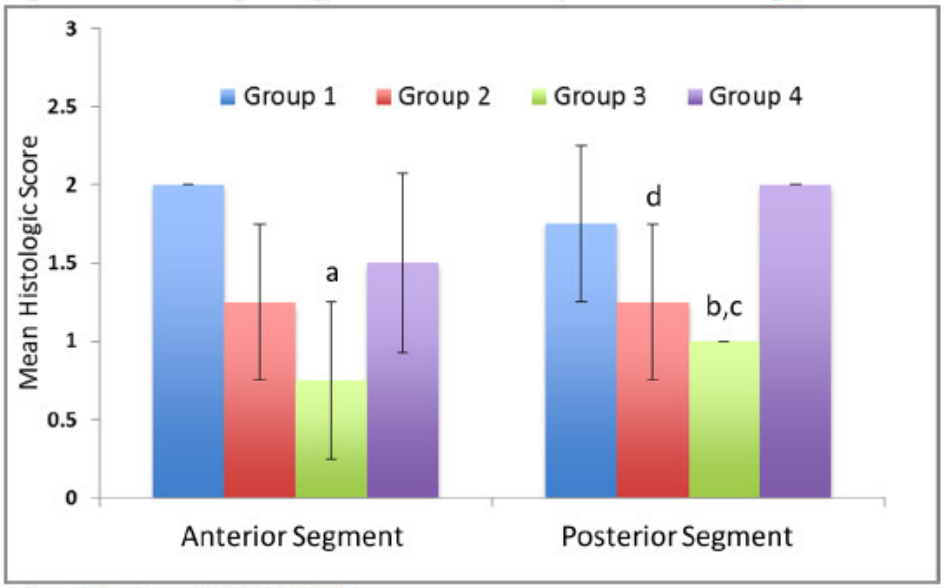


Group 1: Negative control (LPS / BSS SCS)
Group 2: Oral high dose prednisone (LPS / Prednisone1 mg/kg/day PO); c: Group 2 mean cumulative inflammation score on Day 3 was significantly lower than Group 1 ($p < 0.034$).
Group 3: CLS-TA (LPS / 2 mg CLS-TA) a: Group 3 mean cumulative inflammation score on Day 1 was significantly lower than Group 1 ($p = 0.04$); b: Group 3 mean cumulative inflammation score on Day 2 was significantly lower than Group 1 ($p = 0.023$); d: Group 3 mean cumulative inflammation score on Day 3 was significantly lower than Group 1 ($p < 0.034$).
Group 4: Oral low dose prednisone (LPS / Prednisone 0.1 mg/kg/day PO)

Ocular histopathology revealed no signs of inflammation or degeneration associated with SCS injections. TA crystals were visible in the subchoroidal space in each eye

treated with SCS-TA. There was no evidence of test-article related toxicity of the ocular anterior or posterior segment in any group.

Mean histologic inflammation scores of the anterior segment of eyes with SCS-TA were significantly lower than eyes treated with placebo. Mean inflammation scores of the posterior segment of eyes treated with CLS-TA were significantly lower than eyes treated with placebo and eyes treated with low dose oral prednisone.



Group 1: Negative control (LPS / BSS SCS)
Group 2: Oral high dose prednisone (LPS / Prednisone, 1 mg/kg/day PO); d: Group 2 mean histopathology inflammation score was significantly lower than Group 4 ($p < 0.013$), but was not significantly lower than Group 1.
Group 3: CLS-TA (LPS / 2 mg CLS-TA); a: Group 3 mean histopathology inflammation score was significantly lower than Group 1 ($p = 0.018$); b: Group 3 mean histopathology inflammation score was significantly lower than Group 1 ($p < 0.013$); c: Group 3 mean histopathology inflammation score was significantly lower than Group 4 ($p < 0.013$).
Group 4: Oral Low dose prednisone (LPS / Prednisone, 0.1 mg/kg/day PO)

4.3 Safety Pharmacology

Sponsor to rely on 505(b)(2) reference to Kenalog (NDA 014901).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

CLS1001-ADME-002: A 13-week ocular pharmacokinetic study of a single bilateral suprachoroidal injection of triamcinolone acetonide in rabbits

