CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208912Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	208912
Link to EDR	EDR Link
Submission Date	04/12/2017
Submission Type	Standard
Brand Name	Dexycu®
Generic Name	Dexamethasone
Dosage Form and Strength	Suspension; 9% w/w
Route of Administration	Intraocular injection
Proposed Indication	For the treatment of postoperative inflammation.
Applicant	Icon Bioscience, Inc.
Associated IND	IND 105562
OCP Review Team	Abhay Joshi, Ph.D. DCP IV Clinical Pharmacology Reviewer; Philip Colangelo Pharm. D., Ph.D. DCP IV Clinical Pharmacology Team Leader

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1. EXECUTIVE SUMMARY

This submission is a 505(b)(2) NDA for the drug product: Dexycu®, which is 9% w/w dexamethasone sterile suspension for intraocular administration. The proposed indication for Dexycu, also known as IBI-10090, is for the treatment of postoperative inflammation and the proposed dosing is a single 5 µL intraocular injection, which contains 517 µg dexamethasone, into the (b) (4) of the eye after completion of cataract surgery.

The efficacy and safety of IBI-10090 in patients undergoing cataract surgery were evaluated in five clinical studies that included three Phase 2 studies and two Phase 3 studies. The supportive Clinical Pharmacology information for this submission is from the two Phase 3 studies, i.e., Study C13-04 and Study C15-01, that assessed the pharmacokinetic properties of IBI-10090 in a subgroup of patients in each study. The primary focus of the review is the extent of systemic exposure to dexamethasone from the proposed IBI-10090 formulation reported in Study C13-04 and Study C15-01.

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information provided by the Applicant in NDA 208912 and recommends approval of this NDA.

The Reviewer's proposed label changes to the Applicant proposed labeling listed in Section 2.4 will be forwarded to the sponsor.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Clinical Pharmacokinetics

The proposed dosing for IBI-10090 is primarily being supported by the efficacy data from one Phase 2 study: C11-01 and two Phase 3 studies: C13-04 and C15-01. With respect to the Clinical Pharmacology pertinent assessments, the systemic exposure to dexamethasone from IBI-10090 was evaluated in two Phase 3 studies mentioned above, i.e., Study C13-04 and Study C15-01.

Study C13-04 was a Phase 3 study that assessed the efficacy and safety of the two different strengths of IBI-10090 formulation given as a single 5 µL intraocular injection. Specifically, the two IBI-10090 formulations with the strength of 68.4 µg/µL and 103.4 µg/µL dexamethasone were administered as a single 5 µL intraocular injection, which is equivalent to the total dose of 342 µg and 517 µg dexamethasone, respectively. In addition to the efficacy and safety evaluations, blood samples were collected from a subgroup of 25 patients for pharmacokinetic (PK) analysis. Systemic exposure to dexamethasone was assessed based on the dexamethasone concentrations in plasma determined with a validated HLPC-MS/MS assay with the lower limit of quantification of 0.05 ng/mL. Overall, the PK related findings indicated that the systemic exposure to dexamethasone was low and approximately dose proportional. All patients had quantifiable dexamethasone plasma concentrations on post-surgery Day 1. The mean C_{max}, AUC_{0-t}, and T_{max} estimates were 0.380 ng/mL, 1.028 day*ng/mL, and 1.301 day in the 342 µg treatment group and 0.536 ng/mL, 2.210 day*ng/mL, and 1.016 day in the 517 µg treatment

group, respectively. Dexamethasone plasma concentrations declined over time in both the treatment groups with very few patients showing quantifiable concentrations on post-surgery Day 15.

Study C15-01 was also a Phase 3 study that assessed the safety of a single 5 µL intraocular injection of the IBI-10090 formulation that contained 517 µg dexamethasone (i.e., the final clinical formulation). Similar to Study C13-04, blood samples were collected from a subgroup of 13 patients and dexamethasone systemic exposure was assessed based on the observed dexamethasone concentrations in plasma. All patients had quantifiable dexamethasone plasma concentrations on post-surgery Day 1. The mean C_{max}, AUC_{0-t}, and T_{max} estimates were 0.735 ng/mL, 4.642 day*ng/mL, and 1 day, respectively. Dexamethasone plasma concentrations declined over time with very few patients showing quantifiable concentrations on post-surgery Day 30.

