CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA208912 (Addendum)
Related IND #	IND 105562
Drug Name:	Dexycu (dexamethasone intraocular suspension 9%)
Indication(s):	Treatment of Inflammation Associated with Cataract Surgery
Applicant:	Icon Bioscience Inc.
Date(s):	Stamp date: April 12, 2017
	PDUFA date: February 12, 2018
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Abel Tilahun Eshete
Concurring Reviewers:	Yan Wang
Medical Division:	Ophthalmology
Clinical Team:	Medical Reviewer: Jennifer D. Harris
	William Boyd, Medical Team Leader
	Wiley Chambers, Deputy Director of DTOP
Project Manager:	Diana M. Willard

Keywords: Inflammation, Dexamethasone, Cataract surgery.

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1 SUMMARY

1.1 Introduction

This is an addendum for a statistical review for NDA 208912 submitted by Icon Bioscience for Dexycu (Dexamethasone intraocular suspension 9%). The original statistical review, uploaded to DARRTS on December 21, 2017, concluded that Study C13-04 demonstrated the efficacy of Dexycu for the treatment of inflammation (b) (4). The analyses results presented in this addendum do not change the overall conclusion of efficacy arrived in the original review. The main objective of this addendum is to amend some sections of the original statistical review and to present results of additional analyses that were conducted after the completion of the original statistical review. Specifically, this addendum is prepared:

A. To edit some errors identified in the original statistical review.

B. To include the analyses submitted by the applicant in response to the information request by the clinical review team.

C. To include additional analyses for two secondary efficacy endpoints conducted by the reviewer

1.2 Edits made to the original review

This section presents the required edits for Table 1 (Table 11), Table 12 (sensitivity analyses) and the mockup table (Table xx) that was included in the labeling recommendation section of the original review. The confidence intervals for the treatment differences presented in these tables were reported as 97.5% when in fact some of them were 95% confidence intervals. In addition, some results presented in Table 1 and Table 12 had typos. Finally, there was a minor discrepancy between the results presented in the mock-up table and a similar result provided by the applicant (see Appendix for details). The corrected results are presented in Tables A1-A3.

Table A1: Results of the Primary Efficacy Analysis (ITT)

	Treatment			**Difference (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%, 50%)	39% (25%, 53%)
ACC Clearing[2]	16 (20%)	91 (58%)	98 (63%)	38% (24%, 51%)	43% (30%, 56%)
	Rescue Medication use on or Prior to Day 8				
Protocol-criteria met[3]	27 (34%)	3 (2%)	4 (3%)	-32% (-44%, 20%)	-31% (-43%, -19%)
Protocol-criteria not met[4]	15 (19%)	10 (6%)	10 (6%)	-12% (-23%, -2%)	-12% (-23%, -2%)
Total[5]	41(51%)	13(8%)	13(8%)	-43% (-56%, -30%)	-43% (-56%, -29%)

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 (rescue criteria met or not) 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 (rescue criteria met or not).

Table A2: Sensitivity Analysis Results for the Primary Efficacy Endpoint (ITT)

Approaches	Treatment			Difference (%) (Asymptotic 97.5% CI)	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342 vs Placebo	DEX517 vs Placebo
Treatment policy[1]	31 (39%)	99 (63%)	105(67%)	24% (9%, 39%)	29% (14%, 43%)
Per-protocol[2]	15 (26%)	75(61%)	81 (66%)	36% (19%, 52%)	41% (24%, 57%)
Multiple imputation[3]	31 (39%)	102 (65%)	104 (67%)	26% (11%, 41%)	28% (13%, 43%)
LOCF[4]	23 (29%)	99 (63%)	102 (65%)	34% (20%, 48%)	37% (22%, 51%)
Primary[5]	16 (20%)	91 (58%)	98 (63%)	38% (24%, 51%)	43% (30%, 56%)
Rescue Medication[6]	41(51%)	13(8%)	13(8%)	-43% (-56%, -30%)	-43% (-56%, -29%)

[1]Source: Reviewer's analysis. All data including data collected after receiving rescue medication was used in the analysis. Two subjects in the DEX342 (one discontinued study after Day 0 and one subject with missing data at Day 8) were treated as treatment failures.
[2] Source: Adapted from Table 14.2.1.2 of the study report. Only subjects with no major protocol deviations were included in this analysis (N=122 for the two Dexycu groups and N=58 for the Placebo group). Subjects who received rescue medication after meeting the rescue criteria on or before Day 8 were treated as treatment failures.
[3] Source: Adapted from Table 14.2.2.14. Multiple imputation was used to impute an ACC clearing value at a Day 8 if the corresponding ACC grade was missing or a subject received rescue medication on or before a given time point.
[4] Source: Adapted from Table 14.2.2.12 of the study report. The ACC clearing status for subjects with missing data and for subjects who received a rescue medication after meeting the rescue criterion was determined based on observed ACC prior to rescue medication use (LOCF). One subject who discontinued study after Day 0 (LOCF cannot be applied) was treated as failure (The applicant excluded this subject from the analysis).
[5] Source: Reviewer's Analysis: Subjects who received rescue medication on or before Day 8 regardless of whether the protocol-defined rescue criterion was met were set as failures. Data for two subjects with missing ACC data at Day 8 was imputed as failures.
[6]Subjects who received rescue medication regardless of whether a rescue criterion is met on or before Day 8.

