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APPLICATION NUMBER:

211950Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA(s): 211950/SDN-0001	Submission Date(s): 12/19/2018
Drug/Strengths	XIPERE / Triamcinolone Acetonide 40mg/mL injectable suspension
OCP Reviewer	Kunyi Wu, PharmD
OCP Team Leader	Philip M Colangelo, PharmD, PhD
OCP Division	DCP IV
OND Division	DTOP
Applicant	Clearside Biomedical Inc.
Dosage Regimen	The recommended dose of XIPERE is 4 mg (0.1 mL of 40 mg/mL triamcinolone acetonide suprachoroidal injectable suspension).
Indication(s)	Treatment of macular edema (ME) associated with non-infectious uveitis in adults

1. EXECUTIVE SUMMARY

Clearside Biomedical Inc. (Applicant) has submitted a 505(b)(2) NDA for XIPERE, triamcinolone acetonide injectable suspension 40 mg/mL (CLS-TA), for the treatment of macular edema (ME) associated with non-infectious uveitis via suprachoroidal administration. The proposed dosage regimen and route of administration of XIPERE is 4 mg (0.1 mL of 40 mg/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.

2. RECOMMENDATIONS

The Clinical Pharmacology information provided by the Applicant in support of NDA 211950 for XIPERE (triamcinolone acetonide injectable suspension 40 mg/mL) for suprachoroidal administration is acceptable. The Clinical Pharmacology review team recommends approval of this NDA.

Labeling Recommendations
Reviewer's recommended revisions appear in underlined **bold** font, and/or strikethrough.

12.3 Pharmacokinetics

Plasma **triamcinolone acetonide** concentrations were **evaluated** (b) (4) **in** 19 patients (b) (4) dosing of 4 mg **XIPERE** at Day 0 and Week 12, (b) (4). Plasma triamcinolone acetonide concentrations in all 19 patients were below 100 pg/mL at (b) (4) **(range <10 pg/mL (** (b) (4) **of the assay) to 88.9 pg/mL)**, with the exception of one patient (b) (4) with a value of 243.4 pg/mL **prior to the** (b) (4) second dose at Week 12.

Bioanalytical Assay Summary:

- The bioanalytical analyses for Studies CLS1001-301 and CLS1001-302 were conducted by in (b) (4)
- Validated LC/MS method was used to determine TA concentrations in human plasma. Please refer to Table 1 below for the summary of the analytical method.

Table 1. Summary of Analytical Methods for Quantification of Triamcinolone Acetonide in Human Plasma (Adapted from Summary in the Analytical Method Validation Report Project # 135104AIVR)

Validation Parameters	**Results**
Linearity:	$r^2 \geq 0.9931$
Calibration Curve Range:	10.00 to 5000.00 pg/mL
Between-Run Accuracy and Precision:	Biases: -3.28 to 0.82% CV: 3.78 to 12.53%
Within-Run Accuracy and Precision (Hamilton):	Biases: -1.07 to 1.85% CV: 2.48 to 11.68%
Within-Run Accuracy and Precision (Janus):	Biases: -2.61 to 2.56% CV: 2.62 to 9.38%
Lower Limit of Quantitation (LLOQ):	Signal to noise ratio at 10.00 pg/mL: 38
Freeze and Thaw Stability in Matrix:	4 cycles at -20ºC and -80ºC
Short-Term Stability of Analyte in Matrix:	23h15min at room temperature 19h24min at 4°C
Long-Term Stability of Analyte in Matrix:	5, 103, 201 and 435 days at -20ºC 5, 103 and 435 days at -80ºC

Reviewer comment: The bioanalytical assay is acceptable.

Individual Study Summary

STUDY NO. CLS1001-301

STUDY TITLE:
PEACHTREE: A Phase 3, Randomized, Masked, Controlled Clinical Trial to Study the Safety and Efficacy of Triamcinolone Acetonide Injectable Suspension (CLS-TA) for the Treatment of Subjects with Macular Edema Associated with Non-Infectious Uveitis

STUDY DESIGN and PK RESULTS:
One-hundred-sixty (160) subjects were randomized in a 3:2 ratio with 96 subjects randomized to the Active (suprachoroidal CLS-TA) treatment group and 64 subjects randomized to the Control (Sham suprachoroidal procedure) treatment group.

Eligible subjects were randomized to receive 2 unilateral suprachoroidal injections of 4 mg CLS-TA per injection administered to the study eye or 2 unilateral sham injection procedures administered to the study eye, approximately 12 weeks apart (Visit 2 and Visit 5). Follow-up visits were conducted monthly up to 24 weeks (Visit 8). Subjects had a final evaluation conducted at 24 weeks (Visit 8) following initial randomization.

PK samples were collected for a total of twenty-one (21) patients at pre-dose (Visit 2) in Active treatment group. Seventeen (17) of these twenty-one patients with no quantifiable plasma TA concentrations (< 10 pg/mL) at the pre-dose (Visit 2) in the Active treatment group were included for PK evaluation with a plasma PK sample to be taken at randomization, 4 weeks post dose (Visit 3), just prior to administration of the second dose at Week 12 (Visit 5), and at Week 24 (Visit 8). The results are summarized in Table 2 below.