The observed systemic exposure to dexamethasone in Studies C15-01 and C13-04 from a single 5 µL intraocular injection of IBI-10090 (517 µg dexamethasone) is expected to be lower than the exposure from an intravenous and or intramuscular dexamethasone dose of 0.5 to 9 mg/day that is recommended as an initial dose in the Dexamethasone Sodium Phosphate Injection labeling.

2.2.Dosing and Therapeutic Individualization

Clinical Pharmacology study(ies) assessing dosing or therapeutic individualization was not conducted. The proposed drug product is to be administered locally at the intended site of action, i.e., via intraocular injection, and the provided Clinical Pharmacology information on the systemic exposure is not of importance in informing dosing or therapeutic individualization.

2.3.Outstanding Issues

From a Clinical Pharmacology perspective, there are no outstanding issues with this application.

2.4.Summary of Labeling Recommendations

The Reviewer proposed label addition to the Applicant proposed labeling are in *blue underlined* text and suggested deletions are marked as ~~*red strike out*~~ text.

Systemic exposure to dexamethasone was evaluated in a subgroup of patients enrolled in two studies (n=25 for the first study and n=13 for the second study). The patients received a single intraocular injection of DEXYCU containing 342 mcg or 517 mcg of dexamethasone at the end of cataract surgery and blood samples were collected prior to surgery and at several time points post-surgery between Day 1 and up to Day 30. In the first study, the dexamethasone plasma concentrations on post-surgery Day 1 ranged from 0.09 to 0.86 ng/mL and from 0.07 to 1.16 ng/mL following administration of DEXYCU 342 mcg and 517 mcg, respectively. In the second study, dexamethasone plasma concentrations on post-surgery Day 1 ranged from 0.349 to 2.79 ng/mL following administration of DEXYCU 517 mcg. In both the studies, dexamethasone plasma concentrations declined over time and very few patients had quantifiable dexamethasone plasma concentrations at the final time point of sampling (Day 15 or Day 30).

(b) (4)

3. APPENDICES

3.1.Summary of Bioanalytical Method Validation

Dexamethasone concentrations in human plasma were determined using a validated HPLC-MS-MS procedure. Selected information from the method validation report entitled *RBOR2: Quantitation of Dexamethasone in Human Plasma via HPLC with MS/MS Detection* and from the bio-analytical reports for Study C13-04 and Study C15-01 is provided in **Table 1**.

Table 1: Bio-analytical Method Summary

Information from report RBOR2 (February 2014 - March/April 2014)	
Linearity	r ≥ 0.9979
Calibration curve range	0.05 to 50 ng/mL
QC concentrations	0.0500 (QC1), 0.400, 1.50 (QC3), 6.00, and 38.0 (QC5) ng/mL
Between-run accuracy	0 to 3 % difference from theoretical
Between-run precision	5 to 6 %
Within-run accuracy	-4 to 10 % difference from theoretical
Within-run precision	1 to 7 %
Lower limit of quantitation	0.05 ng/mL
Recovery of analyte	73 to 80 % (QC1, QC3, and QC5)
Recovery of internal standard	72 to 80 %
Stability after five freeze/thaw cycles -20°C	-5 to 0 % difference from theoretical, QC1 and QC5
Stability after five freeze/thaw cycles -70°C	-4 to 1% difference from theoretical, QC1 and QC5
Stability in thawed matrix at room temperature for 25 Hours	-9 to 4 % difference from theoretical, QC1 and QC5
Post-preparative extract stability 2 to 8 °C for 80 Hours	-4 to -2 % difference from theoretical, QC1 and QC5
Stability in frozen matrix (-20°C) at Day 9	-1 to 9 % difference from theoretical, QC1 and QC5
Stability in frozen matrix (-20°C) at Day 7	2 to 8 % difference from theoretical, QC1 and QC5
Maximum reported duration of analyte stability in frozen matrix, i.e., at after 401 days at -20 °C	-5 and 12% difference from theoretical, QC1 and QC5[1]