Table A3: Proportion of subjects with Clearing of the Anterior Chamber Cells by Visit (ITT)

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342vs Placebo	DEX517vs Placebo
Day 1	7 (9%)	17 (11%)	26 (17%)	2% (-7%, 11%)	8% (-2%, 18%)
Day 3	13 (16%)	60 (38%)	46 (30%)	22% (9%, 34%)	13% (1%, 26%)
Day 8	16 (20%)	91 (58%)	97 (62%)	38% (24%, 51%)	42% (29%, 56%)
Day 15	21 (26%)	83 (53%)	95 (61%)	26% (12%, 40%)	35% (21%, 49%)
Day 30	28 (35%)	115 (73%)	111 (71%)	38% (23%, 52%)	36% (22%, 51%)

Source: Table 2 of Applicant's response to information request located at \\CDSESUB1\evsprod\NDA208912\0030\m1\us\111-information-amendment. Subjects who received a rescue medication prior to the evaluation of efficacy (rescue criteria met or not) and subjects with no post-treatment ACC outcomes were set as treatment failures. For subjects with missing ACC, the ACC clearing was determined using ACC outcome from the previous visit.

1.3 Additional Analyses

1.3.1 Analyses Submitted by the Applicant in Response to an Information Request from the Clinical Review Ream

The protocol defined rescue medication was **ocular topical** corticosteroids and/or **ocular topical** NSAIDs. However, according to Dr. Wiley Chambers, the use of corticosteroids or NSAID products, **regardless of the route of administration**, could impact the inflammation status of subjects. Consequently, Dr. Chambers recommended that all subjects who received any corticosteroids (excluding study medication) and/or NSAID products **regardless of route of administration** be treated as treatment failures in the analysis of the primary efficacy endpoint. On January 09, 2018, the clinical review team sent an information request to the applicant. Specifically, 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 nominator should be the number of patients being prescribed or having taken, a corticosteroid or NSAID at that visit or at any prior visit

On January 24, 2018, the applicant submitted the requested tables (Table A4 and Table A5) together with the SAS codes and the dataset used to generate these results. The statistical reviewer was able to replicate these results using the dataset submitted. Dr. Chamber's recommended the inclusion of Table A4 (b) (4) and Table A5 in Section 14 of the drug labeling. The statistical team has no objection to the inclusion of Table A4. However, the team preferred Table A6 over Table A5 as Table A6 provides the treatment differences and corresponding 95% confidence intervals. Dr. Chambers preferred Table A5 over Table A6 and stated that the idea of having Table A5 was not to compare the treatment groups with the vehicle but rather to provide clinicians with an approximation of how often they would still need rescue therapy.

Table A4: Proportion of Subjects with Clearing of the Anterior Chamber Cell by Visit (ITT)

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342vs Placebo	DEX517vs 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(53%)	91(58%)	26%(12%,40%)	32%(18%,46%)
Day 30	28(35%)	113(72%)	103(66%)	(b) (4) (22%,51%)	31%(16%,46%)

Source: Table 1 in the applicant's draft updated labeling located at \\CDSESUB1\evsprod\NDA208912\0033\m1\us\114-labeling\draft\labeling.
Subjects who received rescue medication (corticosteroid and/or NSAID regardless of route of administration) prior to the evaluation of efficacy were treated as treatment failures.

Table A5: Proportion of Subjects Who Received an Ocular Corticosteroid or NSAID in the Study Eye

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%

Source: Table 2 in the applicant's draft updated labeling located at \\CDSESUB1\evsprod\NDA208912\0033\m1\us\114-labeling\draft\labeling.

Table A6: Proportion of Subjects Who Received an Ocular Corticosteroid or NSAID in the Study Eye

Visits	Treatments			Difference and 95% CI	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342 vs Placebo	DEX517 vs Placebo
Day 1	10 (13%)	9 (6%)	10 (6%)	-7% (-15%, 1%)	-6% (-14%, 2%)
Day 3	30 (38%)	9 (6%)	16 (10%)	-32% (-43%, -21%)	-28% (-39%, -16%)
Day 8	40 (50%)	12 (8%)	16 (10%)	-42% (-54%, -31%)	-40% (-52%, -28%)
Day 15	43 (54%)	22 (14%)	26 (17%)	-40% (-52%, -28%)	-37% (-49%, -25%)
Day 30	43 (54%)	25 (16%)	31 (20%)	-38% (-50%, -26%)	-34% (-46%, -21%)

Source: Adapted from Table 2 in the applicant's draft updated labeling located at \\CDSESUB1\evsprod\NDA208912\0033\m1\us\114-labeling\draft\labeling. The 95% Confidence intervals for the treatment differences are computed by the statistical reviewer.

