

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
208912Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	N
Application Number(s)	NDA 208912 IND 105562
Priority or Standard	Standard
Submit Date(s)	April 12, 2017
Received Date(s)	April 12, 2017
PDUFA Goal Date	February 12, 2018
Division / Office	DTOP/OAP
Reviewer Name(s)	Jennifer Harris, M.D.
Review Completion Date	October 5, 2017
Established Name	Dexamethasone intraocular suspension, 9%
(Proposed) Trade Name	Dexycu
Therapeutic Class	corticosteroid
Applicant	Icon Bioscience, Inc.
Formulation(s)	Intraocular injection
Dosing Regimen	
Indication(s)	Treatment of postoperative inflammation
Intended Population(s)	Patients who have undergone cataract surgery

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 208-912 Dexycu (dexamethasone intraocular suspension) is recommended for approval for the treatment of postoperative inflammation.

1.2 Risk Benefit Assessment

The clinical trials submitted in support of this NDA demonstrates that dexamethasone intraocular suspension 342 mcg and 517 mcg are both superior to placebo for the clearance of anterior chamber cells after cataract surgery. This superiority starts on day 3 after surgery and continues through post op day 30.

Overall, there were no dose dependent adverse events noted between the 342 mcg and 527 mcg doses of IBI-10090. The rate and types of adverse events were similar between the groups and were consistent with those expected after cataract surgery and with corticosteroid treatment. While corneal endothelial cell loss was the most frequent ocular SAE in patients treated with IBI-10090, the rate of corneal endothelial cell loss was similar between placebo and the 517mcg (to be marketed dose) treatment group. The rate was low (approx. 1.5%) and the number of cells loss in each group is not clinically meaningful (i.e., ECD remains in the normal range).

In addition, the rates of corneal edema and intraocular pressure were similar between the 517 mcg treatment group and placebo group. Both occurred at approximately 3-4 times higher than those subjects treated with prednisolone drops. The higher rates of corneal edema and IOP reported during the trial did not have an effect on the final visual acuity or IOP status of the subjects in any of the treatment groups.

IBI-10090 has a favorable risk benefit profile in the treatment of post-operative inflammation after cataract surgery.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Risk evaluation and mitigation strategies are not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarket requirements/commitments are not recommended.

2 Introduction and Regulatory Background

2.1 Product Information

IBI-10090 (dexamethasone intraocular suspension, 9%) is a, biodegradable, one-time drug-delivery product for the provision of dexamethasone in the eye of cataract surgery patients. The active ingredient in IBI-10090 is dexamethasone. IBI-10090, when deposited by intraocular injection in the (b) (4), forms a sphere and provides for a slow-release of the (b) (4) dexamethasone from the carrier over time.

Composition of IBI-10090 9% in 0.5 mL Vial Fill

Ingredient	Function	Quality Standard	Amount (g/0.575g Vial Fill Weight) ^a	Amount (µg per 5µL Intraocular Injection, DDS) ^{ac}	Amount (wt %)
Formulation:					
Dexamethasone (b) (4)	Drug substance	USP	0.0517	517	9.0
Acetyl Triethyl Citrate (ATEC)	(b) (4)	NF	(b) (4)		
	(b) (4)	NF	(b) (4)		
Total	(b) (4)				

2.2 Tables of Currently Available Treatments for Proposed Indications

NDA	Drug	Indication
206-911	BromSite (bromfenac ophthalmic solution) 0.075%	Treatment of postoperative inflammation and prevention of ocular pain following cataract surgery
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	Treatment of inflammation and pain associated with ocular surgery. Treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel	Treatment of post-operative inflammation and pain

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	0.5% (Lotemax)	following ocular surgery.
20-474	Rimexolone ophthalmic suspension 1% (Vexol)	Treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	Treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664*	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	Treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	Treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	Treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	Treatment of pain and inflammation associated with cataract surgery.
19-700	Ketorolac tromethamine ophthalmic solution 0.5% (Acular)	Treatment of inflammation following cataract surgery Temporary relief of ocular itching due to seasonal allergic conjunctivitis
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	Treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	Treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, dexamethasone, is currently available in the following marketed ophthalmic products:

Ozurdex (dexamethasone intravitreal implant)

Maxidex (dexamethasone sodium phosphate 0.1%)

Ocu-Dex (dexamethasone ophthalmic solution or ointment, 0.1%, 0.5%).

2.4 Important Safety Issues with Consideration to Related Drugs

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Prolonged topical use of steroids is also associated with increased risk of posterior subcapsular cataract formation. Prolonged topical use may also suppress the host immune response and increase the hazard of secondary ocular infections.

Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to corneal perforation.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

EOP2 (CMC) Meeting held 12/03/2013

Pre-NDA (clinical) meeting held 07/20/2015

- Concerns were raised by the Division about the number of cases of corneal injuries reported during development. A detailed assessment of the corneal injuries was requested to be included in the NDA.

Pre-NDA (CMC) meeting held 12/03/2015

Pediatric Study Plan (PSP)

- Initial Pediatric Study Plan submitted 01/29/2014
- Comments provided and revised plan submitted 02/15/2017
- Pediatric study will be initiated after approval in adult patients

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

Site 22 (Dr. Roel) which was an investigative site for Study 13-04 was not able to be inspected by OSI. The investigator at this site has closed his practice and the source documents are not available. A sensitivity analysis on the study results were conducted by omitting the data that was generated from this site. There were no statistical or clinically significant changes in the study results.

3.3 Financial Disclosures

Icon Bioscience, Inc. has certified that none of the investigators involved in the clinical studies for this drug had any disclosable financial interests or arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

IBI-10090 (dexamethasone intraocular suspension 9%) is provided as a sterile suspension in a single use vial that is packaged in a kit with all of the components needed for administration of the drug: The kit includes four individual sterile pouches containing a) one Syringe Assembly (Syringe Ring and Syringe Guide), b) one commercially available syringe, 1 mL, c) one commercially available syringe cannula, 25 G x 8 mm bend; and d) one commercially available syringe needle, 18 G x 11 ½". *See Chemistry review for detailed discussion.*

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

Dexamethasone is an approved drug product with a safety and efficacy profile that is clinically established and supported by appropriate nonclinical studies. The focus of the nonclinical testing program for IBI-10090 was to characterize the in vivo release of drug from the controlled release drug delivery product and its intraocular safety. *See pharmacology/toxicology review.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dexamethasone, a corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells. (class labeling)

4.4.2 Pharmacodynamics

N/A – not conducted as part of this application.

4.4.3 Pharmacokinetics

The extent of systemic exposure to dexamethasone following intraocular (b) (4) delivery of IBI-10090 was determined from a subgroup of patients in two Phase 3 studies. In Study C13-04, a subgroup of 25 patients had blood samples drawn for pharmacokinetic (PK) analysis (four in the placebo group, 13 in the IBI-10090 342 mcg group, and eight in the IBI-10090 517 mcg group). In Study C15-01, a subgroup of 13 patients in the IBI-10090 517 mcg group had blood samples drawn for PK analysis. In both studies, systemic exposure after intraocular injection of IBI-10090 was low. Exposure declined over time indicating an initial rapid release of drug from the formulation, followed by a lower rate of release, until reaching a plateau with regard to drug content on Day 14. *See Biopharmaceutics review for detailed discussion.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study	Study Design (Country)	Study Population	Objectives	Treatment Group (Number Treated)	Treatment (Follow-up Duration)
Phase 2 Studies					
C09-01	Randomized, double-masked, dose-ranging (US)	Patients of age ≥ 40 years who are undergoing cataract surgery	1.To evaluate the efficacy of two dose levels of IBI-10090 in the treatment of inflammation resulting from cataract surgery compared to the IBI-10090 low dose group treatment 2.To evaluate the safety and tolerability of IBI-10090 used for treatment of cataract surgery postoperative inflammation	<u>IBI-10090:</u> 114 mcg (n = 3), 513 mcg (n = 2), 684 mcg (n = 1)	Single anterior chamber injection of 10 mcl (90 days)
C10-01				<u>IBI-10090:</u> 513 mcg (n = 13), 776 mcg (n = 14), 1046 mcg (n = 15)	Single anterior chamber injection of 7.5 mcl (90 days)
C11-01				<u>IBI-10090:</u> 342 mcg (n = 57), 517 mcg (n = 57), 697 mcg (n = 58)	Single anterior chamber injection of 5 mcl (90 days)
Placebo-controlled Phase 3 Study					
C13-04	Randomized, double-masked placebo (vehicle)-controlled (US)	Patients of age ≥ 40 years who are undergoing cataract surgery	1.To evaluate the efficacy of two dose groups of IBI-10090 dexamethasone in the treatment of inflammation resulting from cataract surgery 2.To evaluate the safety and tolerability of IBI-10090 used for treatment of post-cataract surgery inflammation	<u>IBI-10090:</u> 0 mcg (acetyl triethyl citrate vehicle) (n =80) 342 mcg (n =158), 517 mcg (n =156)	Single anterior chamber injection of 5 mcl (90 days)

