# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**208912Orig1s000**

# SUMMARY REVIEW

# Cross-Discipline Team Leader and Deputy Division Director Review for NDA 208912

| | |
|---|---|
| **Date** | February 5, 2018 |
| **From** | William M. Boyd, M.D. and Wiley A. Chambers, M.D. |
| **Subject** | Cross-Discipline Team Leader and Deputy Division Director Review |
| **NDA#** | NDA 208912 |
| **Applicant** | Icon Bioscience, Inc. |
| **Date of Submission** | April 12, 2017 |
| **PDUFA Goal Date** | February 12, 2018 |
| **Proprietary Name** | Dexycu |
| **Established Name** | Dexamethasone intraocular suspension, 9% |
| **Dosage Form(s)** | Intraocular suspension |
| **Indication** | Treatment of postoperative inflammation (b) (4) |
| **Dosing Regimen** | 0.005 mL administered into the posterior chamber inferiorly behind the iris |
| **Regulatory Action** | Approval |

## 1. Benefit-Risk Assessment

Dexycu (dexamethasone intraocular suspension) 9%, also referred to as IBI-10090 within this review, is a biodegradable, one-time drug delivery of dexamethasone in the eye of post-operative cataract surgery patients. The active ingredient in Dexycu is dexamethasone. Dexycu, when deposited by intraocular injection (b) (4), forms a sphere and provides for a slow-release of the (b) (4) dexamethasone from the carrier over time.

The clinical trials submitted in support of this NDA demonstrated that dexamethasone intraocular suspension 342 mcg and 517 mcg were both superior to placebo for the clearance of anterior chamber cells after cataract surgery. This superiority was first observed on day 3 after surgery and continued through post-operative day 30. The proposed to-be-marketed dose is 517 mcg.

Overall, there were no significant differences in adverse events noted between the 342 mcg and 517 mcg doses of Dexycu. Both 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. The rate of corneal endothelial cell loss was similar between placebo and the 517 mcg (to be marketed dose) treatment group at a rate of approximately 1.5%.

The rates of corneal edema and intraocular pressure were similar between the 517 mcg treatment group and placebo group. Both occurred at rates 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.

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

## Benefit-Risk Assessment Framework

**Benefit-Risk Integrated Assessment**

The data contained in this submission establishes the efficacy of Dexycu (dexamethasone intraocular suspension) 0.9% by demonstrating that in patients who underwent cataract surgery, a higher percentage of patients had no observable ocular inflammation during the first postoperative week. Study C13-04 demonstrated that both the 342 mcg dose and the 517 mcg dose are statistically superior to placebo for the clearance of anterior chamber cells (a measure of inflammation).

The most commonly reported adverse reactions occurred in 5-15% of Dexycu treated subjects and included increases in intraocular pressure, corneal edema and iritis. To date, no long term consequences of Dexycu administration have been identified.

The potential benefits of Dexycu (dexamethasone intraocular suspension) 0.9% through reduction of postoperative inflammation outweigh the identified risks as demonstrated in the clinical studies submitted with this NDA application.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | Inflammation, including postoperative inflammation, can lead to permanent damage to the anterior and posterior segments of the eye and to elevations of intraocular pressure which can damage the optic nerve. | Postoperative inflammation can be controlled and managed by the operating physician with the use of nonsteroidal or steroid products in the postoperative setting. |
| **Current Treatment Options** | Currently available treatments for postoperative inflammation following ocular surgery include the use of steroidal or nonsteroidal anti-inflammatory drug products. | This product, if approved, would provide an alternative steroid, administered as a single dose, intraocularly in the posterior chamber of the eye at the end of surgery. |
| **Benefit** | Reduction, specifically clearance, of inflammation, in the form of anterior chamber cells is a benefit; anterior chamber cells can be monitored by direct visualization of the anterior changer of the eye. | Study C13-04 demonstrated that both the 342 mcg dose and the 517 mcg dose are statistically superior to placebo for the clearance of anterior chamber cells. |
| **Risk and Risk Management** | Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. 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. | The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of corticosteroids could be monitored. The observed rates with the use of this product were consistent with rates expected for corticosteroids. |

# 2. Background

This is a 505(b)(2) application. The application relied on the listed drugs Decadron injection (NDA 12-071) and Decadron phosphate solution/drops ophthalmic/otic (NDA 11-984). NDA 11-984, Decadron phosphate ophthalmic solution was discontinued from sale in the United States in 2001, but was not withdrawn for reasons of safety or efficacy.

The active ingredient of Dexycu, 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%).