[1] This information was reported in Method Validation Report Addendum 1, LCMSC 328.1, Project RBOR3

Information from bio-analytical report for Study C13-04 (May 2015)	
Calibration curve range	0.05 to 50 ng/mL
QC concentrations	0.0500 (QC1), 0.400 (QC2), 1.50 (QC3), 6.00 (QC4), and 38.0 (QC5) ng/mL
Within-run accuracy	-6 to 0 % difference from theoretical, QC1 to QC5
Within-run precision	*Not calculated (n=2)*
Lower limit of quantitation	0.05 ng/mL
Sample receipt and analysis	121 plasma samples were received between 26 February 2014 and 02 July 2014. The samples were stored frozen at -20 °C. Samples were analyzed on 26 June 2014.
Information from bio-analytical report for Study C15-01 (November 2016)	
Calibration curve range	0.05 to 50 ng/mL
QC concentrations	0.0500 (QC1), 1.50 (QC2), and 38.0 (QC3) ng/mL
Within-run accuracy	-4 to 8 % difference from theoretical, QC1 to QC3
Within-run precision	2 to 8%
Lower limit of quantitation	0.05 ng/mL
Sample receipt and analysis	52 plasma samples were received between 7 June 2016 and 25 August 2016. The samples were stored frozen at -20 °C. Samples were analyzed between 02 August 2016 and 09 September 2016.

Reviewer's Assessment:

The validation and performance of the bioanalytical assay is acceptable.

3.2.Pharmacokinetic Data

Study C13-04: Pharmacokinetic Report

Title:

A Phase 3, Prospective, Randomized, Double-masked, Placebo-controlled, Parallel-design, Multicenter Study to Evaluate the Efficacy and Safety of IBI-10090 for the Treatment of Inflammation Associated with Cataract Surgery (Study Report: Link, PK Report: Link, Bio-analytical Report: Link)

Trial Information:

Study center[2]:	**Bio-analytical Laboratory**
Hull Eye Center 1739 West Ave J Lancaster, CA 93534	(b) (4)

[2] Of the blood samples that were collected for PK assessments from a sub-group of patients enrolled in Study C13-04, most (>80%) appear to be from Hull Eye Center. However, the exact information in this regard could not be located.

Primary Objective:

To evaluate the efficacy of a single 5 µL intraocular injection of the two IBI-10090 formulations with the strength of 68.4 µg/µL and 103.4 µg/µL dexamethasone, i.e., the total dose of 342 µg and 517 µg dexamethasone, in the treatment of inflammation associated with cataract surgery.

Test Preparation:

IBI-10090 was provided in vials containing suspensions of two different strengths for intraocular injection: 68.4 µg/µL dexamethasone (Lot#10090-002-13I001) and 103.4 µg/µL dexamethasone (Lot#10090-005-13J001). Placebo vial contained vehicle (vehicle Lot#10090-003-13I001).

Study Design:

This was a prospective, randomized, double-masked, placebo-controlled, parallel-design, multicenter study in patients who were undergoing cataract surgery. Patients meeting all inclusion and no exclusion criteria were randomized to one of the following three treatment groups to receive a single 5 µL injection of the assigned treatment in the anterior chamber of eye immediately following their cataract surgery:

- IBI-10090, 68.4 µg/µL dexamethasone, equivalent dexamethasone dose: 342 µg
- IBI-10090, 103.4 µg/µL dexamethasone, equivalent dexamethasone dose: 517 µg
- Placebo/vehicle, 0 µg/µL dexamethasone, equivalent dexamethasone dose: 0 µg

Safety and efficacy evaluations were performed on postoperative day (POD) 1, 3, 8, 15, 30, and 90.