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Study	Study Design (Country)	Study Population	Objectives	IBI-10090 Dose (Treated)	Treatment (Follow-up Duration)
Phase 3 Safety Study					
C15-01	Randomized, open-label, parallel-design (US)	Patients of age ≥ 40 years who are undergoing cataract surgery	To evaluate the safety of IBI-10090 in the treatment of inflammation associated with cataract surgery.	<u>IBI-10090</u> : 517 mcg (n = 126) Eye drops: Prednisolone acetate ophthalmic suspension 1% (n = 55)	Single anterior chamber injection of 5 mc1 (90 days) One drop four times daily for three weeks (90 days)

5.2 Review Strategy

Study C13-04 is an adequate and well-controlled study which was reviewed as the main source for evaluating the efficacy for this product. Study C15-01 was an open label phase 3 study which was conducted to evaluate the safety of the product. The design does not allow for an adequate efficacy evaluation.

The phase 2 studies were dose ranging studies which enrolled small patient populations with different concentrations/dosage volumes and were not reviewed in depth due to the study designs.

5.3 Discussion of Individual Studies/Clinical Trials

Clinical Protocol – Study C13-04

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

Objectives:

The primary objective was to evaluate the efficacy of two dose groups of IBI-10090 (dexamethasone suspension for intraocular injection) in the treatment of inflammation associated with cataract surgery. The secondary objective was to evaluate the safety and tolerability of IBI-10090 used for treatment of inflammation associated with cataract surgery.

Methodology:

The study was a prospective, randomized, double-masked, placebo-controlled, parallel-design, multicenter study in patients who were undergoing cataract surgery. Patients who met all inclusion and exclusion criteria were randomized to one of three treatment groups to receive a single 5-mcl anterior chamber injection of:

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

Patients received a single dose of their assigned treatment in their study eye immediately following their cataract surgery.

Patients underwent safety and efficacy examinations on POD 1, 3, 8, 15, 30, and 90. Efficacy was assessed by slit lamp biomicroscopy to evaluate the anterior chamber cells (ACC) clearing and grade, anterior chamber flare (ACF) clearing and grade, and anterior chamber cells and flare (ACCF) clearing and grade.

Patients were allowed to receive rescue medication after Day 0 if one or both of the following criteria were met:

1. Anterior Chamber Cell grade is 3 (grade 3= 16-30+ cells) or greater
2. Anterior Chamber Flare grade is 3 (grade 3= moderate intensity) or greater

Safety was assessed by adverse events (AEs), intraocular pressure (IOP), best-corrected visual acuity (BCVA), corneal endothelial cell density (ECD), other eye examination outcomes, the use of concomitant medications, and concurrent procedures.

SCHEDULE OF EVENTS

	PRE-OP	Surgery and Post-Operative Study Visits							Early Term
	Screening (Day -45 to -3)	Surgery Day 0	POD #1	POD #3 (+ 1 day)	POD #8 (+1 day)	POD #15 (± 3 days)	POD #30 (± 3 days)	POD #90 (± 7 days)	
Study Drug Injection		X							
Informed Consent	X								
Inclusion/Exclusion	X	X							
Medical and Ophthalmic History	X								
Urine Pregnancy Test (if required)		X					X		X
BCVA/Refraction	X						X	X	X
Visual Acuity (pinhole)			X	X	X	X			
Glare Testing (if required)	X								
Slit Lamp Examination	X		X	X	X	X	X	X	X
Intraocular Pressure (IOP)	X		X	X	X	X	X	X	X
Dilated Ophthalmoscopy	X						X		X
Corneal Endothelial Cell Count	X							X	X
Concomitant Medications		X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X
Concurrent Procedures		X	X	X	X	X	X	X	X

POD = postoperative day

Number of Patients (planned and analyzed):

A sample size of approximately 390 patients (156 patients per IBI-10090 dose group, 78 per placebo/vehicle group) was planned for this study. A total of 395 patients were enrolled, 158 patients were randomly assigned to 342 mcg IBI-10090, 157 to 517 mcg IBI-10090, and 80 to placebo (2:2:1 ratio). One patient assigned to the 517-mcg group did not receive study treatment and was excluded from the intent-to-treat (ITT), safety, and Per-Protocol (PP) analysis sets.

Eligibility Criteria:

Inclusion criteria:

1. Patient provided written informed consent by signing the Informed Consent Form approved by the Institutional Review Board (IRB).
2. Male or female patients at least 40 years of age scheduled for unilateral cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation.
3. BCVA of 20/30 to 20/200 (with glare testing, if necessary) in study eye and better than 20/200 in the fellow eye.
4. Patient was considered by Investigator to have visual acuity potential greater than 20/30 in the study eye.
5. Patient had a corneal endothelial cell density (ECD) by specular microscopy in the study eye of at least 2000 cells/mm² with normal cell morphology.
6. Female patients of childbearing potential must have had a negative pregnancy test on Day 0 and used an effective method of birth control for the duration of the study.
7. The patient must have been willing and able to understand and comply with the study procedures and to communicate meaningfully with study personnel.

Exclusion criteria:

1. Patients who had used any ocular, topical, or oral corticosteroids within seven days prior to Day 0.
2. Patients who had received a periocular corticosteroid injection in the study eye in the three months prior to screening.
3. Patients who had received any intravitreal corticosteroid delivery vehicle (eg, Retisert, Ozurdex, Iluvien) in the study eye at any time.
4. Patients who anticipated requiring treatment with any corticosteroids by any route, except inhalation, during the study.
5. Patients with an allergy or hypersensitivity to dexamethasone.
6. Patients who were known steroid responders (corticosteroid-related IOP elevation in either eye).
7. Patients who had used topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs) in the study eye within 15 days prior to Day 0.
8. Patients who had undergone prior intraocular (non-laser) surgery in the study eye within six months prior to screening.
9. Patients who had undergone prior intraocular laser surgery in the study eye within three months prior to Screening.
10. Patients with planned intraocular or laser surgery in the study eye during the study period.
11. Patients with any signs of intraocular inflammation in either eye at screening.
12. Patients with evidence of corneal abnormality or dystrophy (eg, opacities, guttae, clouding, etc.), or inability to obtain a clear specular micrograph at screening. The

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Reading Center confirmed eligibility based on the specular micrographs submitted by the site.

13. Patients with a history of chronic uveitis from any cause in either eye.
14. Patients who received any prior intravitreal injections in the study eye.
15. Patients with glaucomatous optic neuropathy or glaucomatous visual field loss in either eye.
16. Patients with ocular hypertension with an IOP in the study eye > 21 mmHg at screening with or without treatment with anti-glaucoma monotherapy.
17. Patients with ocular hypertension who received treatment with two or more anti-glaucoma medications.
18. Patients treated with any investigational product within 30 days prior to screening or patients enrolled previously in an Icon Bioscience study.

Efficacy Endpoints:

Each of the efficacy measures were assessed and analyzed at POD 1, 3, 8, 15, and 30.

Primary:

Proportion of patients with clearing of ACC (i.e., ACC grade = 0) 8 days after surgery (i.e., at POD 8).