**Table of Currently Available Treatments for the Proposed Indication**

| 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.<br>Treatment of endogenous anterior uveitis. |
| 202-872 | Loteprednol etabonate ophthalmic gel 0.5% (Lotemax) | Treatment of post-operative inflammation and pain 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<br>201-211<br>202-030<br>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<br>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. |

An EOP2 (CMC) Meeting for IND 105562 was held 12/03/2013.

A Pre-NDA (Clinical) meeting for IND 105562 was 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.

# 3. Product Quality

See the Product Quality review finalized 1/5/2018.

**DRUG SUBSTANCE - Dexamethasone USP Micronized Drug Substance Specifications**

| Test[a] | Test Method | Current Acceptance Criteria | |
|---|---|---|---|
| CofA Verification | Manufacturer | (b) (4) | |
| | Material Name | | |
| | Manufacturer's Part Number | | |
| | Manufacturer's CofA results review | All testing meets the requirements. | |
| Appearance/Description | Visual | A white or almost white, (b) (4) powder | |
| Identification A: Infrared Absorption | Current USP Monograph for Dexamethasone, USP <197K> | IR spectrum of the test sample matches that of the USP Reference Standard | |
| Identification B: Ultraviolet Absorption | Current USP Monograph for Dexamethasone, USP <197U> | Absorptivity at 239 nm, calculated on the dried basis, does not differ by more than 3.0% | |
| Assay: HPLC | Current USP Monograph for Dexamethasone TP-307-501 | 97.0% - 102.0% on a dried basis | |
| Chromatographic Purity: HPLC | Current USP Monograph for Dexamethasone TP-308-501 | Any individual impurity | NMT 1.0% |
| | | Total Impurities | NMT 2.0% |
| | | (b) (4) | |

| Test[a] | Test Method | Current Acceptance Criteria |
|---|---|---|
| Specific Rotation | Current USP Monograph for Dexamethasone, USP <781S> | Between +72° and +80° |
| Loss on Drying | Current USP Monograph for Dexamethasone, USP <731> | NMT 0.5% |
| Residue of Ignition | Current USP Monograph for Dexamethasone, USP <281> | NMT 0.2% |
| Particle Size[b] | (b) (4) | |
| Microbial Enumeration Tests | Current USP <61> | (b) (4) |
| Tests for Specified Microorganisms (Pathogens) | Current USP <62> | |
| (b) (4) | | |

Source: Module 3.2.S.4.1

**DRUG PRODUCT**

## 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)[a,c] | 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 | ---- | ---- | ---- |
| **Total** | | | (b) (4) | | |
| (b) (4) | | | | | |

Source: Module 3.2.P.1.1

## Composition of IBI-10090 Administration Syringe Kit Assembly

| Sterile Pouch | Component | Manufacturer/ Supplier[a] | Manufacturer/ Supplier Part Number |
|---|---|---|---|
| IBI-10090 Syringe Assembly | (b) (4) | | |
| Syringe | | | |
| Syringe Cannula | | | |
| Syringe Needle | | | |

[a] Commercially available except where noted

Source: Module 3.2.P.1.2

## Drug Product Specifications (IBI-10090, 9%)

| Test Parameter | Analytical Method | Current Acceptance Criteria |
|---|---|---|
| Appearance (Description) | Visual | White to off-white opaque suspension |
| Identity (UV)[a] | TM.04062 | Conforms to reference |
| Identity (RRT by HPLC)[a] | | Conforms to reference |
| Assay Label Claim (%) | | 90.0%–110.0% |
| Uniformity of Dosage Units[a] | | USP<905> Content Uniformity acceptance criteria |
| Degradation Products<br>(b) (4)<br>Any Individual Unspecified Degradation Product[c]<br>Total Degradation Products | TM.04061 | <br>NMT (b) (4)%<br>NMT %<br>NMT %<br>NMT %<br><br>NMT % |
| In Vitro Cumulative Release Profile[b,d]<br>1 Day<br>3 Day<br>7 Day<br>14 Day | TM.04797 | <br>(b) (4)%<br>%<br>%<br>NLT (b) (4)% |
| Particle Size<br>10%<br>50%<br>90% | A1102 | <br>(b) (4) µm<br>< µm<br>< µm |
| Osmolality (mOsm/kg) | USP<785><br>TP-316-501 | (b) (4) |
| Viscosity (cP) | USP<912> | |

| Test Parameter | Analytical Method | Current Acceptance Criteria |
|---|---|---|
| pH | (b) (4) | |
| Sterility | | |
| Bacterial Endotoxins | | |
| Container Closure Integrity Dye Immersion (Visual) | | |
| Identity by XRPD | | |
| Redispersibility (Visual) | | |

a Release tests only

b Improved dissolution method in (b) (4)

c Report any unspecified impurity above (b) (4) according to the Reporting Threshold of (b) (4) for (b) (4) (ICH Q3B (R2), Attachment 1)

d Revised based on FDA IR SN0027. Each specification acceptance criterion must conform to (b) (4) testing described in (b) (4)

Source: Module 3.2.