Efficacy was assessed by slit lamp biomicroscopy to evaluate the anterior chamber cells clearing and grade, anterior chamber flare clearing and grade, and anterior chamber cells and flare clearing and grade. Safety was assessed by recording adverse events, intraocular pressure, best-corrected visual acuity, corneal endothelial cell density, other eye examination outcomes, the use of concomitant medications, and concurrent procedures.

For the assessment of IBI-10090 pharmacokinetics (PK), blood samples were withdrawn from a subset of patients, i.e., a PK sub-group, on the day of surgery (or any time during Screening, but before surgery), POD 1, POD 3, POD 8, and POD 15.

Demographic Information:

From the total of 395 patients who were enrolled, 158 patients were assigned to the 342 µg IBI-10090 treatment group, 157 patients were assigned to the 517 µg IBI-10090 treatment group, and 80 patients were assigned to the placebo group (2:2:1 ratio). One patient assigned to the 517 µg IBI-10090 treatment group did not receive treatment and was excluded from the intent-to-treat, safety, and per-protocol analysis sets. The PK sub-group consisted 25 patients, from whom blood samples were withdrawn for the pharmacokinetic (PK) assessments. The selected demographic information from the patients in the PK sub-group is summarized in **Table 1**.

Table 1: Reported Demographic Information for the PK Sub-Group Patients

Treatment Arm	Average Age (±SD)	N (Male, Female)
Placebo	74(±8)	4 (2,2)
IBI-10090,342 µg	70(±6)	13 (7,6)
IBI-10090,517 µg	69(±9)	8 (4,4)
	Total	25 (13,12)

Sample Collection and Bioanalysis:

From each of the 25 patients in the PK sub-group, five blood samples were planned to be collected, i.e., on Day 0 (prior to administration of study drug), and on POD Day 1, 3, 8, and 15.

In total, 121 plasma samples were analyzed to determine dexamethasone concentrations using a validated assay method, with the quantification range of 0.05 to 50 ng/mL. The Reviewer could not locate information on the missing four of the planned 125 samples. Review of the information from the submitted bio-analytical report is provided in **Table 2.** Additional details are summarized in Section 3.1.

Table 2: Review Summary of the Bio-Analytical Method

Study Samples Analysis	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable	☒ Yes ☐ No
	Chromatograms provided (At least 5% of total samples from all subjects)	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Overall performance acceptable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected	☐ Yes ☒ No

Pharmacokinetic Measures

Reported estimates: C_{max}, T_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$

Safety and Efficacy Results:

Please refer to the Medical Officer's review.

Pharmacokinetic Results:

Dexamethasone concentrations in plasma were below limit of detection in all the samples from the placebo group patients (N = 4). The mean dexamethasone concentrations in plasma declined from 0.394 ng/mL to 0.010 ng/mL between POD 1 and POD 15 for the 342 µg treatment group and from 0.536 ng/mL to 0.023 ng/mL between POD 1 and POD 15 for the 517 µg treatment group. The mean plasma concentration time-curves from both the treatment groups are presented in **Figure 1**. Dose dependent increase in systemic exposure to dexamethasone was observed. On POD 1, all patients in both the treatment groups had quantifiable dexamethasone concentrations in plasma, with mean C_{max},

AUC_{0-t}, and T_{max} estimates of 0.380 ng/mL, 1.028 day*ng/mL, and 1.301 day in the 342 µg treatment group and 0.536 ng/mL, 2.210 day*ng/mL, and 1.016 day in the 517 µg treatment group, respectively (**Table 3**).