Secondary:

- ACC clearing -Anterior chamber cell clearing rate (ACC=0 or not)
- ACF clearing -Anterior chamber cell clearing rate (ACF=0 or not)
- ACCF clearing –Anterior chamber cell and flare rates (0 = Absent, > 0 = Present)
- ACC grade -Mean anterior chamber cell score (0=absent, 1=1-5 cells, 2=6-15 cells, 3=16-30+ cells, 4=hypopyon)
- ACF grade - Mean anterior chamber flare score (0=absent, 1=trace, 2=mild intensity, 3=moderate intensity, 4=strong intensity)
- ACCF grade - Mean anterior chamber cell and flare score

Efficacy analyses:

The primary and secondary outcome measures were analyzed using both the ITT and PP analysis sets. Primary efficacy analysis results were those from the ITT analysis set. The PP analysis set was used only to support efficacy results. Statistical tests were performed at the 0.05 significance level, unless otherwise specified. The test of interaction was performed at the 0.10 significance level. All tests were 2-sided. Models used for data analysis were a generalized linear mixed model (GLMM) and a mixed-effect model repeated measure (MMRM) using generalized linear model.

For the *primary efficacy* parameter (proportion of patients with ACC = 0 in study eye at POD 8 based on last observation carried forward [LOCF] data), the number and percentage of patients with ACC clearing or not, derived from the ACC grade, was summarized. In addition, parameter estimates, standard errors of the estimates, odds ratios, and 95% CIs for the odds ratios and p-values of the odds ratio estimates were reported by treatment group and time point. The group proportions (expressed in percentages), 95% CI of group proportions, difference between group

proportions (IBI-10090 517-mcg group minus placebo and IBI-10090 342-mcg group minus placebo), and 95% CI of difference between group proportions were presented by time point. The two-group chi-square test of equal proportions was used for analysis of the primary efficacy endpoint, with significance level set at 0.025 for comparing between the placebo and IBI-10090 groups the proportion of patients with ACC clearing.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Treatment of postoperative inflammation.

6.1.1 Methods

The description of the clinical trial design is contained in section 5.3.

6.1.2 Demographics

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	Placebo (N=80)	IBI-10090 342 mcg (N=158)	IBI-10090 517 mcg (N=156)	Total (N=394)
Study Eye				
OD	37 (46.3%)	87 (55.1%)	75 (48.1%)	199 (50.5%)
OS	43 (53.8%)	71 (44.9%)	81 (51.9%)	195 (49.5%)
Age (years)^a				
n	80	158	156	394
Mean (SD)	70.7 (8.79)	69.7 (8.84)	70.1 (8.96)	70.0 (8.87)
Median	71.5	70.0	71.0	71.0
Min, Max	46, 90	43, 86	46, 90	43, 90
<65 years	17 (21.3%)	41 (25.9%)	41 (26.3%)	99 (25.1%)
≥65 years	63 (78.8%)	117 (74.1%)	115 (73.7%)	295 (74.9%)
Sex				
Male	39 (48.8%)	75 (47.5%)	69 (44.2%)	183 (46.4%)
Female	41 (51.3%)	83 (52.5%)	87 (55.8%)	211 (53.6%)
Race				
White	67 (83.8%)	129 (81.6%)	123 (78.8%)	319 (81.0%)
Black or African American	11 (13.8%)	17 (10.8%)	21 (13.5%)	49 (12.4%)
American Indian or Alaska Native	0	1 (0.6%)	3 (1.9%)	4 (1.0%)
Asian	1 (1.3%)	4 (2.5%)	1 (0.6%)	6 (1.5%)
Native Hawaiian or Other Pacific Islander	0	2 (1.3%)	1 (0.6%)	3 (0.8%)
Other	1 (1.3%)	5 (3.2%)	7 (4.5%)	13 (3.3%)
Ethnicity				
Hispanic or Latino	14 (17.5%)	19 (12.0%)	23 (14.7%)	56 (14.2%)
Not Hispanic or Latino	66 (82.5%)	139 (88.0%)	133 (85.3%)	338 (85.8%)

Note: Percentages were calculated based on patients with non-missing data in each treatment group.

^a Age was calculated as the difference between date of birth and date of informed consent, in years.

Source Listing 16.2.4.1

Source: \\con Bioscience\C13-04\TLGs\Programs\t_demog_itt.sas cchesbrough Run date: 09MAR15 19:09 SDTM data version date: 2015-02-05

6.1.3 Subject Disposition

Patient Enrollment and Disposition All Randomized Patients				
	Placebo (N=80)	IBI-10090 342 mcg (N=158)	IBI-10090 517 mcg (N=157)	Total (N=395)
Patients who were randomized	80	158	157	395
Randomized patients who did not receive study drug	0	0	1	1
Number (%) patients in ITT Analysis Set ^a	80 (100%)	158 (100%)	156 (99.4%)	394 (99.7%)
Number (%) patients in PP Analysis Set ^b	58 (72.5%)	122 (77.2%)	122 (77.7%)	302 (76.5%)
Number (%) patients in Safety Analysis Set ^c	80 (100%)	158 (100%)	156 (99.4%)	394 (99.7%)
Number (%) patients in PK Analysis Set ^d	4 (5.0%)	13 (8.2%)	8 (5.1%)	25 (6.3%)
Patients in ITT/Safety Analysis Set^b				
Number (%) patients who completed the study up to POD 30	77 (96.3%)	157 (99.4%)	154 (98.7%)	388 (98.5%)
Number (%) patients who terminated the study prior to POD 30	3 (3.8%)	1 (0.6%)	2 (1.3%)	6 (1.5%)
Number (%) patients who completed the study up to POD 90	76 (95.0%)	156 (98.7%)	154 (98.7%)	386 (98.0%)
Number (%) patients who terminated the study prior to POD 90	4 (5.0%)	2 (1.3%)	2 (1.3%)	8 (2.0%)
Primary reason for early termination for all randomized patients^d				
Other	3 (3.8%)	1 (0.6%)	3 (1.9%)	7 (1.8%)
Withdrawal of consent	1 (1.3%)	1 (0.6%)	0	2 (0.5%)

POD = Post Operative Day.

^a Percentages were calculated based on the total number of randomized patients in each treatment group.

^b Percentages were calculated based on the total number of Safety Analysis Set patients in each treatment group.

Source Listing 16.2.1

6.1.4 Analysis of Primary Endpoint(s)

Patients with Clearing of ACC	Placebo (n = 80)	IBI-10090 342 mcg (n = 158)	IBI-10090 517 mcg (n = 156)
POD 8 ACC Clearing (LOCF)			
n	80	158	156
Yes	20 (25.0%)	99 (62.7%)	103 (66.0%)
Difference (IBI-10090 - placebo) (%)		37.7%	41.0%
95% CI of Difference		25.5%, 49.8%	29.0%, 53.1%
p-value from Chi-square test		< 0.001	< 0.001
POD 30 ACC Clearing (LOCF)			
n	80	158	156
Yes	40 (50.0%)	127 (80.4%)	122 (78.2%)
Difference (IBI-10090 - placebo) (%)		30.4%	28.2%
95% CI of Difference		17.8%, 43.0%	15.5%, 40.9%
p-value from Chi-square test		< 0.001	< 0.001

Source: CSR C13-04 Table 14.2.1.1

ACC = anterior chamber cells; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; POD = postoperative day.