**CONTAINER CLOSURE SYSTEM**

The IBI-10090 Administration Syringe Kit Assembly consists of four individual sterile pouches containing a) one IBI-10090 Syringe Assembly (one syringe guide and one syringe ring), b) one commercially available syringe, c) one commercially available syringe cannula, and d) one commercially available syringe needle.

**Photo of Proposed Commercial Outer Carton Holding IBI-10090 Drug Product Vial and Four Components of IBI-10090 Administration Syringe Kit Assembly**

(b) (4)

Source: Module 3.2.P.7.2

**Market Package**

(b) (4)

Source: Module 3.2.P.7.3

**FACILITY INSPECTIONS**

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 208912 were found to be acceptable.

**Summary of Drug Substance Facility Information**

| Establishment Name and Address | FEI Number | Responsibilities and profile codes | Initial Risks Identified | Final Recommendation |
|---|---|---|---|---|
| (b) (4) | | | | **Adequate** – Based on manufacturing capabilities and inspectional history |

**Summary of Drug Product Facility Information (continued)**

| Establishment Name and Address | FEI Number | Responsibilities and profile codes | Initial Risks Identified | Final Recommendation |
|---|---|---|---|---|
| (b) (4) | | | | **Adequate** – Based on manufacturing capabilities and inspectional history |
| | | | | **Adequate** – Based on PAI for the subject application |
| | | | | **Adequate** – Based on testing capabilities and inspectional history |
| | | | | **Adequate** – Based on testing capabilities and inspectional history |
| | | | | **Adequate** – Based on testing capabilities and inspectional history |

**OPQ Summary Statement:** NDA 208912, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product, Dexamethasone intraocular suspension 9%. All information request and review issues have been addressed and there are no pending approvability issues.

The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approval" recommendation was entered in Panorama by the Office of Process and Facilities (OPF) on 11-29-2017.

NDA 208912 is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

## 4. Nonclinical Pharmacology/Toxicology

See the Pharmacology/Toxicology review in DARRTS dated 1/19/2018.

The NDA was submitted under the 505(b)(2) pathway. The listed drugs (LD) were Decadron injection (NDA 12-071) and Decadron solution/drops ophthalmic/otic (NDA 11-984). A sufficient bridge to the LD was demonstrated, based on comparison of dose of dexamethasone,

as described in Decadron Injection labeling (up to 9 mg/day), and that of the applicant's drug product (0.517 mg/single intraocular injection). The total dose of the dexamethasone following ocular administration of Dexycu is much lower than that of Decadron at the maximum approved dose. As such, reliance on Decadron for systemic safety (including safety pharmacology and genotoxicity assessment) is scientifically appropriate.

# 5. Clinical Pharmacology

See the Clinical Pharmacology review in DARRTS dated 1/11/2018.

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.

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 Cmax, AUC0-t, and Tmax 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 Cmax, AUC0-t, and Tmax 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.

# 6. Clinical Microbiology

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

# 7. Clinical/Statistical- Efficacy

| 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<br>2.To evaluate the safety and tolerability of IBI-10090 used for treatment of cataract surgery postoperative inflammation | IBI-10090:<br>114 mcg (n = 3),<br>513 mcg (n = 2),<br>684 mcg (n = 1) | Single anterior chamber injection of 10 mcl (90 days) |
| C10-01 | | | | IBI-10090:<br>513 mcg (n = 13),<br>776 mcg (n = 14),<br>1046 mcg (n = 15) | Single anterior chamber injection of 7.5 mcl (90 days) |
| C11-01 | | | | IBI-10090:<br>342 mcg (n = 57),<br>517 mcg (n = 57),<br>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<br>2.To evaluate the safety and tolerability of IBI-10090 used for treatment of post-cataract surgery inflammation | IBI-10090:<br>0 mcg (acetyl triethyl citrate vehicle) (n =80)<br>342 mcg (n =158),<br>517 mcg (n =156) | Single anterior chamber injection of 5 mcl (90 days) |

| 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. | *IBI-10090:*<br>517 mcg (n = 126)<br><br>Eye drops:<br>Prednisolone acetate ophthalmic suspension 1% (n = 55) | Single anterior chamber injection of 5 mcl (90 days)<br><br>One drop four times daily for three weeks<br>(90 days) |

Study C13-04 was an adequate and well-controlled trial which was reviewed as the main source for evaluating the efficacy for this product. Study C15-01 was an open label parallel-design Phase 3 trial which evaluated efficacy, but was considered primarily in the evaluation of safety because of the potential bias associated with knowing the assigned treatment arm.