1.3.2 Analysis of Secondary Efficacy Endpoints Conducted by the Reviewer

In the original review, the statistical reviewer conducted the analyses of two secondary efficacy endpoints, namely, the proportion of subjects with clearing of anterior chamber flare and the proportion of subjects with clearing of anterior chamber flare and cell. However, in those analyses, only subjects who received rescue medication **after meeting the protocol defined rescue criteria** [*ACC grade ≥ 3 and/or anterior chamber flare (ACF) grade ≥ 3 at a follow up visit after the surgery day*] were treated as treatment failures. There were however additional subjects who received the rescue medication without meeting the pre-specified criteria (Table A1).

In this addendum, the analysis of these endpoints is conducted with all subjects who received **the protocol-mandated rescue medication** (*including subjects who received the rescue medication without meeting the rescue criteria*) treated as treatment failures. The results are summarized in Table A7 and Table A8. In addition, in line with the analysis of the primary efficacy endpoint conducted by the applicant and summarized in Table A4, the statistical reviewer conducted the analysis of the two secondary efficacy endpoints with all subjects who received corticosteroids (excluding study medication) and/or NSAID products **regardless of route of administration** treated as treatment failures. The results are presented in Table A9 and Table A10.

Table A7: Proportion of Subjects with Clearing of the Anterior Chamber Flare by Visit (ITT)

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342vs Placebo	DEX517vs Placebo
Day 1	44(55%)	87(55%)	91(58%)	0%(-15%,16%)	3%(-12%,19%)
Day 3	31(39%)	114(73%)	114(73%)	34%(19%,48%)	34%(20%,49%)
Day 8	24(30%)	135(86%)	130(83%)	56%(43%,69%)	53%(40%,67%)
Day 15	29(36%)	121(77%)	120(77%)	41%(27%,55%)	41%(26%,55%)
Day 30	34(43%)	127(81%)	121(78%)	38%(24%,53%)	35%(21%,50%)

Source: Reviewer's Analysis. One subject in DEX342 with on post-treatment ACF data at all timepoints and subjects who received rescue medication (rescue criteria met or not) prior to the evaluation of efficacy were treated as treatment failures. Data from a prior visit was used for subjects with missing outcomes at a given visit.

Table A8: Proportion of Subjects with Clearing of the Anterior Chamber Cells and Flare by Visit (ITT)

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342vs Placebo	DEX517vs Placebo
Day 1	6(8%)	14(9%)	26(17%)	1%(-7%,10%)	9%(0%,19%)
Day 3	12(15%)	55(35%)	45(29%)	20%(8%,32%)	14%(2%,26%)
Day 8	13(16%)	91(58%)	97(62%)	42%(29%,54%)	46%(33%,59%)
Day 15	21(26%)	83(53%)	91(58%)	27%(12%,41%)	32%(18%,46%)
Day 30	27(34%)	113(72%)	108(69%)	38%(24%,53%)	35%(21%,50%)

Source: Reviewer's Analysis. One subject in DEX342 with on post-treatment ACF data at all timepoints and subjects who received rescue medication (rescue criteria met or not) prior to the evaluation of efficacy were treated as treatment failures. Data from a prior visit was used for subjects with missing outcomes at a given visit.

Table A9: Proportion of Subjects with Clearing of the Anterior Chamber flare by Visit (ITT)

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342vs Placebo	DEX517vs Placebo
Day 1	44(55%)	87(55%)	87(56%)	0%(-15%,15%)	1%(-15%,16%)
Day 3	34(43%)	114(72%)	112(72%)	30%(15%,44%)	29%(15%,44%)
Day 8	23(29%)	134(85%)	125(80%)	56%(43%,69%)	51%(38%,65%)
Day 15	27(34%)	120(76%)	115(74%)	42%(28%,56%)	40%(26%,54%)
Day 30	32(40%)	124(78%)	113(72%)	38%(24%,53%)	32%(18%,47%)

Source: Reviewer's Analysis. One subject in DEX342 with on post-treatment ACF data at all timepoints and subjects who received rescue medication (corticosteroid and/or NSAID regardless of route of administration) prior to the evaluation of efficacy were treated as treatment failures. Data from a prior visit was used for subjects with missing outcomes at a given visit.

Table A10: Proportion of Subjects with Clearing of the Anterior Chamber Cell and Anterior Chamber Flare by Visit (ITT)

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342vs Placebo	DEX517vs Placebo
Day 1	6(8%)	14(9%)	24(15%)	1%(-7%,10%)	8%(-1%,17%)
Day 3	12(15%)	55(35%)	43(28%)	20%(7%,32%)	13%(1%,25%)
Day 8	13(16%)	90(57%)	94(60%)	41%(28%,53%)	44%(31%,57%)
Day 15	21(26%)	83(53%)	87(56%)	26%(12%,40%)	30%(15%,44%)
Day 30	27(34%)	111(70%)	100(64%)	37%(22%,51%)	30%(16%,45%)

Source: Reviewer's Analysis. One subject in DEX342 with on post-treatment ACCACCF data at all timepoints and subjects who received rescue medication (corticosteroid and/or NSAID regardless of route of administration) prior to the evaluation of efficacy were treated as treatment failures. Data from a prior visit was used for subjects with missing outcomes at a given visit.