Figure 1: Dexamethasone Concentration-Time Profiles After Intraocular Administration of IBI-10090: Mean (± SD) Concentrations on Linear and Semi-Logarithmic Scales *(source: Report C-13-PK, Figure 1)*

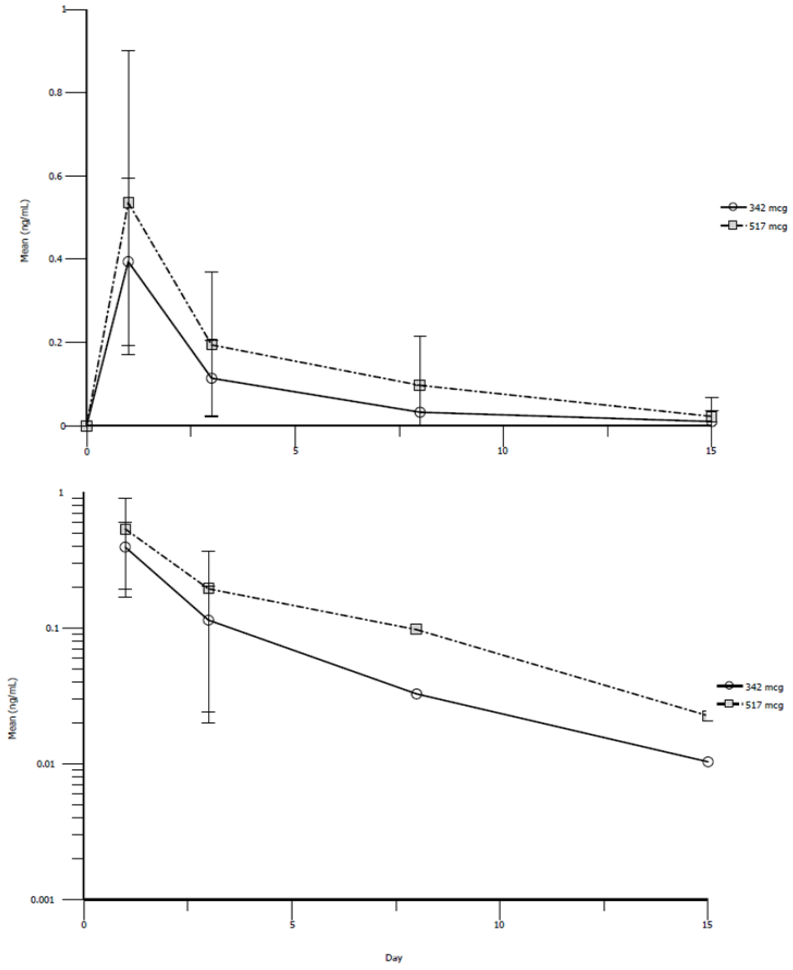


Table 3: Pharmacokinetic Parameters Estimates Following Intraocular Administration of IBI-10090

(source: Adapted from report C-13-PK, Table 2)

	Placebo (N=4)	IBI-10090 342 mcg (N=13)	IBI-10090 517 mcg (N=8)	Total (N=25)
C_{max} (ng/mL)				
n	4	13	8	25
Mean (SD)	0.000 (0.0000)	0.380 (0.1997)	0.536 (0.3652)	0.369 (0.3014)
Median	0.000	0.376	0.504	0.376
Min, Max	0.00, 0.00	0.09, 0.86	0.07, 1.16	0.00, 1.16
T_{max} (day)				
n	0	13	8	21
Mean (SD)		1.301 (0.8167)	1.016 (0.1399)	1.192 (0.6536)
Median		1.092	1.026	1.061
Min, Max		0.82, 3.99	0.72, 1.18	0.72, 3.99
AUC_{0-t} (day*ng/mL)				
n	4	13	8	25
Mean (SD)	0.000 (0.0000)	1.028 (0.7651)	2.210 (2.1245)	1.242 (1.4843)
Median	0.000	1.126	1.992	1.126
Min, Max	0.00, 0.00	0.04, 3.00	0.02, 6.79	0.00, 6.79
AUC_{0-inf} (day*ng/mL)				
n	0	0	2	2
Mean (SD)			5.605 (3.0400)	5.605 (3.0400)
Median			5.605	5.605
Min, Max			3.46, 7.75	3.46, 7.75

AUC = area under the concentration time curve, C_{max} = Maximum concentration observed, AUC_{0-t} = AUC up to the last measurable concentration, AUC_{0-inf} = AUC curve to infinite time, t_{max} = Time at which the maximum concentration (C_{max}) is observed.