The phase 2 studies were dose ranging studies which enrolled small patient populations with different concentrations/dosage volume.

**ANALYSIS OF PRIMARY ENDPOINT: C13-04**
**Proportion of patients with ACC = 0 in study eye based on last observation carried forward [LOCF] data. Day 8 was considered the primary endpoint.**

| 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 ≥ 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.

Both the 342 mcg 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.

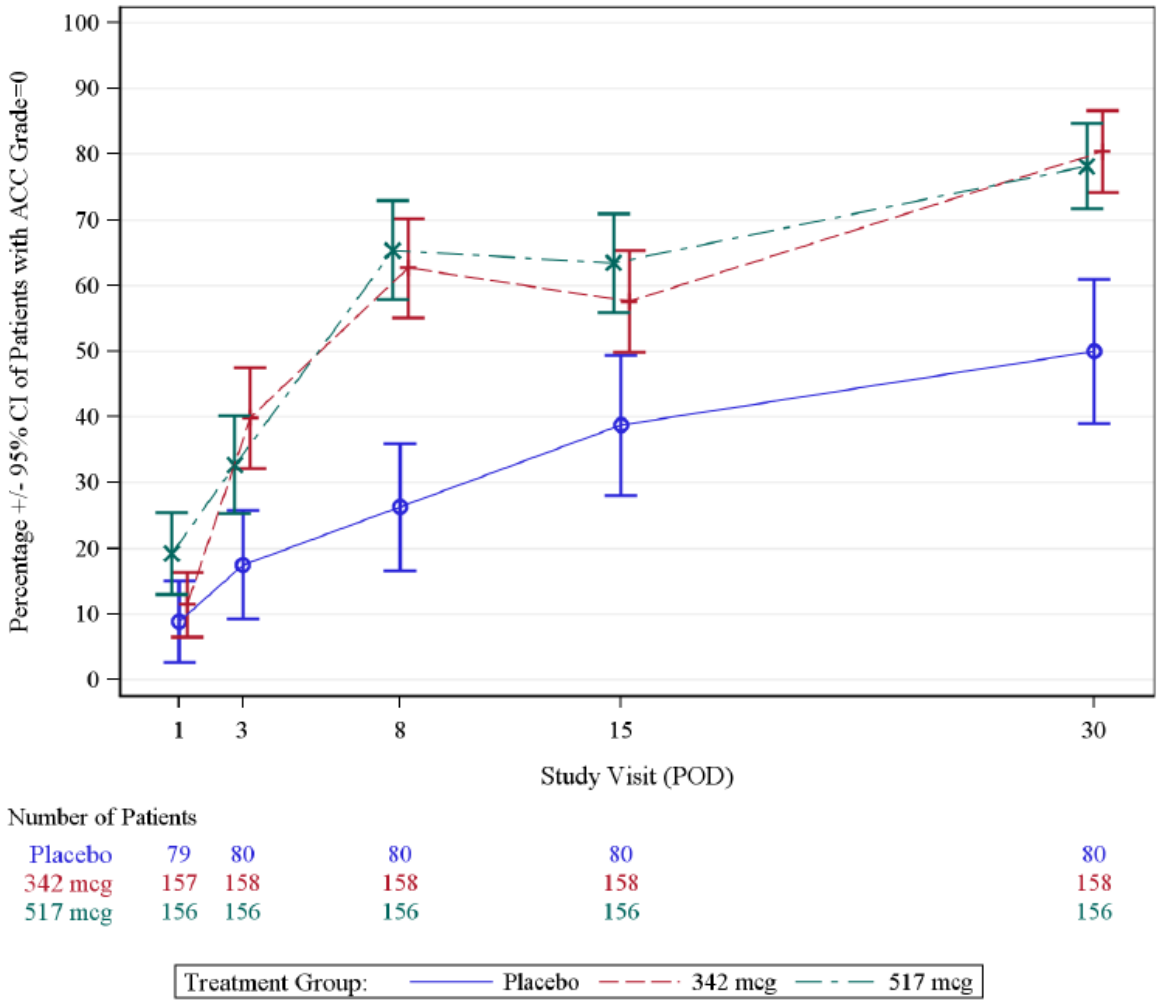
**ANALYSIS OF SECONDARY ENDPOINT(S) : C13-04**

There were multiple secondary endpoints measured over multiple timepoints for this trial. Total resolution of anterior chamber cells is considered supportive of the primary efficacy endpoint.