2 Appendix

The statistical reviewer conducted the analysis of the primary efficacy outcome with all subjects who received a rescue medication (*whether or not the rescue medication criteria were met*) treated as treatment failures. The statistical review team agreed that these results should be included in the drug labeling Section 14 (b) (4) Consequently, on December 22, 2017, the summary results were sent to the applicant for verification. The applicant provided responses on December 29, 2017. The applicant concurred with the results for the placebo arm. However, the applicant stated that 3 more subjects (one subject in the DEX 342 arm and 2 subjects in the DEX517 arm), who received a prohibited medication, should be treated as treatment failures in this analysis (see the applicant's summary response in Table A13). The summary results from the reviewer's and the applicant's analyses are presented in Table A11. As can be seen, the discrepancy between the two analyses were very small and the overall conclusion does not change regardless of how these subjects were treated in the analysis (see results in red).

After discussion with Dr. Wiley Chambers, the team leader, Dr. Yan Wang, concurred with the applicant's evaluation that the three subjects should be treated as treatment failures in the analysis of the primary efficacy outcome for the time points following the use of the prohibited medications. The reviewer was able to replicate the applicant's results by treating the aforementioned three subjects as treatment failures at the appropriate time points.

Table A11: Summary results for the Proportion of Subjects with Clearing of the Anterior Chamber Cell by Visit (ITT) (FDA and ICON analysis)

	FDA Analysis			ICON Analysis			FDA Analysis		ICON Analysis	
	Treatments			Treatments			Difference and 97.5% CI		Difference and 97.5% CI	
Visits	Placebo N = 80	DEX342 N = 158	DEX517 N = 156	Placebo N = 80	DEX342 N = 158	DEX517 N = 156	DEX342 vs Placebo	DEX517 vs Placebo	DEX342 vs Placebo	DEX517 vs Placebo
Day 1	7 (9%)	17 (11%)	26 (17%)	7 (9%)	17 (11%)	26 (17%)	2% (-7%, 11%)	8% (-2%, 18%)	2% (-7%, 11%)	8% (-2%, 18%)
Day 3	13 (16%)	60 (38%)	47 (30%)	13 (16%)	60 (38%)	46 (30%)	22% (9%, 34%)	14% (1%, 26%)	22% (9%, 34%)	13% (1%, 26%)
Day 8	16 (20%)	91 (58%)	98 (63%)	16 (20%)	91 (58%)	97 (62%)	38% (24%, 51%)	43% (30%, 56%)	38% (24%, 51%)	42% (29%, 56%)
Day 15	21 (26%)	83 (53%)	95 (61%)	21 (26%)	83 (53%)	95 (61%)	26% (12%, 40%)	35% (21%, 49%)	26% (12%, 40%)	35% (21%, 49%)
Day 30	28 (35%)	116 (73%)	113 (72%)	28 (35%)	115 (73%)	111 (71%)	38% (24%, 53%)	37% (23%, 52%)	38% (23%-52%)	36% (22%-51%)

Source: Table 2 of Applicant's response to information request located at \\CDSESUB1\evsprod\NDA208912\0030\m1\us\111-information-amendment.

Reviewer's Remarks: *The statistical reviewer provided the following reasoning why the three subjects were treated as treatment success in the original review:*

Subjects considered by the reviewer to have received a rescue medication without meeting the rescue criteria were subjects for whom the protocol deviation coded term (DVDECOD) has a value of "Ocular topical corticosteroids and/or ocular topical NSAIDs used in the study eye before Day 30, and pre-specified rescue criteria not met. (Protocol Page 26)." Note, ocular topical corticosteroids and/or ocular topical NSAIDs were the protocol defined rescue

medications. With this, according to this reviewer, although subject [redacted] received the protocol defined rescue medication, the time at which this medication was taken is listed as Day 122 in the data set. Consequently, in the analysis, the efficacy outcome for this subject was not treated as failure for Days 1, 3, 8, 15 and 30. [redacted] (b) (6) did not receive the protocol defined rescue medication. While subject 17-006 received the rescue medication on Day 1 (Surgery day based on the analysis window), given that the treatment was not meant as prophylaxis, but rather a treatment for inflammation following to cataract surgery, the reviewer did not treat the outcomes for Days 1,3, 8, 15 and 30 as treatment failures for this subject as well.