Sponsor's Conclusion:

- Dexamethasone plasma concentrations indicated that systemic exposure is low after intraocular injection of IBI-10090 in both the active treatment groups.
- Systemic exposure to dexamethasone after intraocular injection was approximately dose proportional.
- Dexamethasone plasma concentrations declined over time in both the active treatment groups with very few patients showing quantifiable concentrations at POD 15. These data are in accordance with in vitro drug release profiles of IBI-10090 indicating an initial rapid release of drug from the formulation, [redacted] (b) (4)

Reviewer's Assessment:

The Sponsor's conclusions are reasonable; however, the provided data are not adequate to support the claim [redacted] (b) (4) *e*

[redacted] (b) (4)

Also, please see the Reviewer's Assessment under Study C15-01: Pharmacokinetic Report for additional notes related to the observed systemic exposure to dexamethasone.

Study C15-01: Pharmacokinetic Report

Title:

A Phase 3, Prospective, Randomized, Open Label, Parallel-design, Multicenter Study to Evaluate the Safety of IBI-10090 for the Treatment of Inflammation Associated with Cataract Surgery (Study Report: Link, PK Report: Link, Bio-analytical Report: Link)

Trial Information:

Study center:	**Bio-analytical Laboratory**
1. Barranca Surgery Center 3500 Barranca Parkway, Suite 130 Irvine, CA 92606 2. Cincinnati Eye Institute Ambulatory Surgery Center 1945 CEI Drive Cincinnati, OH 45242 3. Mark B. Kislinger, MD, PhD, Inc. 210 S. Grand Ave. Glendora, CA 91741	[redacted] (b) (4)

Primary Objective:

To evaluate the safety of a single 5 µL intraocular injection of IBI-10090 in the treatment of inflammation associated with cataract surgery.

Test Preparation:

IBI-10090 was provided in vials containing suspensions for intraocular injection containing 103.4 µg/µL dexamethasone (Lot#504-501-003).

Study Design:

This was a prospective, randomized, open-label, parallel-design, multicenter study in patients ≥ 40 years of age undergoing cataract surgery. Patients meeting all inclusion and no exclusion criteria were randomized to one of two treatment groups to receive either a single 5 µL intraocular injection of IBI-10090 containing 517 µg dexamethasone at the conclusion of cataract surgery, or three weeks of treatment with prednisolone acetate ophthalmic suspension 1% eye drops (one drop , four times daily [QID] for three weeks).

For safety assessments, patients were followed for 90 days after the day of surgery to record treatment-emergent adverse events, complete ophthalmic examinations in the study eye and use of concomitant medications and concurrent procedures. The use of ocular topical corticosteroids in the study eye was not allowed and was not to be initiated through Day 30, unless the pre-specified rescue criteria were met.

For the assessment of IBI-10090 pharmacokinetics (PK), blood samples were collected from a subset of patients, a PK sub-group, on the day of surgery (or any time during Screening, but before surgery), POD 1, POD 8, and POD 30.

Demographic Information:

From the total of 194 patients who were enrolled, 181 received study drug and were included in the intent-to-treat and safety analysis sets. From 181 patients, 126 patients were enrolled in the IBI-10090 treatment group and 55 were enrolled in the prednisolone treatment group. The per-protocol population included 162 patients; specifically, 112 in the IBI-10090 treatment group and 55 in the prednisolone treatment group. The PK sub-group consisted 13 patients from the IBI-10090 treatment group that included five male patients and eight female patients. The average age (±SD) of the patients in the PK sub-group was 68 (±11) years.

Sample Collection and Bioanalysis:

From 13 patients in the PK sub-group, four blood samples were planned to be collected from each patient on Day 0 (prior to administration of study drug), and on POD Day 1, 8, and 30.