**Subpopulation Analysis:**

The 517 mcg group was statistically superior to placebo for all subpopulations evaluated (i.e., gender, age).

**Patients with ACC Grade=0 Over Time (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\f_hilo_itt_accc.sas cchesbrough Run date: 21MAR15 10:54 SDTM data version date: 2015-02-05

Both the 342 mcg dose and 517 mcg dose are superior to placebo for the clearance of anterior chamber cells. This superiority was observable on day 3 after surgery and continued through postoperative day 30.

**RESCUE MEDICATIONS**

The protocol defined rescue medications was ocular topical corticosteroids and/or ocular topical NSAIDs. The use of corticosteroids or NSAID products, regardless of the route of administration, could potentially influence the inflammation seen in subjects

The applicant was requested to provide the following two tables:

1. Table with percentage of patients with an anterior chamber cell score of zero
   a. The denominator for each column should be the number of patients randomized to that group.
   b. The numerator should be the number of patients who did not receive any corticosteroids (excluding study medication) or non-steroidal anti-inflammatory drug (NSAID) products by any route of administration prior to that particular visit and having an anterior chamber cell score of zero.
   i. If there is no evaluation at a particular visit, the patient should be counted as a success if the most recent postoperative visit in which the patient was examined had an anterior chamber cell score of zero, otherwise, the patient should be considered a failure.
   ii. Any patient who receives any corticosteroid (excluding the study medication) or non-steroidal drug product should be considered a failure at each visit after they received the corticosteroid or NSAID.

2. Table with the percentage of patients taking rescue medications (regardless of reason)
   a. The denominator for each column should be the number of patients randomized to that group.
   b. The numerator should be the number of patients being prescribed or having taken, a corticosteroid or NSAID at that visit or at any prior visit.

Proportion of subjects with clearing of the anterior chamber cells by visit

| Visits | Treatments | | | Difference and 97.5% CI | |
|---|---|---|---|---|---|
| | Placebo N=80 | DEX342 N=158 | DEX517 N=156 | DEX342 vs Placebo | DEX517 vs Placebo |
| Day 1 | 7 (9%) | 17 (11%) | 24 (15%) | 2% (-7%, 11%) | 7% (-3%, 16%) |
| Day 3 | 13 (16%) | 60 (38%) | 44 (28%) | 22% (9%, 34%) | 12% (0%, 24%) |
| Day 8 | 16 (20%) | 90 (57%) | 94 (60%) | 37% (24%, 50%) | 40% (27%, 54%) |
| Day 15 | 21 (26%) | 83 (52%) | 91 (58%) | 26% (12%, 40%) | 32% (18%, 46%) |
| Day 30 | 28 (35%) | 113 (72%) | 103 (66%) | 36% (22%, 51%) | 31% (16%, 46%) |

*Subjects who received rescue medication were treated as failure.*

Table 2: Proportion of subjects receiving rescue medications

| Visits | Number (Percent) of Patients Receiving Rescue Medication, and 95% CI | | |
|---|---|---|---|
| | Placebo N=80 | DEX342 N=158 | DEX517 N=156 |
| Day 1 | 10 (13%); 6%, 22% | 9 (6%); 3%, 10% | 10 (6%); 3%, 12% |
| Day 3 | 30 (38%); 27%, 49% | 9 (6%); 3%, 10% | 16 (10%); 6%,16% |
| Day 8 | 40 (50%); 39%, 61% | 12 (8%); 4%, 13% | 16 (10%); 6%,16% |
| Day 15 | 43 (54%); 42%, 65% | 22 (14%); 9%, 20% | 26 (17%); 11%, 24% |
| Day 30 | 43 (54%); 42%, 65% | 25 (16%); 10%, 22% | 31 (20%); 14%, 27% |

*Subjects who received an ocular corticosteroid or NSAID in study eye.*

**Study C15-01**

Study C15-01 was a Phase 3 clinical trial comparison between Dexycu and topical prednisolone acetate suspension. The interpretation of the efficacy results is limited because the participants were informed of their treatment arm and efforts to minimize potential bias were not taken.