Table A12: Rescue medication Use and Efficacy Data for Subjects 10-002, 17-006 and 18-004

				Anterior Chamber Cell			Rescue, Prohibited, or Protocol Deviation		
Patient ID/ Analysis Set	Visit	Assessment Date	Study Day	Grade		Clearing	Type	Start Date [Study Day]	Medication Detail
[redacted] (b) (6)	SCREENING	[redacted] (b) (6)	-21 BL	0		Yes	Prohibited	[redacted]	PRED FORTE
	POD 1		2 A	1		No			
	POD 3		4 A	1		No			
	POD 8		9 A			No [IMPUTED]			
	POD 15		15 A	1		No			
	POD 30		22	1		No			
	POD 30		32 A	0		No [IMPUTED]			
	SCREENING		-11 BL	0		Yes	Prohibited, Protocol Deviation		PREDFORTE
	POD 1		2 A	1		No			
	POD 3		4 A	2		No			
	POD 8		7 A	1		No			
	POD 15		14 A	1		No			
	POD 30		30 A	0		No [IMPUTED]			
	SCREENING		-12 BL	0		Yes	Prohibited		OMNIPRED 1%
	POD 1		2 A	2		No			
	POD 3		4 A	0		No [IMPUTED]			
	POD 8		9 A	0		No [IMPUTED]			
	POD 15		16 A	1		No			
	POD 30		30 A	0		No [IMPUTED]			

Source: Applicant's Post Hoc listing included in the response to information request located at \\CDSESUB1\evsprod\NDA208912\0030\m1\us\111-information-amendment

Table A13: List of discrepancies between FDA and Icon Analysis for Prohibited Medications Considered Rescue Medications.

Subject ID	Rescue Prohibited Medication	Start Day	Difference between FDA/Icon Analysis	Icon Response
Placebo				
(b) (6)	TOBRADEX	15	FDA imputed this subject.	We confirm that in the original CSR this patient was imputed and included in 16.2.6 as receiving rescue medication. The analysis submitted December 22, 2017 erroneously did not include the proper imputed data at Day 30.
	PREDNISOLONE ACETATE	2	FDA noted this patient was treatment failure in the original CSR and imputed in their analyses	We confirm that in the original CSR analysis, this patient was imputed. The analysis submitted December 22, 2017 erroneously did not include the proper imputed data at Day 3, 8,15 and 30.
	PREDNISOLONE ACETATE	2	FDA noted this patient was treatment failure in the original CSR and imputed in their analyses	We confirm that in the original CSR analysis, this patient was imputed. The analysis submitted December 22, 2017 erroneously did not include the proper imputed data at Day 8,15 and 30.
			FDA did not impute this subject.	We have examined this patient and they were not listed as having received a rescue or prohibited medication in Listing 16.2.6. This patient was erroneously imputed in the December 22, 217 output.
342 DEX				
(b) (6)	**PREDNISOLONE ACETATE**	**15**	**FDA did not impute this subject.**	**We imputed day 8 (based on LOCF) and imputed this patient as receiving prednisolone starting Day 15.**
	DIFLUPREDNATE	14	FDA imputed this subject.	This subject was imputed in original analysis in CSR and erroneously not imputed in previous analysis submitted December 22, 2017.
517 DEX				
(b) (6)	**PREDNISOLONE ACETATE**	**1**	**FDA did not impute this subject.**	**We believe this patient should be included as imputed as having received rescue medication at Day 1. They were a treatment success on Day 30 and we imputed this in our analysis.**
517 DEX (cont.)				
(b) (6)	**PREDNISOLONE ACETATE**	**2**	**FDA did not impute this subject.**	**We believe this patient should be imputed starting on Day 2 as they received prednisolone acetate in the study eye.**
	LIDOCAINE	1	FDA did not impute this subject.	This subject who only received Lidocaine was erroneously imputed in the December 22, 2017 analysis. We agree to not impute this patient.

Source: Table 1 of Applicant's response to information request located at \\CDSESUB1\evsprod\NDA208912\0030\m1\us\111-information-amendment

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/s/

ABEL T ESHETE
02/06/2018

YAN WANG
02/06/2018
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

This is a statistical review of a 505(b) (2) New Drug Applications (NDA) submitted by Icon Bioscience for Dexycu (Dexamethasone intraocular suspension 9%). The proposed indication is [redacted] (b) (4) 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.

Study C13-04 was a Phase 3, prospective, multicenter, randomized, parallel-arm, double-masked, placebo controlled study. The primary objective of this study was to evaluate the efficacy and safety of two doses of Dexycu (342 µg and 517 µg; hereafter referred to as DEX342 and DEX517) in the treatment of inflammation associated with cataract surgery. A total of 395 subjects were randomized to receive either placebo (N=80), DEX342 (N=158), or DEX517 (N=156). At the completion of the cataract surgery, each subject received a single intraocular dose of his/her assigned treatment in the study eye. Subjects in the placebo arm received a non-drug delivery vehicle. The duration of the study was 90 days with efficacy and safety assessments conducted at post-operative Days 1, 3, 8, 15 and 30, with a final safety visit at Day 90.