This study evaluated the ocular tissue distribution and systemic pharmacokinetics of two formulations of triamcinolone acetonide (TA) for 13 weeks following a single bilateral suprachoroidal administration using Clearside microneedles. Female New Zealand white rabbits were given bilateral suprachoroidal injections, (4 mg/eye in 0.1mL) of a marketed formulation of triamcinolone acetonide (40 mg/mL TA) or CLS1001 suspension (40 mg/mL TA). Two animals/group/time point were euthanized on Study

Days 1 (24 hours postdose), 15, 29, 63, and 91. Blood and ocular tissues [retina, sclera/choroid/RPE, aqueous humor, vitreous humor, and all remaining ocular tissues in the eye globe were collected and analyzed for TA.

The total TA mass balance in the ocular tissues analyzed at 24 hours post-dose (Day 1) was 96.3% following the suprachoroidal injection of the commercial suspension and 98.8% following the suprachoroidal injection of CLS1001. By 91 days post-dose, only 0.00403% and 0.0444% of the administered TA dose following suprachoroidal injection of the commercial formulation and CLS1001, respectively, was recovered in the ocular tissues. Most of the mass of TA was recovered at the dose site (sclera-choroid-RPE).

The results were similar for both formulations of TA. For CLS1001, C_{max} in plasma was 4.22 ng/mL at 24 hours post-dose and declined to 1.26 ng/mL by Day 29. By Days 58 and 63 plasma levels were below the limit of quantitation (LLOQ=0.5ng/mL). The highest concentrations of TA were found at the site of dosing, the sclera-choroid-RPE at 24 hours post-dose with the elimination half-life of 5.95 days from this tissue. TA was present in this tissue over the entire 91-day study. There was limited exposure in the vitreous humor following suprachoroidal injection, with maximum mean concentrations of 281 ng/mL on Study Day 15 . Concentrations in the aqueous humor were BLQ at all times assayed (LLOQ=10ng/mL).

Pharmacokinetics and ocular distribution of CLS1001:

Matrix		Collection Time Point (Day) 1	15	29	58[a]	63	91
		Concentration of Triamcinolone Acetonide (ng/mL)					
Plasma	Mean	4.22	1.77	1.26	0.00	0.00	0.00
Aqueous Humor	Mean	0.00	0.00	0.00	0.00	0.00	0.00
	SD	0.00	0.00	0.00	NA	0.00	0.00
Retina	Mean	42800	96800	129000	17700	6350	32.6
	SD	63800	56500	142000	NA	6980	38.5
Sclera-Choroid-RPE	Mean	11600000	7710000	3270000	231000	236000	6210
	SD	635000	1150000	2140000	NA	92300	5360
Vitreous humor	Mean	148	281	258	0.00	92	0.00
	SD	173	441	317	NA	184	0.00

NA Not applicable.
SD Standard deviation.
a Mean represents one value.

6 General Toxicology

6.1 Repeat dose Toxicity

Study title: A single and repeat administration toxicity and toxicokinetics study of CLS1001 suprachoroidal injectable suspension in albino rabbits with a 13-week recovery period

Study no.:	CLS1001-TOX-002 ((b) (4) C93U27612)
Study report location:	\\cdsesub1\evsprod\nda211950\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\cls1001-tox-002\cls1001-tox-002.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2-15-2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Triamcinolone acetonide; Batch#SLBB0079V; 99% purity

Methods

Doses:	4 mg
Frequency of dosing:	Day 0 and Day 90
Route of administration:	Suprachoroidal injection
Dose volume:	0.1mL
Formulation/Vehicle:	Clinical vehicle*
Species/Strain:	Rabbit / New Zealand White
Number/Sex/Group:	4/sex/group (terminal necropsy: Day 180; interim sacrifices on Days 1 and 90; n=4/sex/time point).
Age:	2 – 3 months
Weight:	2.3 – 2.8 kg
Unique study design:	Single dose arm: Sacrifice performed 24 hours following dose administration Repeat dose arm: Interim sacrifice on Day 90; Terminal sacrifice on Day 180
Deviation from study protocol:	External / subconjunctival reflux of test article occurred in some animals (see below) This deviation was not expected to affect integrity or interpretability of results

*The sodium chloride content of the vehicle and test article was (b) (4) % while the proposed clinical formulation has a sodium chloride content of 0.55%. All other excipients in the test article were formulated at the same concentration as the proposed clinical formulation.