**ANALYSIS OF PRIMARY ENDPOINT: C15-01**
**Proportion of patients with ACC = 0 in study eye based on last observation carried forward [LOCF] data**

Summary and Analysis of Anterior Chamber Cell Clearing (LOCF) Over Time ITT Analysis Set

| **POD 1 ACC Clearing** | **IBI-10090 517 mcg (N=126)** | **Prednisolone Drops (N=55)** |
|---|---|---|
| N | 124 | 55 |
| Yes | 18 (14.5%) | 6 (10.9%) |
| 95% Exact CI of Yes | 8.8%, 22.0% | 4.1%, 22.2% |
| Difference (IBI-10090 - Drop) (%) | 3.6% | |
| 95% CI of Difference | -6.7%, 13.9% | |
| **POD 8 ACC Clearing** | | |
| n | 126 | 55 |
| Yes | 65 (51.6%) | 28 (50.9%) |
| 95% Exact CI of Yes | 42.5%, 60.6% | 37.1%, 64.6% |
| Difference (IBI-10090 - Drop) (%) | 0.7% | |
| 95% CI of Difference | -15.2%, 16.5% | |
| **POD 30 ACC Clearing** | | |
| n | 126 | 55 |
| Yes | 88 (69.8%) | 41 (74.5%) |
| 95% Exact CI of Yes | 61.0%, 77.7% | 61.0%, 85.3% |
| Difference (IBI-10090 - Drop) (%) | -4.7% | |
| 95% CI of Difference | -18.7%, 9.3% | |
| **POD 90 ACC Clearing** | | |
| n | 123 | 52 |
| Yes | 121 (98.4%) | 52 (100%) |
| 95% Exact CI of Yes | 94.2%, 99.8% | 93.2%, 100% |
| Difference (IBI-10090 - Drop) (%) | -1.6% | |
| 95% CI of Difference | -3.9%, 0.6% | |

No significant differences in efficacy were observed between groups. The percentage of patients with resolved inflammation was consistent between Study C15-01 and C13-04.

**Efficacy Summary Statement**

Both the 342 mcg dose and the 517 mcg dose were statistically superior to placebo for the clearance of anterior chamber cells. There was no statistical or clinical difference between the two dose groups in the primary efficacy endpoint. 517 mcg is the proposed to-be-marketed dose.

# 8. Safety

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 Dexycu dose groups of 342 mcg (N=215), 517 mcg (N=339), 697 mcg (N=58).

**DEATHS**
No deaths were reported during any of the five clinical studies of Dexycu.

**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 loss | 0 | 0 | 3 1.4%) | 1 0.3%) |
| 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

Corneal endothelial cell loss was the most frequent (7/612) ocular SAE in patients treated with Dexycu. Three out of four (3/4) of these events occurred in the lower dose group (342 mcg).

## 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 (64%) | 13 (24%) | 152 (45%) |
| **Ocular AEs** | | | |
| Anterior Chamber Cell | 8 (10%) | 0 | 6 (2%) |
| Anterior chamber inflammation | 10 (12.5%) | 0 | 9 (3%) |
| Blepharitis | 0 | 2 (4%) | 4 (1%) |
| Corneal endothelial cell loss | 1 (1%) | 0 | 5 (1.5%) |
| Corneal edema | 8 (10%) | 1 (2%) | 24 (7%) |
| Cystoid Macular Edema | 3 (4%) | 1 (2%) | 6 (2%) |
| Dry eye | 0 | 0 | 11 (3%) |
| Eye Inflammation | 0 | 0 | 5 (1.5%) |
| Eye pain | 7 (9%) | 2 (4%) | 7 (2%) |
| Foreign body sensation in eye | 0 | 2 (4%) | 11 (3%) |
| Iritis | 11 (14%) | 0 | 17 (5%) |
| Photophobia | 3 (4%) | 1 (2%) | 4 (1%) |
| Posterior capsule opacification | 2 (2.5%) | 0 | 12 (3.5%) |
| Vision Blurred | 1 (1%) | 1 (2%) | 4 (1%) |
| Visual Acuity Reduced | 2 (2.5%) | 0 | 4 (1%) |
| Vitreous detachment | 1 (1%) | 0 | 4 (1%) |
| Vitreous floaters | 0 | 1 (2%) | 5 (1.5%) |
| **Injury, poisoning, and procedural complications** | | | |
| Post procedural complication | 0 | 1 (2%) | 7 (2%) |
| **Investigations** | | | |
| Intraocular pressure increased | 7 (9%) | 2 (4%) | 39 (11.5%) |
| **Systemic AEs** | | | |
| Hypertension | 0 | 0 | 3 (1%) |

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.

There was no significant difference overall in the rate of systemic adverse events or ocular events in the study between placebo and Dexycu 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.