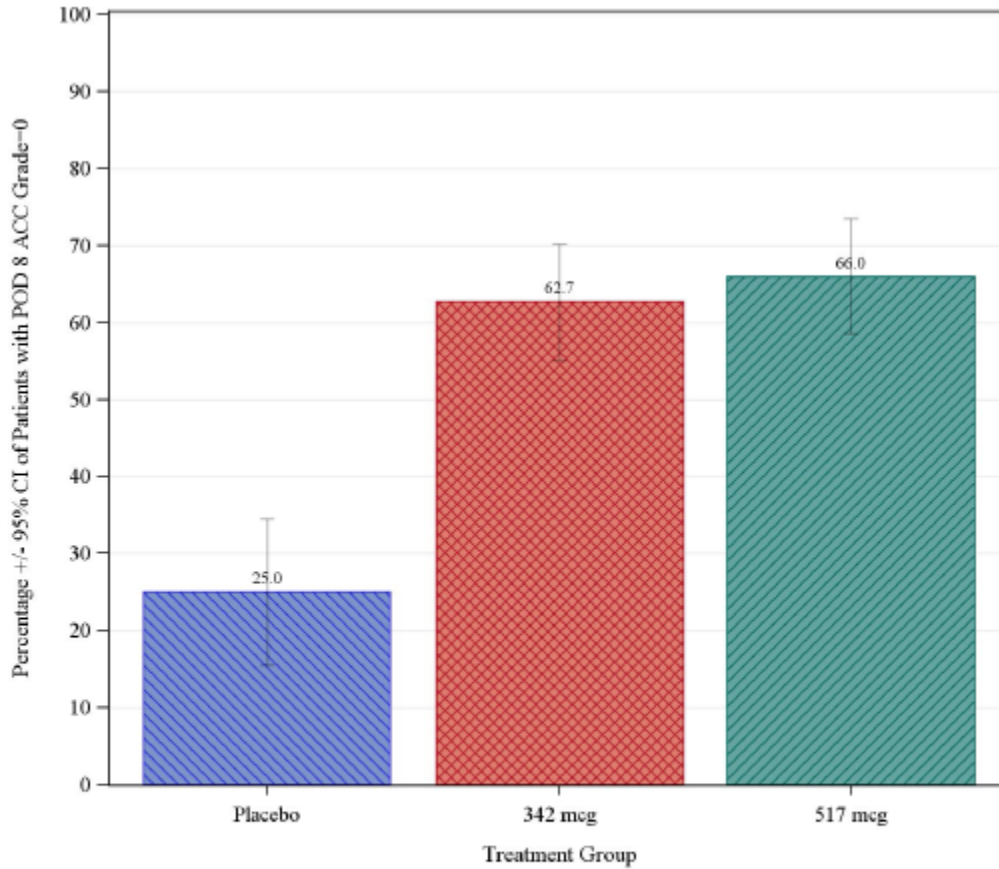
Note: Treatment failure (ie, ACC grade $\geq$ 1) was assumed, if a patient did not have postdose data or received rescue medication.

The p-value is based on 2-group chi-square (continuity corrected) test of equal proportion.

Comments:

Both the 342mcg dose and the 517 mcg dose are statistically superior to placebo for the clearance of anterior chamber cells. There is no statistical or clinical difference between the two dose groups.

Percentage of Patients with ACC Grade=0 at POD 8 (ITT Analysis Set)



CI = confidence interval, POD = Post Operative Day.

Note: Treatment failure was assumed, if a subject did not have post dose data or received rescue medication.

Source Listing 16.2.6

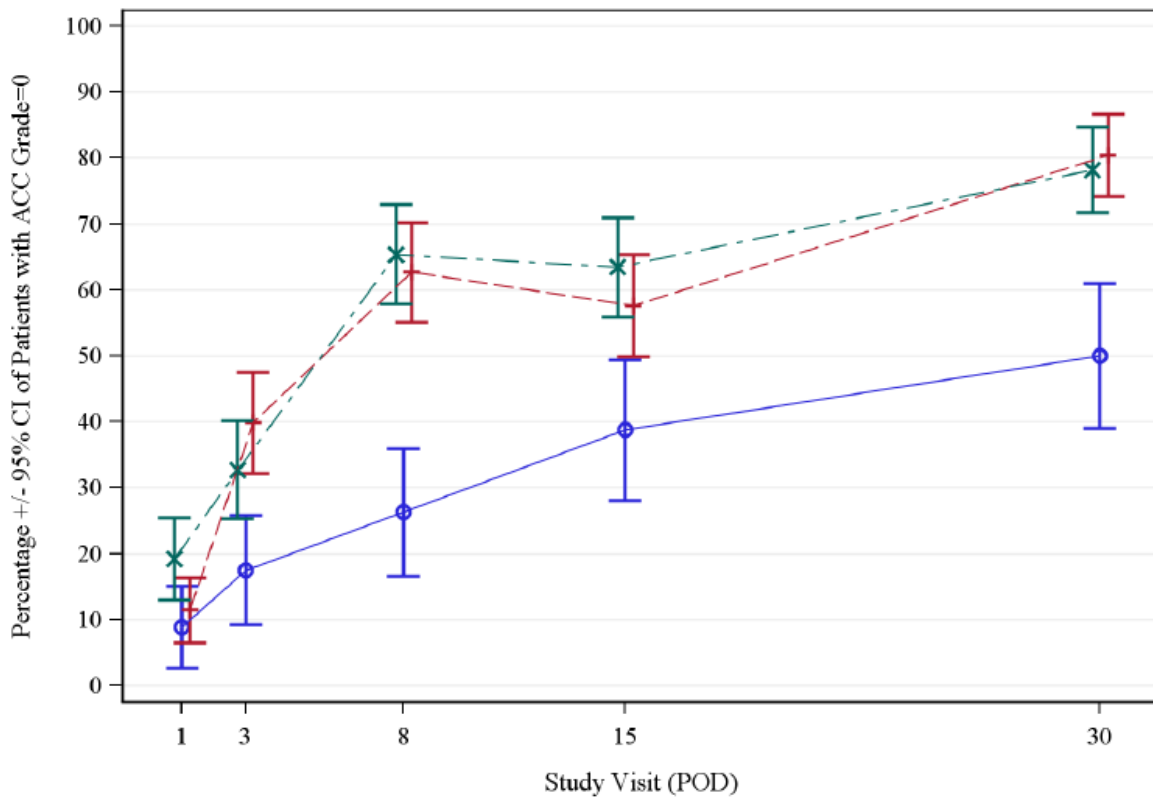
Source: \\Icon Bioscience\C13-04\TLGs\Programs\l_bar_itt_acc.sas cchesbrough Run date: 21MAR15 10:53 SDTM data version date: 2015-02-05

6.1.5 Analysis of Secondary Endpoints(s)

Comments:

There were multiple secondary endpoints measured over multiple timepoints for this trial. (see section 5.3). The endpoints that measure total resolution of anterior chamber cell and/or flare are shown here for completeness as support of the primary efficacy endpoint.

Patients with ACC Grade=0 Over Time (ITT Analysis Set)



Number of Patients

Placebo	79	80	80	80	80
342 mcg	157	158	158	158	158
517 mcg	156	156	156	156	156

Treatment Group: — Placebo - - - 342 mcg - - - 517 mcg

CI = confidence interval, POD = Post Operative Day.

Note: Treatment failure was assumed, if a subject did not have post dose data or received rescue medication.

Source Listing 16.2.6

Source: \Icon Bioscience\C13-04\TLGs\Programs\hilo_itt_accs.sas cchesbrough Run date: 21MAR15 10:54 SDTM data version date: 2015-02-05

Comments:

Both the 342 mcg dose and 517 mcg dose are superior to placebo for the clearance of anterior chamber cells. This superiority starts on day 3 after surgery and continues through post op day 30.