For each subject, a slit lamp examination was performed and the number of anterior chamber cells (ACC) was quantified and graded as: 0 (0 cells), 1 (1 to 5 cells), 2 (6 to 15 cells), 3 (16 to 30+ cells), or 4 (hypopyon). The primary efficacy endpoint was the proportion of subjects with absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 8. Rescue treatment with ocular topical corticosteroids/NSAIDS was allowed per protocol-defined criteria: ACC grade $\geq$ 3 and/or anterior chamber flare (ACF) grade $\geq$ 3 at a follow up visit after the surgery day. The primary efficacy analysis was conducted based on all randomized subjects who received the study drug (ITT). Subjects who received a rescue medication prior to the evaluation of the primary efficacy endpoint, and subjects with no post-treatment values were set as treatment failures (ACC score of >0) in the primary efficacy analysis. For missing data due to other reasons, the inflammation status was determined based on the last non-missing inflammation score from a prior visit. A Bonferroni testing procedure was used to control the Type-I error rate for the comparison of the two Dexycu arms against placebo.

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).

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.

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).

Labeling recommendation: This reviewer recommends the following text and efficacy summary table for Section 14 (Clinical studies) of the drug labeling (See Section 6.4 for details):

In a randomized, multicenter, double-masked, parallel group, vehicle-controlled trial, subjects received Dexycu or its non-drug delivery vehicle immediately upon completion of cataract surgery. In this trial, Dexycu had a higher percentage of subjects who achieved clearing of the anterior chamber cell without receiving a rescue medication. Results are shown in Table xx.

Table xx: 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**	**DEX342vs Placebo**	**DEX517vs Placebo**
Day 1	7 (9%)	17 (11%)	26 (17%)	2% (-6%, 10%)	8% (-1%, 16%)
Day 3	13 (16%)	60 (38%)	47 (30%)	22% (11%, 33%)	14% (3%, 25%)
Day 8	16 (20%)	91 (58%)	98 (63%)	38% (26%, 49%)	43% (31%, 54%)
Day 15	21 (26%)	83 (53%)	95 (61%)	26% (14%, 39%)	35% (22%, 47%)
Day 30	28 (35%)	116 (73%)	113 (72%)	38% (26%, 51%)	37% (25%, 50%)

Subjects who received a rescue medication are set as treatment failures.

2 INTRODUCTION

This NDA included safety and efficacy data from one Phase 3 study (C13-04) to support the safety and efficacy of Dexycu for the treatment of post-surgical inflammation in subjects who have undergone cataract surgery. Additional safety data from one Phase 3 safety study (Study C15-01) and one Phase 2 dose ranging study (Study C11-01) are also included in this submission. Because the efficacy evaluations in the two additional studies were purely exploratory, only the efficacy results from Study C13-04 were considered to demonstrate the efficacy of Dexycu. Detailed summaries of the design and the exploratory efficacy results of the two studies (C11-01 and C15-01) are presented in Section 8. The safety summaries from the two additional studies are presented in Section 3.3.

Note: The applicant also conducted two small Phase 2 dose-ranging studies (Study C09-01 and C10-01). However, per the applicant, these studies used different concentrations (and dosage volumes) of Dexycu, as well as different delivery systems. Thus, the results from these two studies are not included in the main safety summary in this review. A summary of these studies is presented in Section 8.3.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the specific studies reviewed.

2.1.1 Drug Class and Indication

Per the applicant, Dexycu™ is a novel bioabsorbable, controlled drug delivery product designed for the short-term delivery of therapeutic levels of dexamethasone (the active ingredient) in the eye. The applicant states that, when deposited in the posterior chamber, anterior chamber, or vitreous of the eye, Dexycu forms a sphere that releases the active ingredient over a targeted time.

2.1.2 History of Drug Development

The protocols and the statistical analyses plans for all studies included in this NDA were reviewed under IND105562. The applicant had a Type-C guidance meeting with the agency on July 22, 2013. During this meeting, the applicant requested the agency whether one adequate and well controlled Phase 3 study with supportive evidence from a Phase 2 study is sufficient for the approval of Dexycu. The FDA stated that, efficacy is expected to be demonstrated in more than one adequate and well controlled study, and that the results from the proposed Phase 2 and Phase 3 studies could support registration. FDA also stated that 500 or more subjects using the test drug at a dose that is at least as high as recommended in the proposed labeling will be suitable to support registration. As part of the meeting package for the July 22, 2013 meeting, the applicant submitted a protocol synopsis for a Phase 3 study (C13-04). The applicant proposed the last-observation carried forward (LOCF) approach to deal with missing outcomes. For subjects who receive a rescue medication, the measurement prior to the rescue

medication would be carried forward. The statistical team reviewed the synopsis and recommended that subjects who receive a rescue medication prior to the evaluation of the primary efficacy endpoint be treated as treatment failures in the primary efficacy analysis; the applicant agreed. Additionally, the applicant agreed to conduct sensitivity analyses using a multiple imputation based approach.