In total, 52 plasma samples were analyzed to determine dexamethasone concentrations using a validated assay method, with the quantification range of 0.05 to 50 ng/mL. Review of the information from the submitted bio-analytical report is provided in **Table 1**. Additional details are summarized in Section 3.1.

Table 1: Review Summary of the Bio-Analytical Method

Study Samples Analysis	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable	☒ Yes ☐ No
	Chromatograms provided (At least 5% of total samples of all subjects)	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Overall performance acceptable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected	☐ Yes ☒ No

Pharmacokinetic Measures

Reported estimates: C_{max}, T_{max}, $AUC_{(0-t)}$, and AUC_{all}

Safety and Efficacy Results:

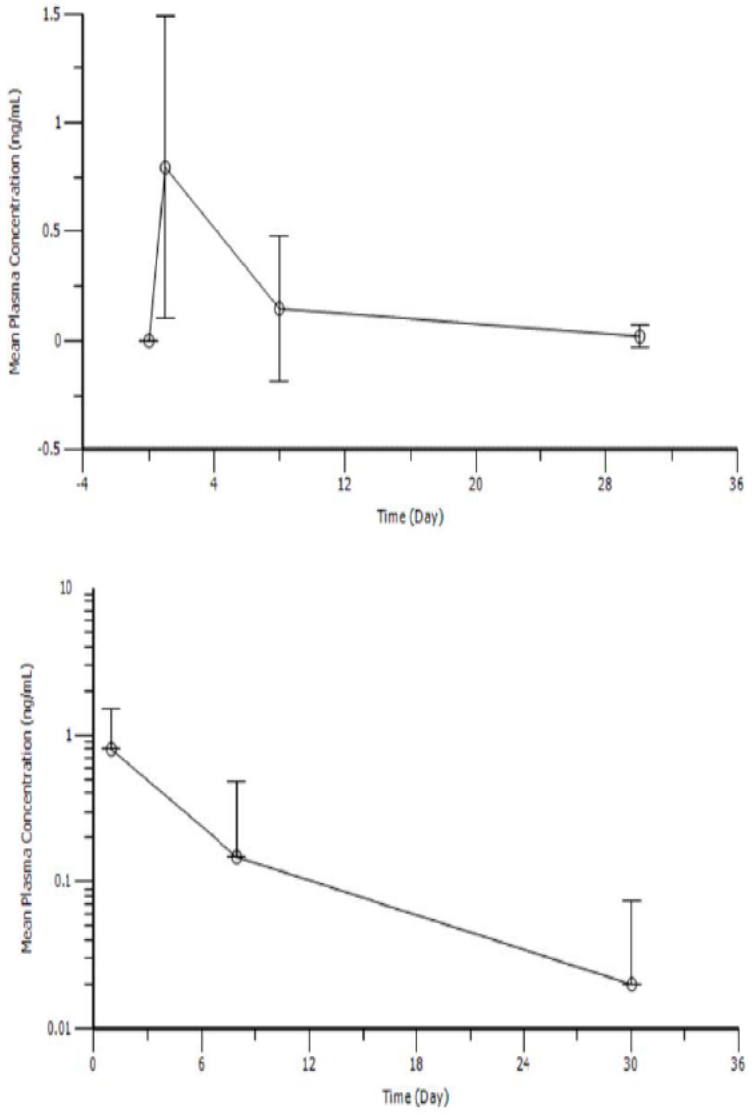
Please refer to the Medical Officer's review.

Pharmacokinetic Results:

On POD 1, dexamethasone concentrations in plasma were above the limit of detection in all the samples from all the patients in the IBI-10090 treatment group. Specifically, dexamethasone concentrations in plasma ranged from 0.349 to 2.79 ng/mL on POD 1. However, POD 30 samples from only 2 patients showed quantifiable dexamethasone concentrations, which ranged from 0.0748 to 0.187 ng/mL. Overall mean of the dexamethasone concentrations in plasma declined from 0.796 ng/mL to 0.0201 ng/mL between POD 1 and POD 30. The mean plasma concentration time-curves from the IBI-10090 treatment group is presented in **Figure 1**. The mean estimates for C_{max}, AUC_{0-t}, and T_{max} were 0.735 ng/mL, 4.64 day*ng/mL, and 1 day in the IBI-10090 treatment group (**Table 2**).