Table 2. Summary Statistics for Triamcinolone Acetonide (TA) Plasma Concentrations by Visit / Week in Study CLS1001-301 (adapted from Table 2 in Summary of Clinical Pharmacology Studies)

Visit/ Timepoint	Number of Patients	Number of Patients with TA Concentrations Above LLOQ	Mean (pg/mL)	Min (pg/mL)	Max (pg/mL)
Visit 2 Pre-dose	17	0	0	0	0
Visit 3 Week 4	17	11	52.9	0	88.9
Visit 5 Week 12	17	5	67.3	0	243.4
Visit 8 Week 24	17	7	25.8	0	47.0

Notes: LLOQ = Lower Limit of Quantitation = 10.0 pg/mL

Based on the results shown in Table 2, systemic exposures to TA following 4 mg suprachoroidal administration were ≤ 243.4 pg/mL at any timepoint across the 24-week study. The Sponsor also reported that for the 23 measurable PK samples, 96% (22/23) samples were below 100 pg/mL, the exception being one subject with a value of 243.4 pg/ml at Week 12 (Visit 5).

Reviewer Comment: The reviewer agrees with the Appicant's conclusion / interpretation of the PK results from this study.

STUDY NO. CLS1001-302 (Safety Only)

STUDY TITLE: Open-Label Safety Study of Suprachoroidal Triamcinolone Acetonide Injectable Suspension in Patients with Noninfectious Uveitis

STUDY DESIGN and PK RESULTS:
Thirty-eight (38) patients were enrolled and were assessed over a maximum of 29 weeks. Patients received 2 unilateral suprachoroidal injections of 4 mg CLS-TA per injection administered to the study eye, approximately 12 weeks apart (Visit 2 and Visit 5). Follow-up visits were conducted every 4 weeks up to 24 weeks (Visit 8). Patients had a final evaluation conducted at 24 weeks (Visit 8) following first treatment.

PK samples were collected for a total of seven (7) patients at pre-dose (Visit 2), and of these 7, two (2) patients were BLQ (< 10pg/mL). The Applicant stated measurable concentrations of TA at pre-dose may be due to the previous use of TA. The plasma concentrations of TA for these two patients are summarized in Table 3 below.

Table 3. Summary Statistics for Triamcinolone Acetonide (TA) Plasma Concentrations by Visit / Week at Pre-dose in Safety Study CLS1001-302 (Adapted from Table 3 in Summary of Clinical Pharmacology Studies)

Visit/ Timepoint	Number of Patients	Mean (pg/mL)	Min (pg/mL)	Max (pg/mL)
VISIT 2 Pre-dose	2	(b) (6)		
VISIT 3 Week 4	2			
VISIT 5 Week 12	2			
VISIT 8 Week 24	2			

Notes: LLOQ = Lower Limit of Quantitation= 10.0 pg/mL

Based on the results shown in Table 3, the systemic exposures to TA after a 4 mg suprachoroidal administration were <50 pg/mL in these two patients at any timepoint across the 24-week study.

Reviewer Comment:

- *The reviewer agrees with the Appicant's concusion / interpretation of the PK results from this study.*

COMPARISON OF SYSTEMIC TA EXPOSURES RESULTING FROM XIPERE ADMINISTRATION TO TA ADMINISTRATION VIA THE INTRAVITREAL OR ORAL ROUTES

- According to Degenring and Jonas[1],TA serum concentrations in 18 of 20 patients after an intravitreal dose of 20 to 25 mg were not detectable with the lower limit of detection of <500 pg/mL over an average of 13 days post-injection. The serum TA levels for the other two patients were 500 pg/mL and 800 pg/mL, respectively.
- According to Derendorf et al.[2], after an oral dose of 5mg TA, the mean peak plasma TA concentration is 10,500 pg/mL.
- Most plasma TA concentrations in all patients (18 of 19) were below 100 pg/mL at all timepoints in Studies CLS1001-301 and CLS1001-302, except for one patient in Study CLS1001-301, who had a pre-dose TA concentration of 243.4 pg/mL at Week 12.
- The TA plasma concentrations after suprachoroidal injection of XIPERE are substantially lower than the TA concentrations after taking an oral dose of 5mg TA.

OVERALL REVIEWER CONCLUSION:

Plasma concentrations of TA from 19 patients (17 patients from Study CLS1001-301 and 2 patients from Study CLS1001-302) were evaluated. Based on the results shown in Table 2 and Table 3, plasma TA concentrations in all 19 patients were below 100 pg/mL at all timepoints across the studies, except for one patient with a concentration of 243.4 pg/mL prior to the second dose at Week 12.

[1] Degenring R and Jonas J. Serum Levels of Triamcinolone Acetonide After Intravitreal Injection. American Journal of Ophthalmology June 2004: 1142-43

[2] Derendorf H et al. Pharmacokinetics of Triamcinolone Acetonide After Intravenous, Oral, and Inhaled Administration. J Clin Pharmacol 1995; 35:302-305

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