The applicant also had an End-of-Phase 2 meeting with the agency on December 3, 2013. During this meeting, the applicant provided an update on their CMC program and discussed the initiation of their Phase 3 clinical study and the overall strategy for the continued CMC development and NDA filing for Dexycu. The applicant submitted an amended protocol and a statistical analysis plan (SAP) for Study C13-04 on January 30, 2014. This SAP stated that the LOCF method would be used for patients who had missing data or received a rescue medication prior to Day 8 in the primary analysis. In addition, the SAP stated that, as sensitivity analysis, subjects who receive a rescue medication prior to Day 8 would be treated as treatment failures. The statistical team reiterated that subjects who receive a rescue medication should be treated as treatment failures in the primary efficacy analysis (b) (4) The applicant listed both a generalized linear mixed model (GLMM) and a chi-square test for the primary efficacy analysis. The statistical team recommended that the chi-square test be used as a primary efficacy analysis method with the GLMM used to confirm the results. Furthermore, the statistical team (b) (4) On May 05, 2014, the applicant provided responses to the comments communicated to them following the review of the statistical analysis plan. The applicant stated that, if subjects receive any rescue medication on or before a given post-operative day (3, 8, 15, and 30), the ACC clearing will be set to treatment failure (ACC>0) on or after that day. They also noted that, in the previous study (C11-01), only three subjects on active drug required treatment with rescue medication. Based on this information, they anticipated that a larger number of subjects in the placebo arm might receive a rescue medication, thereby showing the effect in favor of the active drug. They proposed to utilize the LOCF method for subjects who have missing data (without receiving a rescue medication).

The applicant also had a pre-NDA meeting with the agency on July 20, 2015 to discuss the results of the completed Phase 3 study (C13-04). The applicant argued that, because the DEX517 treatment group showed a more rapid onset of effect, they proposed to select the DEX517 dose to go forward for commercial development. The agency accepted the proposal conditional on the results of the endothelial cell density analysis that was not sufficiently discussed in the meeting package.

(b) (4) Based on the time at which the first subject was enrolled into this study, it appears that this study was conducted after the completion of Study C13-04. The primary objective of this study was to generate additional safety data in support of Dexycu.

2.1.3 Studies Reviewed

This NDA review was conducted mainly based on data from Study C13-04 with additional safety information garnered from studies C11-01 and C15-01. Study C13-04 enrolled 395 subjects from a total of 27 sites. A total of 194 subjects from 11 sites, and 172 subjects from 13 sites were enrolled in studies in C15-01 and C11-01 respectively. The investigational sites in all the three studies are located within the US. The brief summaries for each of these studies are presented in Table 2.

Table 2: Summary of Studies (C13-04, C15-01 and C11-01)

Study	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
C13-04	A Phase 3, Prospective, Randomized, Double-masked, Placebo-controlled, Parallel-design, Multicenter Study to Evaluate the Efficacy and Safety of DEXYCU for the Treatment of Inflammation Associated with Cataract Surgery	– DEX342: N=158 – DEX517: N=157 – Placebo: N=80	Primary Endpoints: – Absence of cells (score of zero) in the anterior chamber cell of the study eye at Day 8 The primary efficacy analysis of evaluating superiority of the two DEXYCU arms against Vehicle was conducted on the ITT population consisting of all randomized and treated subjects. A Bonferroni correction was used to protect the overall Type I error rate at 0.05 for the analysis of the primary efficacy endpoints. For the analysis of the primary efficacy variable, subjects who received a rescue medication prior to POD 8 were treated as treatment failures. For missing data due to other reasons, the last observed value was used.	The study was successful in meeting its primary efficacy endpoints of demonstrating superiority of the two DEXYCU arms over placebo in the proportion of subjects with absence of ocular inflammation in the study eye at the Day 8 Visit. There was a statistically significant difference between each of the DEXYCU treatment groups and the placebo group ($p < 0.001$) for the proportion of subjects with clearing of ACC at POD 8. For the ITT population, clearing of ACC at POD 8 was observed for 62.7% of subjects in the 342µg treatment group and 66.0% of subjects in the 517µg treatment group, compared with 25.0% of subjects in the placebo group.
C15-01	A Phase 3, Prospective, Randomized, Open Label, Parallel-design, Multicenter Study to Evaluate the Safety of DEXYCU for the Treatment of Inflammation Associated with Cataract Surgery	– DEX517: N=130 – Prednisolone: N=64	Primary Endpoints: – Treatment emergent Adverse events – Absence of cells, flare in the study eye (exploratory efficacy endpoints) There was no formal sample size and power estimation for this study, since the objective of this study was to generate additional safety data in support of DEXYCU; no formal statistical testing was performed. The sample size of 180 subjects (randomized 2:1 DEXYCU 517 µg vs prednisolone eye drops) was selected to allow a robust assessment of safety and to augment the available safety data from the previously completed clinical trials of DEXYCU.	A total of 53/126 subjects (42.1%) in the 517µg group and 12/55 subjects (23.6%) in the prednisolone group had one or more adverse event (AE) in the study eye. The most frequently reported ocular AEs in the 517 µg group (occurring in 5% or more subjects) were increased IOP (11.1%) and iritis (6.3%). No AEs occurred in 5% or more subjects in the prednisolone group. The incidence of AEs in the fellow eye was similar between the treatment groups (9.5% in the 517 µg group and 7.3% in the prednisolone group). No TEAEs of corneal endothelial cell loss were reported.