Study Deviation

External or subconjunctival reflux, as well as issues associated with flow of test item or vehicle through the microneedle, were documented (summarized in table below). This reflux was noted as slight (4% of the animals), moderate (92%) or severe (4%) for the CLS1001 group and it was noted as moderate (98%) or severe (2%) for the vehicle

group, and was similar across the treatment groups. Therefore, the actual volume injected was likely slightly less than the theoretical volume.

Day of injection	Day 0		Day 90	
Treatment groups	External reflux	Subconjunctival reflux	External reflux	Subconjunctival reflux
CLS1001	17/47* = 36%	30/47* = 64%	2/16 = 13%	13/16 = 81%
Vehicle	0/48 = 0%	44/48 = 92%	0/16 = 0%	15/16 = 94%
Total	17/95 = 18%	74/95 = 78%	2/32 = 18%	28/32 = 78%

Observations and Results

Mortality

- No animals died prior to scheduled sacrifice.

Clinical Signs

- No changes in clinical signs attributed to the test article.

Body Weights

- No changes in body weight attributed to the test article.

Feed Consumption

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy (slit lamp biomicroscopy / fundoscopy; scored using modified McDonald-Shadduck scale)

The following observations were recorded in both vehicle and test article treated animals with similar incidence and severity. The findings are not considered related to the test article.

- Conjunctival congestion (slight)
- Conjunctival discharge (slight)
- Corneal staining (slight)
- Corneal scratching (trace)
- Fibrin in anterior vitreous
- Lens defects (considered anatomic variations)

Intraocular pressure

- Increased intraocular pressure
    - Day 7 - Day 89 or 90:

        - Mean IOP of the CLS1001-treated group was slightly increased when compared with the vehicle group (approximately 2-3 mmHg corresponding to an approximately 10% increase). This slight increase was statistically significant.
    - Day 97 - Day 118 (7 and 28 days after the second suprachoroidal injection, respectively):
        - Mean IOP of the CLS1001 group was slightly increased compared with the vehicle group (approximately 4-5 mmHg corresponding to an approximately 18% increase). This slight increase was statistically significant.
    - Days 28 - 104, the mean IOP of the vehicle group was decreased when compared with baseline or the CLS1001 group.

Central corneal thickness

- No effects on central corneal thickness attributed to the test article. On Day 1, a slight decrease (~10%) in the central corneal thickness from baseline was observed in both the CLS1001 and vehicle groups. Corneal thickness recovered by Day 89 observation.

ERG

- No changes in ERG parameters (amplitude / implicit time) attributed to the vehicle or test article.

Hematology

- No changes in hematological parameters attributed to the test article or vehicle.

Clinical Chemistry

- No changes in clinical chemistry parameters attributed to the test article or vehicle.

Gross Pathology

- No changes in macroscopic observations attributed to the test article or vehicle.

Histopathology

Adequate Battery: Eye only (included optic nerve)

Peer Review: No

Histological Findings:

- On Day 1, microscopic ocular findings included the presence of conjunctival extravasated lymphocytes, areas of de-epithelialized cornea due to scratching, and presence of test item in the suprachoroidal space with inflammatory cells. Of these findings, conjunctival extravasated lymphocytes, corneal de-

epithelialization and inflammatory cells in suprachoroidal space were attributed to the suprachoroidal injection procedure with possible enhancement by CLS1001, as they were noted across all groups with a higher incidence in the CLS1001 group.

- No microscopic findings were observed 13 weeks after the first or second suprachoroidal injections (Day 90 and Day 180, respectively).

Toxicokinetics

Day of Injection	Dose (mg TA/eye)	Mean C_{max} (ng/mL)	Mean T_{max} (day)	Mean AUC (ng*day/mL)	Mean $t_{1/2}$ (day)
1	4	11.6	1	331[a]	14.0
90	4	11.4	91	299[b]	18.2
Additional Information: Also presented are the data from the second dose (Day 90).					