**DROPOUTS/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 |
| | | 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 |

**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.

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 | 1 (1%) | 0 | 6 (3%) | 5 (1.5%) | 9 (15.5%) |
| Corneal Edema | 8 (10%) | 1 (2%) | 14 (6.5%) | 24 (7%) | 3 (5%) |
| Increased Ocular Pressure | 7 (9%) | 2 (4%) | 19 (9%) | 39 (11.5%) | 3 (5%) |

**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 | 2398 | 2561 | 2536 |
| | | | | |
| POD 90 (cells/mm$^2$) | | | | |
| N | 74 | 51 | 148 | 270 |
| Mean | 2123 | 2106 | 2171 | 2131 |
| | | | | |

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)

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

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.

**Safety Summary Statement**
Overall, there were no significant differences in adverse events noted between the 342 mcg and 527 mcg doses of Dexycu. 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.

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of Dexycu. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular

inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

While corneal endothelial cell loss was the most frequent ocular SAE in patients treated with Dexycu, the rate of corneal endothelial cell loss was similar between placebo and the 517mcg (to be marketed dose) treatment group. The rate was approximately 1.5% and the number of cells loss in each group was similar in each group (placebo=15%, prednisolone drops=12% and Dexycu=16%).

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.

## 9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## 10. Pediatrics

The product triggers PREA as a new dosage form and new route of administration. An Initial Pediatric Study Plan was submitted 01/29/2014. Agency comments were provided, and a revised plan submitted 02/15/2017; the sponsor plans to study pediatric patients (b) (4) (b) (4)

The application was presented at PeRC on 11/29/2017. The PeRC concurred with the applicant's plan to request a deferral of pediatric studies as outlined in the Agreed iPSP. The deferred pediatric study will be required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) as a required postmarketing study. This required study is listed below:

3334-1 A Phase 3/4, Prospective, Randomized, Active Treatment-controlled, Parallel-design, Multicenter Trial to Evaluate the Safety of IBI-10090 for the Treatment of Inflammation Following Ocular Surgery for Childhood Cataract.

| | |
|---|---|
| Final Protocol Submission: | 08/2018 |
| Study/Trial Completion: | 12/2021 |
| Final Report Submission: | 06/2022 |

# 11. Other Relevant Regulatory Issues

**DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)**
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Dexycu, and granted conditional acceptance on 7/25/2017. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA completed a labeling review of the originally submitted labeling on 12/4/17.

**OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)**
The Office of Prescription Drug Promotion (OPDP) completed a formal review of the substantially complete package insert on 12/29/17 and was present at the formal team labeling meetings.

**FINANCIAL DISCLOSURE**
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)**
Per the Office of Scientific Investigations review completed on 12/1/2017:

The Applicant submitted this NDA to support the use of Dexycu (IBI-10090, dexamethasone intraocular injection) in the treatment of post-operative inflammation (b) (4) .

Inspections were requested for the following protocol in support of this application:

**Protocol C13-04**, "A Phase 3, Prospective, Randomized, Double-masked, Placebo-controlled, Parallel-design, Multicenter Study to Evaluate Efficacy and Safety of IBI-10090 for the Treatment of Inflammation Associated with Cataract Surgery"

This study was conducted at 27 domestic study sites enrolling 395 subjects. The clinical sites of Drs. Sampson and Nordlund were selected for inspection because they enrolled relatively large numbers of subjects and have not been previously inspected.

| Site #/ Name of CI/ Address | Protocol #/ # of Subjects (enrolled) | Inspection Dates | Classification |
|---|---|---|---|
| Site #09<br><br>Reginald Sampson, M.D.<br>Hull Eye Center 1739 West Avenue<br>Lancaster, CA 93534 | C13-04<br>Subjects: 35 | 14-18 Aug 2017 | VAI |
| Site #27<br><br>Michael L. Nordlund, M.D., Ph.D.<br>Cincinnati Eye Institute<br>4760 Red Bank Expressway, Suite 108<br>Cincinnati, OH 45227<br><br>Cincinnati Eye Institute Ambulatory Surgery Center<br>945 CEL Drive<br>Cincinnati, OH 45227 | C13-04<br>Subjects: 24 | 11-18 Oct 2017 | VAI |

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Based on the results of these inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of both of these inspections was Voluntary Action Indicated (VAI).

**BIOSTATISTICS:**
Per the Biostatistics reviews completed on 12/21/2017 and 2/6/2018:

The main objective of this review is to evaluate whether the efficacy findings from Study C13-04 support the indication sought by the applicant for dexamethasone 517 µg.