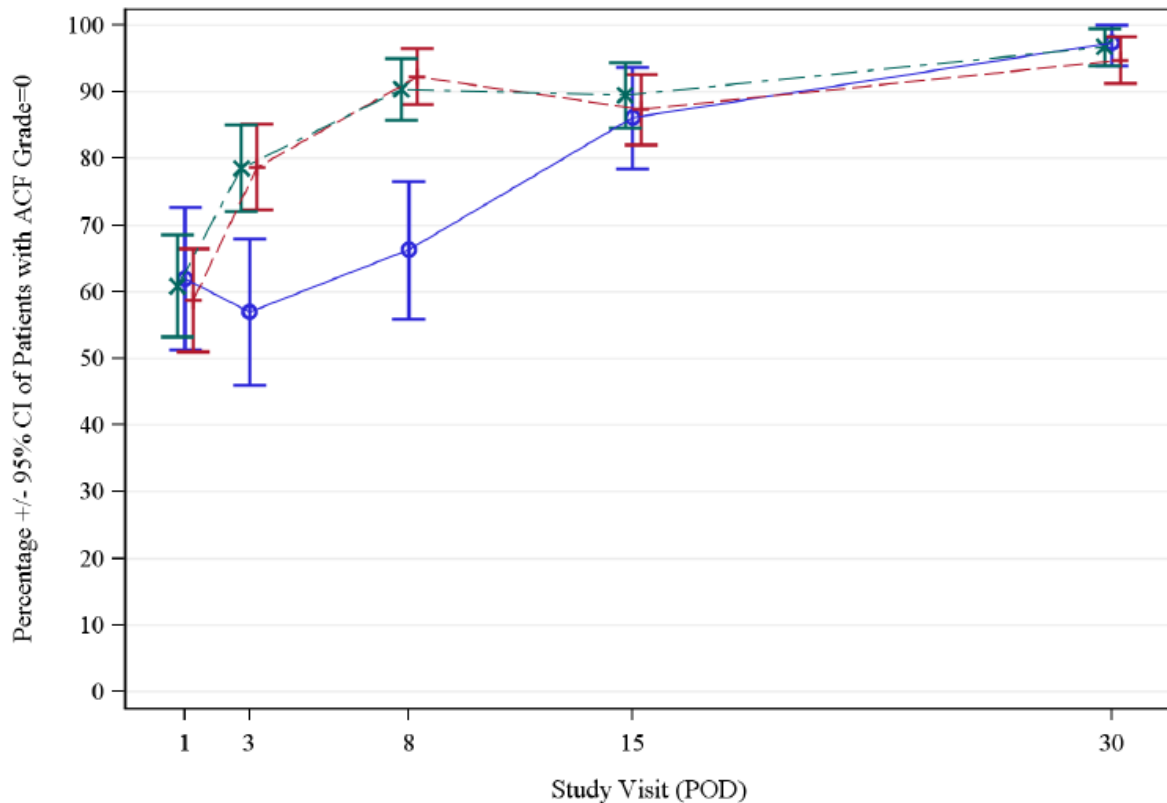
Patients with ACF Grade=0 Over Time (ITT Analysis Set)

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Number of Patients

Placebo	79	79	80	79	78
342 mcg	155	155	156	151	154
517 mcg	156	154	156	152	152

Treatment Group: — Placebo — 342 mcg — 517 mcg

CI = confidence interval, POD = Post Operative Day.

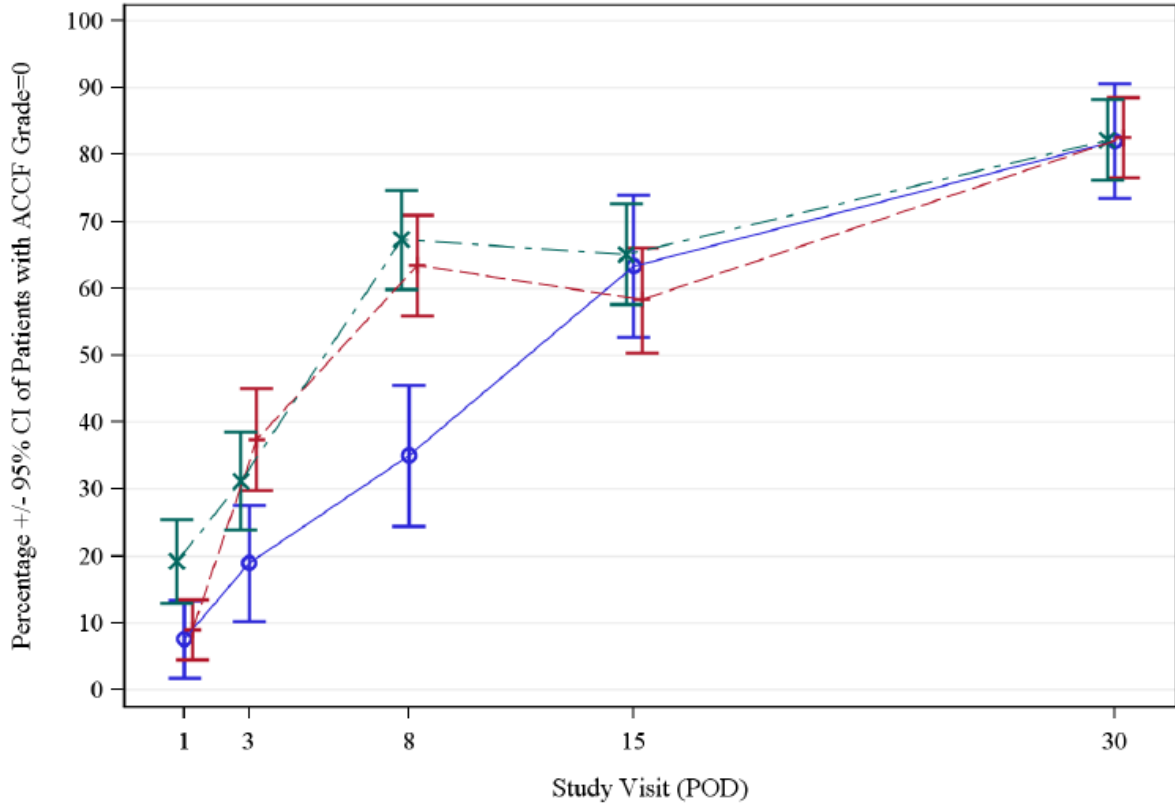
Source Listing 16.2.6

Source: \Icon Bioscience\C13-04\TLGs\Programs\fhilo_itt_acfc.sas cchesbrough Run date: 21MAR15 10:55 SDTM data version date: 2015-02-05

Comments:

Both the 342 mcg dose and 517 mcg dose are superior to placebo for the clearance of anterior chamber flare starting and day 3. There is not difference between the doses and placebo starting at day 15.

Patients with ACCF Grade=0 Over Time (ITT Analysis Set)



Number of Patients

Placebo	79	79	80	79	78
342 mcg	155	155	156	151	154
517 mcg	156	154	156	152	152

Treatment Group: — Placebo — 342 mcg - - 517 mcg

CI = confidence interval, POD = Post Operative Day.
 Source Listing 16.2.6

Source: \Icon Bioscience\C13-04\TLGs\Programs\hilo_itt_accfc.sas cchesbrough Run date: 21MAR15 10:56 SDTM data version date: 2015-02-05

6.1.6 Other Endpoints

Mean AC Cell Score at Each Post-op Day – Study C13-04

Visits	Treatments			Mean Difference (95% CI)	
	Placebo Mean (SE)	DEX342 Mean (SE)	DEX517 Mean (SE)	DEX342 vs. Placebo	DEX517 vs. Placebo
Day 1	1.468 0.0797)	1.269(0.0567)	1.218(0.0567)	-0.199(-0.391, -0.007)	-0.25(-0.442, -0.059)
Day 3	1.392 0.0797)	0.677(0.0569)	0.844(0.0571)	-0.715(-0.907, -0.523)	-0.548(-0.74, -0.356)
Day 8	0.95 0.0792)	0.404(0.0567)	0.397(0.0567)	-0.546(-0.737, -0.355)	-0.553(-0.744, -0.362)
Day 15	0.494 0.0797)	0.523(0.0576)	0.487(0.0574)	0.03(-0.163, 0.222)	-0.007(-0.199, 0.186)
Day 31	0.218 0.0802)	0.188(0.0571)	0.204(0.0574)	-0.03(-0.223, 0.163)	-0.014(-0.207, 0.179)

LS mean and 95% CI.