$AUC_{time\ 1\ to\ time\ 2}$ = area under the curve in ng/g or ng/mL of structure X day calculated using the trapezoidal rule; CLS-TA = triamcinolone acetonide injectable suspension, 40 mg/mL; F = female; CMC = carboxymethylcellulose; LC-MS/MS = liquid chromatography tandem mass spectrometry; M = male; NZW = New Zealand White; PS80 = polysorbate 80; $t_{½}$ = elimination phase half-life; T_{max} = time to maximum observed concentration

[a] $AUC_{Days\ 1\text{-}90}$

[b] $AUC_{Days\ 91\text{-}180}$

Dosing Solution Analysis

- Test item was stable over the course of the treatment period ([(b) (4)]% nominal).

Study title: A single administration toxicity and toxicokinetics study of CLS1001 suprachoroidal injectable suspension and intravitreal Eylea in Albino rabbits with a 28-day recovery period

Study no.:	CLS1001-TOX-004 ([(b) (4)] C93U28013)
Study report location:	\\cdsesub1\evsprod\nda211950\0001\m4\42-stud-rep\423-tox\4231-single-dose-tox\cls1001-tox-004\cls1001-tox-004.pdf
Conducting laboratory and location:	[(b) (4)]
Date of study initiation:	12-20-2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Triamcinolone acetonide; Batch#FG-13-0174; 99.3% purity

Methods

Doses:	4 mg administered 30 minutes following Eylea injection (see below)
Frequency of dosing:	Day 0
Route of administration:	Suprachoroidal injection
Dose volume:	0.1mL
Formulation/Vehicle:	Clinical vehicle
Species/Strain:	Rabbit / New Zealand White
Number/Sex/Group:	6/sex/group (terminal necropsy: Day 29; interim sacrifices on Days 1; n=4/sex/time point).
Age:	2 – 3 months
Weight:	2.0 – 2.5 kg
Unique study design:	Eylea® (aflibercept; 2mg) administered as 0.05mL intravitreal injection on Day 0, Time 0.
Deviation from study protocol:	External / subconjunctival reflux of test article occurred in some animals (see below) This deviation was not expected to affect integrity or interpretability of results

Study Deviation

External or subconjunctival reflux were documented (summarized in table below). This reflux was noted as slight except for 2 animals injected with vehicle into the suprachoroidal space which showed more significant reflux. Therefore, the actual volume injected was likely slightly less than the theoretical volume.

Group No.	*Treatment in Both Eyes on Day 0*		External Reflux	Subconjunctival Reflux
	Intravitreal Injection (50 µL)	Suprachoroidal Injection (100 µL)		
1 and 5	Vehicle 2	CLS1001	2/38 = 5%	5/38 = 13%
2 and 6	Eylea	Vehicle 1	5/40 = 13%	12/40 = 30%
3 and 7*	Eylea	CLS1001	1/40 = 3%	11/40 = 28%
4 and 8*	Vehicle 2	Vehicle 1	2/42 = 5%	5/42 = 12%
Total			10/160 = 6%	32/160 = 20%

Observations and Results

Mortality

- Several animals died prior to scheduled sacrifice. None of the deaths were attributed to the test article.
  - Vehicle IV + CLS1001 SCS:
    - Animal M#59
      - Euthanized moribund on Day 1 with gastric ulcer
  - Eylea IV + Vehicle SCS

        - Animals F#53 and F#56
            - Found dead during anesthesia for ERG evaluations (Day 28 and Day 1, respectively)
    - Eylea IV + CLS1001 SCS
        - Animal M#20
            - Found dead during anesthesia for ERG evaluations (Day 1)
        - Animals M#68 and F#71
            - Found dead during anesthesia for ERG evaluations (Day 28)
        - Animal F#70
            - Euthanized moribund with eye infection due to injection procedure

Clinical Signs

- No changes in clinical signs attributed to the test article.

Body Weights

- No changes in body weight attributed to the test article.