This study met its primary objective of demonstrating the efficacy of Dexycu for the treatment of inflammation following cataract surgery. Compared to placebo, a higher proportion of subjects in the two Dexycu arms achieved clearing of the anterior chamber cells at Day 8 (Table 1). The observed treatment differences were [63% vs 26%; difference (97.5% CI): 36% (22%, 40%)] for DEX342 versus placebo; and [65% vs 26%; difference (97.5% CI): 39% (25%, 53%)] for DEX517 vs. placebo. A far higher proportion of placebo randomized subjects received a rescue medication based on the protocol defined criteria compared to subjects randomized to the two Dexycu arms (34% vs. 3%). In addition, a higher proportion of subjects in the placebo arm received a rescue medication without meeting the protocol defined rescue criteria (19% vs 6%; Table 1).

**Table 1: Results of the Primary Efficacy Analysis**

| | Treatment | | | Difference (%) (Asymptotic 97.5% CI) | |
|---|---|---|---|---|---|
| **Efficacy** | **Placebo N=80** | **DEX342 N=158** | **DEX517 N=156** | **DEX342 vs Placebo** | **DEX517 vs Placebo** |
| ACC Clearing[1] | 21(26%) | 99(63%) | 102(65%) | 36% (22%, 40%) | 39% (25%, 53%) |
| ACC Clearing[2] | 16 (20%) | 91 (58%) | 98 (63%) | 38% (26%, 49%) | 43% (31%, 54%) |
| | **Rescue Medication use on or Prior to Day 8** | | | | |
| Protocol-criteria met[3] | 27 (34%) | 3 (2%) | 4 (3%) | -32% (-42%, 21%) | -31% (-42%, 20%) |
| Protocol-criteria not met[4] | 15 (19%) | 10 (6%) | 10 (6%) | -13% (-22%, -3%) | -12% (-22%, -3%) |
| Total[5] | 41(51%) | 13(8%) | 13(8%) | -43% (-55%, -31%) | -43% (-55%, -31%) |

Source: [1] Applicant's primary analysis (Table 10 of the study reports). Subjects who received rescue medication on or before Day 8 **after meeting the rescue criteria** were treated as failures. Two subjects in the DEX342 arm had missing values and were imputed as failures. The 97.5% CI was calculated by the reviewer.
Source: [2] Reviewer's analysis. All subjects who received rescue medication on or before Day 8 (regardless of meeting a rescue criteria) were treated as failures. The two subjects with missing data at Day 8 were imputed as failures.
[3] Subjects who met the protocol defined rescue criteria on or before Day 8 and consequently received a rescue medication.
[4] Subjects who did not meet the protocol defined rescue criteria on or before Day 8 but received a rescue medication.
[5] Total number of subjects who received a rescue medication on or before Day 8 (with or without meeting the protocol defined rescue criteria).

Analyses of the primary efficacy endpoint were also conducted across various subject subgroups and using different methods to deal with intercurrent events (rescue use and study discontinuation). Results from these analyses are generally consistent with the primary efficacy analysis findings. Additionally, the analyses of several secondary efficacy endpoints provide supportive evidence for the efficacy of Dexycu.

Regarding safety, the most common adverse events (AEs) reported in the two Dexycu doses were increased intraocular pressure (IOP), eye pain, dry eye, corneal oedema, endothelial cell loss and iritis. The incidence of serious adverse events appears to be low in this study with only one ocular serious adverse event (corneal decomposition) reported in the DEX342 arm and no deaths reported. In conclusion, the results of the analyses presented in this statistical review demonstrate the efficacy of Dexycu for the treatment of post-operative inflammation.

## 12. Labeling

Labeling was submitted on 1/24/18 (package insert) and 1/29/2018 (carton and container labeling) following discussion and recommendations from the Agency. The final submitted labeling was found to be consistent with 21 CFR 201.57.

## 13. Postmarketing Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Agency is deferring submission of the pediatric study until June 2022, because this product is ready for approval for use in adults and the pediatric study has not been completed.

The deferred pediatric study will be required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) as a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

3334-1 A Phase 3/4, Prospective, Randomized, Active Treatment-controlled, Parallel-design, Multicenter Trial to Evaluate the Safety of IBI-10090 for the Treatment of Inflammation Following Ocular Surgery for Childhood Cataract.

| | |
|---|---|
| Final Protocol Submission: | 08/2018 |
| Study/Trial Completion: | 12/2021 |
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13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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WILLIAM M BOYD
02/08/2018

WILEY A CHAMBERS
02/09/2018