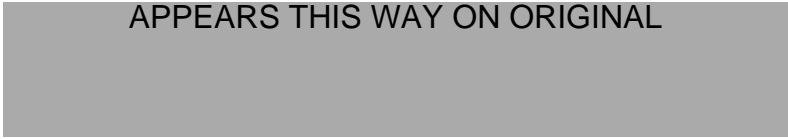
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6.1.7 Subpopulations

Summary and Analysis of Anterior Chamber Cell Clearing At POD 8 (LOCF) by Subgroup ITT Analysis Set – Study C13-04*

	Placebo (N=80)	IBI-10090 342 mcg (N=158)	IBI-10090 517 mcg (N=156)
Male			
n	39	75	69
Yes	10 (25.6%)	43 (57.3%)	51 (73.9%)
Difference (IBI-10090 - Placebo) (%)		31.7%	48.3%
95% CI of Difference		14.0%, 49.4%	31.1%, 65.5%
P-value from Chi-square test ^a		0.003	<.001
Female			
n	41	83	87
Yes	10 (24.4%)	56 (67.5%)	52 (59.8%)
Difference (IBI-10090 - Placebo) (%)		43.1%	35.4%
95% CI of Difference		26.5%, 59.6%	18.7%, 52.1%
P-value from Chi-square test ^a		<.001	<.001
<65 Years Old			
n	17	41	41
Yes	3 (17.6%)	20 (48.8%)	23 (56.1%)
Difference (IBI-10090 - Placebo) (%)		31.1%	38.5%
95% CI of Difference		7.4%, 54.9%	14.8%, 62.1%
P-value from Chi-square test ^a		0.056	0.017
>=65 Years Old			
n	63	117	115
Yes	17 (27.0%)	79 (67.5%)	80 (69.6%)
Difference (IBI-10090 - Placebo) (%)		40.5%	42.6%
95% CI of Difference		26.7%, 54.4%	28.8%, 56.4%
P-value from Chi-square test ^a		<.001	<.001

CI = confidence interval, LOCF = last observation carried forward, POD = Post Operative Day.

^a The p-value is based on two-group chi-square (continuity corrected) test of equal proportion.

Source Listing 16.2.6

Source: \Icon Bioscience\C13-04\TLGs\Programs\t_eff_locf_itt_accs_sexage.sas cchesbrough Run date: 09MAR15 19:18 SDTM data version date: 2015-02-05

*Subgroup analyses of efficacy were only performed for study C 13-04.

Comments:

The 517 mcg group is statistically superior to placebo for all subpopulations evaluated. The 342 mcg group is statistically superior to placebo for each of the subpopulations evaluated with exception of patients less than 65 y.o.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is no additional information relevant to dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

IBI-10090 is biodegradable by design and is intended to only be present in the eye long enough during the immediate postoperative period to reduce inflammation during the healing process. Therefore, studies to evaluate long-term efficacy have not been conducted.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues requiring review.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 5.1 for table of trials. The Phase 2 studies C09-01 and C10-01 had small patient populations and used different concentrations (and dosage volumes) of IBI-10090, as well as different delivery systems; therefore, safety data from these studies were not included in the pooled safety study. Safety data from the remaining Phase 2 study (C11-01) was pooled with data from the two Phase 3 studies, resulting in combined IBI-10090 dose groups of 342 mcg (N = 215), 517 mcg (N = 339), 697 mcg (N = 58).

7.1.2 Categorization of Adverse Events

Adverse events were coded to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 for Studies C11-01, C13-04, and C15-01. Treatment-emergent AEs reported during the pooled studies are summarized by SOC and PT. A TEAE is defined as an AE that starts on or after the day when study drug was administered. Related AEs are those events reported as possibly or probably related to study drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from Phase 2 study (C11-01) was pooled with data from the two Phase 3 studies, resulting in combined IBI-10090 dose groups of 342 mcg (N = 215), 517 mcg (N = 339), 697 mcg (N = 58).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Included in the Pooled Population							
C11-01 (N=172)			C13-04 (N=394)			C15-01 (N=181)	
342 mcg	517 mcg	697 mcg	Placebo	342 mcg	517 mcg	Prednisolone	517 mcg
57	37	58	80	158	156	55	126

Not Included in the Pooled Population				
C09-01 (N=6)			C10-01 (N=42)	
114 mcg	513 mcg	684 mcg	513 mcg	776 or 1046 mcg
3	2	1	13	29 ^a

^aFor Study C10-01, 14 patients received 776 mcg and 15 patients received 1046 mcg of IBI-10090.

Reviewer's comments: *Approximately 400 subjects have been exposed to the to-be-marketed dose (517 mcg) or higher during the development program.*

7.2.2 Explorations for Dose Response

IBI-10090 was evaluated at two dose levels in the phase 3 trials; 342µg and 517µg. A 697 µg dose was also evaluated in a phase 2 dose ranging trial. See section 7.2.1 for dose/duration data.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of this drug product (i.e. biomicroscopy, visual acuity, IOP, etc) were adequately addressed in the design and conduct of this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Biopharmaceutics review for detailed discussion.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are several ocular complications associated with the use of corticosteroids. These include but are not limited to increased intraocular pressure, posterior subcapsular cataract formation, secondary ocular infections, and corneal and scleral thinning. The applicant's trial design adequately assessed these known adverse events.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during any of the five clinical studies of IBI-10090.

7.3.2 Nonfatal Serious Adverse Events

System Organ class	Placebo (N=80) n(%)	Prednisolone Eye Drops (N=55) n(%)	Pooled IBI-10090 342 mcg (N=215) n(%)	Pooled IBI- 10090 517 mcg (N=339) n(%)
Patients Reporting Any TEAE in the Study Eye				
Ocular SAEs				
Corneal decompensation	0	0	1(0.5)	0
Corneal endothelial cell	0	0	3 (1.4)	1 (0.3)

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Corneal edema	0	0	2(0.9)	0
Diabetic retinopathy	0	0		1 (0.3)
Endophthalmitis	0	0	1(0.5)	0
Systemic SAEs				
Influenza	0	0		1 (0.3)

2.7.4 Summary of Clinical Safety Table 7

Comment:

Corneal endothelial cell loss was the most frequent (7/612) ocular SAE in patients treated with IBI-10090. Three out of four (3/4) of these events occurred in the lower dose group (342 mcg) This SAE was also reported in 3/58 (5.2%) of patients receiving 697 mcg which is not included in the pooled database.

7.3.3 Dropouts and/or Discontinuations

Study C13-04	Subject ID	Treatment	Study Day	Reason for Discontinuation
	(b) (6)	517 mcg	9	Lost to follow-up
		517 mcg	16	Lost to follow-up
		342 mcg	42	Withdrawal of consent
		342 mcg	1	Lost to follow-up
		Placebo	9	Withdrawal of consent
		Placebo	30	Withdrawal of consent
		Placebo	29	Lost to follow-up
		Placebo	29	Lost to follow-up
Study C15-01				
		517 mcg	91	Protocol Deviation
		517 mcg	9	Withdrawal of Consent
		517 mcg	9	IOL dislocation
		517 mcg	22	Withdrawal of Consent
		Prednisolone	134	Lost to follow-up
		Prednisolone	6	IOL dislocation

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	(b) (6)	Prednisolone	9	Lost to follow-up
Study C11-01				
		517 mcg	16	Withdrawal of Consent
		517 mcg	30	Lost to follow-up
		342 mcg	4	Withdrawal of Consent
		342 mcg	69	Withdrawal of Consent

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuations are presented in section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns

During the pre-NDA meeting held for this product, it was noted that throughout the development program, there had been a number of cases of corneal injuries (corneal edema, decreased corneal cell counts, corneal decompensation, etc). Corneal endothelial cell loss was also the most frequent (7/612) ocular SAE in patients treated with IBI-10090. See section 7.3.2.

Additional evaluation of these events were done to examine the scope and any potential adverse associated adverse outcomes. IOP was also evaluated since it is a known common adverse associated with steroid use and can lead to endothelial cell loss and edema.