Even though, PK estimates were derived from the dexamethasone plasma concentration data from all 13 patients it is noteworthy that five patients, i.e., patients (b) (6) had measurable dexamethasone levels at pre-dose (Day 0). For four of the patients, i.e., patients 07-(b) (6), it was determined later from bioanalytical and clinical investigation that the Day 0 samples were collected after surgery and not prior to surgery as per protocol. For patient (b) (6), an exact cause could not be assigned despite bioanalytical and clinical investigation. The Day 0 concentrations data for the five patients mentioned above were excluded from the dataset. These data were excluded from the summary data for AUC_{all} and AUC_{0-t}. In addition, one patient, i.e., Patient (b) (6), did not have sufficient volume in the POD 1 blood sample to allow for bioanalysis.

Figure 1: Dexamethasone Concentration-Time Profiles After Intraocular Administration of IBI-10090: Mean (± SD) Concentrations on Linear and Semi-Logarithmic Scales *(source: PK Report for IBI Study C15-01, Figure 1)*



Note: Only +SD is displayed for the semi-log scale figure.
Values at Surgery Day 0 for patients (b) (6) were excluded from the mean plots due to quantifiable plasma dexamethasone concentrations.

Table 2: Pharmacokinetic Parameters Estimates Following Intraocular Administration of IBI-10090

(source: PK Report for IBI Study C15-01, Table 2)

	IBI-10090 517 mcg (N=13)
C_{max} (ng/mL)	
n	13
Mean (SD)	0.735 (0.701)
Median	0.468
Min, Max	0.000, 2.79
T_{max} (day)	
n	12
Mean (SD)	1.00 (0.000)
Median	1.00
Min, Max	1.00, 1.00
AUC_{0-t} (day*ng/mL)	
n	8
Mean (SD)	4.64 (10.1)
Median	0.249
Min, Max	0.175, 29.5
AUC_{all} (day*ng/mL)	
n	8
Mean (SD)	6.03 (9.56)
Median	2.56
Min, Max	1.52, 29.5

Note: AUC = area under the concentration time curve, AUC_{0-t} = AUC up to the last measurable concentration, AUC_{all} = AUC up to the last concentration, C_{max} = Maximum concentration observed, t_{max} = Time at which the maximum concentration (C_{max}) is observed.
Data from patients (b) (6) were excluded from the summary statistics for AUC_{0-t} and AUC_{all} due to quantifiable plasma dexamethasone concentrations at Surgery Day 0. These Surgery Day 0 data were excluded from AUC calculations and the resulting AUCs were therefore underestimated.

Sponsor's Conclusion:

- Dexamethasone plasma concentrations indicated that systemic exposure is low after intraocular injection of IBI-10090.
- Dexamethasone plasma concentrations declined over time with very few patients showing quantifiable concentrations at POD 30.

Reviewer's Assessment:

The Sponsor's conclusions are reasonable.

The maximum observed dexamethasone concentration in plasma following an intraocular administration of a single 5 µL intraocular injection of the IBI-10090 formulation, which contains 517 µg dexamethasone, was 2.79 ng/mL in this study, i.e., Study C15-01, and was 1.16 ng/mL in Study C13-04.

The observed systemic exposure to dexamethasone in Studies C15-01 and C13-04 from a single 5 µL intraocular injection of IBI-10090 (517 µg dexamethasone) is expected to be lower than the exposure from an intravenous and or intramuscular dexamethasone dose of 0.5 to 9 mg/day that is recommended as an initial dose in the Dexamethasone Sodium Phosphate Injection labeling.

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/s/

ABHAY JOSHI
01/11/2018

PHILIP M COLANGELO
01/11/2018