Feed Consumption

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy (slit lamp biomicroscopy / fundoscopy; scored using modified McDonald-Shadduck scale)

- Vehicle IV / CLS1001 SCS:
    - Conjunctival congestion (slight and transient)
    - Inflammation (slight, Day 1)
    - Moderate anterior chamber inflammation (score of 2; Day 1)
    - Corneal fluorescein staining (slight to severe, Days 1 – 4, Week 4.
        - Applicant considers response not to be related to treatment and possibly related to ERG measurement performed before observation (recording electrodes in contact with cornea).
    - Vitreous (loss of transparency; Day 1)

- Eylea / Vehicle SCS:
    - Conjunctival congestion (slight and transient; Day 1)
    - Corneal opacity (slight)
    - Corneal staining (slight to severe: Day 1 - Day 4; slight: Week 4)
    - Fibrin in the anterior part of the vitreous (Day 1)
    - Inflammation in the anterior chamber (Week 2 to Week 4)
    - Iritis (slight to moderate)
    - Vitreous (loss of transparency)
    - Haze in the aqueous humor (Weeks 2 and 4)

  - One rabbit (F#38) showed a circle in the lens in both eyes on Day 4, the nucleus of the lens abnormally visible associated with a slight default of the lens in the anterior part on Day 7, and a white cluster in the anterior chamber on Week 2. Moreover, for this animal, a pannus was observed from Week 3 to Week 4 in both eyes. No mydriasis was observed in both eyes from Week 2 to Week 4 for this animal.

- Eylea IV / CLS1001 SCS:
  - Conjunctival congestion (slight and transient; Day 1)
  - Conjunctival swelling (slight; Day 1)
  - Discharge (slight; Day 4)
  - Corneal staining (light to severe)

- Vehicle IVT / Vehicle SCS:
  - Conjunctival congestion (slight and transient; Day 1 - 4, Week 2,
  - Swelling (slight; Day 1)
  - Corneal opacity (slight)
  - Fibrin in the anterior part of the vitreous (Day 4 - 7)
  - For animal F#78,

Intraocular pressure

- No changes in intraocular pressure were attributed to the vehicle, test article or combination with Eylea.

ERG

- No changes in ERG parameters (amplitude / implicit time) attributed to the vehicle, test article, or combination with Eylea.

Gross Pathology

- No changes in macroscopic observations attributed to the test article.

Histopathology

Adequate Battery: Eye only (included optic nerve)

Peer Review: No

Histological Findings:

  - No adverse histological findings attributed to the test article or combination with Eylea.

Toxicokinetics:

Treatment	Dose (mg CLS-TA/eye)	Mean C_{max} (ng/mL)	Mean T_{max} (day)	Mean $AUC_{Days\ 1\text{-}28/29}$ (ng*day/mL)	Mean $t_{1/2}$ (day)
aflibercept (EYLEA) Vehicle/CLS-TA	4	11.34	1	143	4.6
aflibercept (EYLEA)/ CLS-TA	4	8.44	1	131	9.2

7 Genetic Toxicology

The Applicant relies on NDA 014901. No information is available in the labeling.

8 Carcinogenicity

The Applicant relies on NDA 014901. No information is available in the labeling.

9 Reproductive and Developmental Toxicology

Limited information is available in the Kenalog label and a record of review of those studies conducted for approval was not found.

11 Integrated Summary and Safety Evaluation

The Applicant has conducted nonclinical studies which support 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 repeat administration of the test article administered as a 4 mg suprachoroidal injection on Days 1 and 90.

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). The highest suggested doses in the labeling are 100 mg per day or higher. These doses far exceed the dose proposed for Xipere and therefore a scientific bridge is justified based on dose comparison.

Kenalog® was approved in 1965 and details of the Pharmacology/Toxicology review (if recorded) were not found. Limited information is available in the Kenalog label regarding developmental and reproductive toxicity, genotoxicity and carcinogenesis. The limited information which was available was used in the proposed labeling. The labeling for Xipere should be updated if new information becomes available in the future.

12 Appendix/Attachments

Current approved labeling for Kenalog (NDA 014901):
Reviewer's note: The current labeling for the RLD, Kenalog, is not in PLR or PLLR format. The following sections were found with relevant nonclinical data:

Pregnancy

Teratogenic Effects

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

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