IOP and Cornea Related Adverse Events – Pooled Population

	Placebo (N=80)	Prednisolone Eye Drops (N=55)	Pooled IBI-10090		
			342 mcg (N=215)	517 mcg (N=339)	697 mcg (N=58)
Corneal Endothelial Cell Loss N(%)	1 (1.3)	0	6 (2.8)	5 (1.5)	9 (15.5)
Corneal Edema N (%)	8 (10.0)	1 (1.8)	14 (6.5)	24 (7.1)	3 (5.2)
Increased Ocular Pressure N (%)	7 (8.8)	2 (3.6)	19 (8.8)	39 (11.5)	3 (5.2)

Corneal Endothelial Cell Density (Based on Central Reading Center) – Pooled Population

	Placebo (N=80)	Prednisolone Eye Drops (N=55)	Pooled IBI-10090	
			342 mcg (N=215)	517 mcg (N=339)
Baseline (cells/mm ²)				
N	80	55	158	280
Mean	2506.34	2398.33	2561.32	2536.24
POD 90 (cells/mm ²)				
N	74	51	148	270
Mean	2123.09	2106.39	2171.34	2131.13

Source: 2.7.4 Summary of Clinical Safety Table 8

Note: Corneal endothelial measurements was not performed by the Reading Center for Study 11-01 (IBI-10090 697 mcg group)

Comments:

The rate of corneal endothelial cell loss is similar between placebo and the 517mcg (to be marketed dose) treatment group. The rate is 16%.

While the adverse event rates of corneal edema and intraocular pressure are similar between the 517 mcg treatment group and placebo, both occur at approximately 3-4 times higher than those subjects treated with prednisolone drops. The higher rates of corneal edema and IOP reported during the trial do not have an effect on the final visual acuity or IOP status of the subjects in any of the treatment groups.

Visual Acuity and IOP – Pooled Population

	Placebo (N = 80)n (%)	Prednisolone Eye Drops (N = 55) n (%)	Pooled IBI-10090 517 mcg (N = 339) n (%)
Visual Acuity Mean (SD)			
Baseline	0.35 (0.21)	0.36 (0.26)	0.33 (0.21)
POD 90 (EOS)	0.07 (0.114)	0.05 (0.012)	0.06 (0.11)
IOP (SD)			
Baseline	15 (2.9)	14.4 (2.7)	15 (2.9)
POD 90 (EOS)	13.4 (2.9)	12.7 (2.9)	13.4 (2.7)

Source ISS Table 3.1.1 and 3.2.1

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent Adverse Events in the Study Eye with an Incidence of 1% or Greater in the Pooled IBI-10090 517 mcg Dose Group

System Organ Class/ Preferred Term	Placebo (N = 80)n (%)	Prednisolone Eye Drops (N = 55) n (%)	Pooled IBI- 10090 517 mcg (N = 339) n (%)
System Organ Class			
Patients Reporting Any TEAE in the Study Eye	51 (63.8)	13 (23.6)	152 (44.8)
Ocular AEs			
Anterior Chamber Cell	8 (10)	0	6 (1.8)
Anterior chamber inflammation	10 (12.5)	0	9 (2.7)
Blepharitis	0	2 (3.6)	4 (1.2)

Corneal endothelial cell loss	1 (1.3)	0	5 (1.5)
Corneal edema	8 (10.0)	1 (1.8)	24 (7.1)
Cystoid Macular Edema	3 (3.8)	1 (1.8)	6 (1.8)
Dry eye	0	0	11 (3.2)
Eye Inflammation	0	0	5 (1.5)
Eye pain	7 (8.8)	2 (3.6)	7 (2.1)
Foreign body sensation in eye	0	2 (3.6)	11 (3.2)
Iritis	11 (13.8)	0	17 (5.0)
Photophobia	3 (3.8)	1 (1.8)	4 (1.2)
Posterior capsule opacification	2 (2.5)	0	12 (3.5)
Vision Blurred	1 (1.3%)	1 (1.8)	4 (1.2)
Visual Acuity Reduced	2 (2.5%)	0	4 (1.2)
Vitreous detachment	1 (1.3%)	0	4 (1.2)
Vitreous floaters	0	1 (1.8)	5 (1.5)
Injury, poisoning, and procedural complications			
Post procedural complication	0	1 (1.8)	7 (2.1)
Investigations			
Intraocular pressure increased	7 (8.8)	2 (3.6)	39 (11.5)
Systemic AEs			
Hypertension	0	0	3 (0.9)

Note: The placebo group were patients in Study C13-04 only. The prednisolone eye drops group were patients in Study C15-01 only. The pooled IBI-10090 517 mcg dose group were patients in Studies C11-01, C13-04, and C15-01.

Source: [ISS Table 2.2.1](#).

Comments:

Overall, there was no significant difference in the rate of systemic adverse events or ocular events in the study between placebo and IBI-10090 517 mcg. The majority of adverse events occurred at a numerically higher rate in the placebo group compared to drug. The majority of reported adverse events are consistent with those related to cataract surgery.

7.4.2 Laboratory Findings

No postdose clinical laboratory evaluations were conducted in studies of IBI-10090.

7.4.3 Vital Signs

No postdose vital signs or physical examination evaluations were conducted in studies of IBI-10090.

7.4.4 Electrocardiograms (ECGs)

No postdose vital signs or physical examination evaluations were conducted in studies of IBI-10090.

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

Evaluation of immunogenicity was not conducted in the studies of IBI-10090.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no dose dependent adverse events noted between the 342 mcg and 527 mcg doses of IBI-10090. The rate and types of adverse events were similar between the groups.

7.5.2 Time Dependency for Adverse Events

There were no time dependent adverse events noted for IBI-10090. It is dosed as a single injection.

7.5.3 Drug-Demographic Interactions

No drug-interaction studies have been conducted with IBI-10090.

7.5.4 Drug-Disease Interactions

No drug-interaction studies have been conducted with IBI-10090.

7.5.5 Drug-Drug Interactions

No drug-interaction studies have been conducted with IBI-10090.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No nonclinical safety studies investigating the potential for mutagenicity, reproductive toxicity, or carcinogenicity were conducted with IBI-10090.

7.6.2 Human Reproduction and Pregnancy Data

Safety for use in pregnancy and lactation has not been established. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical administration.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric studies have not been conducted with IBI-10090 at the time of this NDA submission. A pediatric plan was submitted with this NDA. The primary objective of the study is to evaluate the safety of the new formulation of dexamethasone (IBI-10090) compared to an active control (dexamethasone ophthalmic suspension) in the pediatric population (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

During the Phase 3 Study C13-04, there were 14 instances of patients receiving higher amount of drug than intended (i.e. 30 mcg versus 5.75 mcg). This was due to the markings on the syringe and inadequate training of staff. The syringe was redesign and staff training was updated to correct this problem for study C15-01.

No cases of drug abuse with IBI-10090, placebo, or prednisolone eye drops were reported in the clinical studies. No drug withdrawal or rebound effects were observed in any patient receiving IBI-10090 during the clinical studies. No such effects are expected with the use of IBI-10090.

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7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

IBI-10090 has not been approved for marketing in any country to date.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

The following label is the substantially completely label incorporating the input from all review disciplines.

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

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9.3 Advisory Committee Meeting

9.4 List of Investigators Study C13-04

Site No.	Investigator Name	Sub-Investigator(s) Name	Number of Patients Randomized
01	William P. Blase, MD California Eye Professionals 41637 Margarita Rd, Ste 100 Temecula, CA 92591	(b) (6)	15
	California Eye Professionals 29826 Haun Rd, Ste 100 Menifee, CA 92586		
	California Eye Professionals 2390 E. Florida Ave, Ste 207 Hemet, CA 92544		
	Temecula Valley Day Surgery Center 25495 Medical Center Dr, Ste 101 Murrieta, CA 92562		
	Hemet Healthcare Surgi Center 301 N. San Jacinto Ave, Ste 100 Hemet, CA 92543		
02	Stephen Bylsma, MD Shepard Eye Center 1414 E. Main St. Santa Maria, CA 93454	(b) (6)	23
	Premier Surgery Center of Santa Maria 816 Enos Suite B Santa Maria, CA 93454		
	Kendall-Shepard Eye Center 425 West Central Ave. Lompoc, CA 93436		
03	Gregg Feinerman, MD Feinerman Vision Center 320 Superior Ave, Suite 390 Newport Beach, CA 92663	None	9
	Barranca Surgery Center 3500 Barranca Parkway, Suite 130 Irvine, CA 92606		

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{Dexycu (dexamethasone intraocular suspension, 9%)}

Site No.	Investigator Name	Sub-Investigator(s) Name	Number of Patients Randomized
04	Carl T. Hartman, MD Lakewood Eye Physicians and Surgeons, Inc. 3300 E. South St., Suite 105 Long Beach, CA 90805	(b) (6)	21
05	Vicky C. Pai, MD Foothill Eye Institute 2619 E. Colorado Blvd. #100 Pasadena, CA 91107	(b) (6)	18
	Azusa Surgery Center 830 S. Citrus Ave. #101 Azusa, CA 91702		
	Mark B. Kislinger, MD, PhD, Inc. 210 S. Grand Ave. #106 Glendora, CA 91741		
	Azusa Surgery Center 830 S. Citrus Avenue #101 Azusa, CA 91702		
	Mark B. Kislinger, MD, Inc. – Satellite 1135 S. Sunset Avenue, Suite 304 West Covina, CA 91790		
06	Michael Savetsky Mark B. Kislinger, MD, PhD, Inc. 210 S. Grand Ave. Suite 106 Glendora, CA 91741	(b) (6)	34
	Azusa Surgery Center 830 S. Citrus Avenue #101 Azusa, CA 91702		
	Foothill Eye Institute 2619 E. Colorado Blvd. #100 Pasadena, CA 91107		
	Mark B. Kislinger, MD, Inc. – Satellite 1135 S. Sunset Avenue, Suite 304 West Covina, CA 91790		

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Site No.	Investigator Name	Sub-Investigator(s) Name	Number of Patients Randomized
07	Thomas LoBue, MD LoBue Laser and Eye Center, Inc. 40700 California Oaks Road, Suite 106 Murrieta, CA 92563	None	23
	The Oaks Surgery Center 40740 California Oaks Road Murrieta, CA 92563		
	LoBue Laser & Eye Medical Centers, Inc. 40945 Winchester Road Temecula, CA 92591		
08	G.M. Sally Mellgren, MD G.M. Sally Mellgren, M.D., Inc. 3621 Vista Way Oceanside, CA 92056	(b) (6)	12
	Center for Surgery of Encinitas 477 N. El Camino Real Building C. Suite 100 Encinitas, CA 92024		
	North Coast Surgery Center 3903 Waring Road Oceanside, CA 92056		
09	Reginald Sampson, MD Hull Eye Center 1739 West Ave J Lancaster, CA 93534	(b) (6)	35
	Hull Eye Laser and Surgery Center 1741 West Ave J Lancaster, CA 93534		
10	Ehsan Sadri, MD, FACS Atlantis Eyecare 7777 Edinger Ave. Suite # 234 Huntington Beach, CA 92647	(b) (6)	8
	Talbert Surgical Associates 7677 Center Ave. Suite 104 Huntington Beach, CA 92647		
	Magnolia Surgery Center 14571 Magnolia Ave. Suite 107 Westminster, CA 92683		

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11	Robert C. Sorenson, MD, PhD Inland Eye Specialists 3953 W. Stetson Ave. Hemet, CA 92545	(b) (6)	19

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Site No.	Investigator Name	Sub-Investigator(s) Name	Number of Patients Randomized
12	R. Duncan Johnson, MD Inland Eye Specialists 25395 Hancock Ave. Suite 100 Murrieta, CA 92562	(b) (6)	21
	Inland Eye Specialists 521 E. Elder Street, Suite 102 Fallbrook, CA 92028		
13	Albert T. Milauskas, MD Milauskas Eye Institute Medical Group 72057 Dinah Shore Drive, Suite D Rancho Mirage, CA 92270	(b) (6)	12
	Eye Surgery Center of the Desert 72301 Country Club Drive, Suite 101 Rancho Mirage, CA 92270		
	Milauskas Eye Institute Medical Group 78560 Highway 111 La Quinta, CA 92253		
	Milauskas Eye Institute Medical Group 41990 Cook St. Bldg. E #502 Palm Desert, CA 92211		
14	Stephen Khachikian MD Black Hills Regional Eye Institute 2800 Third St. Rapid City, SD 57701	(b) (6)	14
16	Jeffrey Whitman Key Whitman Eye Center 2801 Lemmon Ave. Dallas, TX 75204	(b) (6)	4
17	Lawrence Roel, MD, PhD, FACS Eastside Westside Eye Center 735 E. Main Street Spartanburg, SC 29302	(b) (6)	22

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Site No.	Investigator Name	Sub-Investigator(s) Name	Number of Patients Randomized
18	Dwayne K. Logan, MD Atlantis Eyecare 5991 E. Spring Street Long Beach, CA 90808	(b) (6)	9
	Healthcare Partners Ambulatory Surgery Center 2600 Redondo Ave. Long Beach, CA 90806		
	Atlantis Eyecare 7777 Edinger Ave. Suite 234 Huntington Beach, CA 92647		
	Talbert Surgical Associates 7677 Center Ave. Suite 104 Huntington Beach, CA 92647		
	Magnolia Surgery Center 14571 Magnolia Ave. Suite 107 Westminster, CA 92683		
	Pacific Hills Surgery Center 24022 Calle De La Plata, Suite 180 Laguna Hills, CA 92653		
19	Satish Modi, MD, CPI Alterman, Modi & Wolter 23 Davis Avenue Poughkeepsie, NY 12603	(b) (6)	12
21	Subba Gollamudi Ridgelake Ambulatory Surgery Center 825 Ridgelake Blvd Memphis, TN 38120	(b) (6)	10
	Eye Specialty Group 825 Ridgelake Blvd Memphis, TN 38120		
22	Trinh T. Nhu, MD Lakewood Eye Physicians and Surgeons, Inc. 3801 Katella Ave. Suite #130 Los Alamitos, CA 90720	(b) (6)	5
	Southern California Eye Physicians and Associates 3300 E. South St. Suite 107 Long Beach, CA 90805		

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Site No.	Investigator Name	Sub-Investigator(s) Name	Number of Patients Randomized
24	Miguel Unzueta, MD Mercy Eye Care, Inc. 1700 E. Cesar E. Chavez Ave, Ste #3400 Los Angeles, CA 90033	(b) (6)	10
	White Memorial Hospital 1720 Cesar E. Chavez Ave Los Angeles, CA 90033		
	Mercy Eye Care, Inc. 1717 W. Beverly Blvd Montebello, CA 90640		
25	Farrell C. Tyson, MD Argus Research at Cape Coral Eye Center 4120 Del Prado Blvd. Cape Coral, FL 33904	None	13
26	Faisal Haq Key Whitman Eye Center Plano 3060 Communications Pkwy Plano, TX 75093	(b) (6)	8
	Key Whitman Surgery Center 2801 Lemmon Ave Dallas, TX 75204		
27	Michael L. Nordlund, MD, PhD Cincinnati Eye Institute 4760 Red Bank Expressway, Suite 108 Cincinnati, OH 45227	(b) (6)	24
	Cincinnati Eye Institute Ambulatory Surgery Center 945 CEL Drive Cincinnati, OH 45227		
28	John Linn, MD Southern College of Optometry 1245 Madison Ave. Memphis, TN 38104	(b) (6)	4
	Eye Specialty Group 825 Ridgelake Blvd Memphis, TN 38120		
	Ridgelake Ambulatory Surgery Center 825 Ridgelake Blvd Memphis, TN 38120		

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Site No.	Investigator Name	Sub-Investigator(s) Name (b) (6)	Number of Patients Randomized
29	Zachary K. Segal, MD South Florida Surgery Center 6110 SW 70th St. Miami, FL 33143		9
	MedEye Associates 5950 Sunset Drive Miami, FL 33143		
30	Cynthia Matossian, MD Matossian Eye Associates 2 Capital Way, Suite 326 Pennington, NJ 08534		1
	Surgery Center of Central New Jersey 107 North Center Drive North Brunswick, NJ 08902		

Note: Site numbers 15, 20, and 23 are not applicable.

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/s/

JENNIFER D HARRIS
12/13/2017

WILLIAM M BOYD
12/14/2017