Study	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
C11-01	A Phase 2 prospective, randomized, double-masked, dose-ranging, parallel-group, multicenter study.	– DEX342: N=58 – DEX517: N=56 DEX 697: N=58	Primary Endpoints: – Absence of cells (score of zero) in the anterior chamber cell of the study eye at Day 8	By dose group, clearing of ACC at POD 8 was observed for 50.0%, 51.8%, and 60.3% of subjects in the 342 µg, 517 µg, and 697 mcg groups, respectively

Source: Applicant's submitted study reports.

2.2 Data Sources

The data sources for this review included the applicant's clinical study reports and SAS datasets electronically submitted both as SDTM and ADAM data formats. The datasets used in this review are located at: \\Cdsesub1\evsprod\NDA208912\0001\m5\datasets. The inflammation outcomes, intraocular pressure and best corrected visual acuity measurements collected at screening and subsequent measurement times are included in the "adeff.xpt" dataset. An indicator variable (PARAMCD) is included to distinguish between the different outcomes. For the primary efficacy analysis of the inflammation outcome, the variable AVALC which takes a value of "Yes" if the inflammation score is zero or "No" if the inflammation score is greater than zero or the subject received a rescue medication prior to Day 8 is provided. The treatment variable, given both as numeric (TRT01P) and character (TRT01PN), is also included in the above dataset. The treatment exposure and adverse events reported during the study is included in the "adae.xpt" dataset. The rescue use flag (RESCUEFL) and the start date (CMSTDTC) and end date (CMENDTC) of rescue use were also provided in the contaminant medication dataset "adcm.xpt". The reason for protocol deviations is summarized in the "adpd.xpt" dataset.

3 STATISTICAL EVALUATION

This section provides a detailed summary of the studies included in this review.

3.1 Data and Analysis Quality

The quality of the datasets was sufficient for our review purposes. It was possible to reproduce the applicant's primary efficacy and safety results using the submitted datasets. The final statistical analysis plan and the amended protocols were all submitted.

One issue noted during the review was that the applicant did not properly distinguish between imputed and observed outcomes for the anterior chamber cell scores in the efficacy dataset. An information request for clarification was sent to the applicant on 09/19/2017. The applicant provided written responses on 09/29/17. The responses clarified the applicant's approach. (\\Cdsesub1\evsprod\NDA208912\0014\m1\us\112-other-correspondence). This however has not impacted the timely analysis and review of the primary and secondary efficacy endpoints.

3.2 Evaluation of Efficacy

This section summarizes the design and efficacy results of Study C13-04.

3.2.1 Study Design and Endpoints

Study C13-04 was a prospective, randomized, double-masked, placebo-controlled, parallel-design, multicenter study. This study enrolled 395 subjects who were undergoing cataract surgery. Inclusion criteria required male and female subjects to be ≥40 years of age with best corrected visual acuity (BCVA) of 20/30 to 20/200 in the study eye and better than 20/200 in the fellow eye. There was also to be evidence of a corneal endothelial cell density (ECD) in the study eye of at least 2000 cells/mm^2 with normal cell morphology.

Exclusion criteria disallowed subjects who used any ocular, topical, or oral corticosteroids within seven days prior to surgery day (Day 0). Also excluded were subjects who had received a periocular corticosteroid injection in the study eye in the three months prior to screening, subjects who had received any intravitreal corticosteroid delivery vehicle (e.g., Retisert®, Ozurdex®, Iluvien®) in the study eye at any time, and subjects with planned intraocular or laser surgery in the study eye during the study period.

Subjects who met all inclusion and no exclusion criteria were randomized to receive either placebo (N=80), DEX342 (N=158), or DEX517 (N=156). Randomization was done on the same day that study drug was administered at the completion of the cataract surgery in the study eye (Day 0). At the completion of the cataract surgery, subjects received a single dose of their respective treatments in the study eye ((b) (4) (acetyl triethyl citrate) for the placebo arm).

Subjects underwent safety and efficacy examinations on post-operative days (POD) 1, 3, 8, 15, and 30 with a final safety evaluation on Day 90. The schedule of events and the window used to determine analysis days is presented in Table 17. For each subject, a slit lamp examination was performed and the number of anterior chamber cells (ACC) was quantified and graded as: 0 (0 cells), 1 (1 to 5 cells), 2 (6 to 15 cells), 3 (16 to 30+ cells), or 4 (hypopyon). The primary efficacy endpoint was the proportion of subjects with absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 8. Secondary efficacy assessments included ACC clearing and grade at each visit, anterior chamber flare (ACF) clearing and grade (0=absent, 1=trace, 2=mild, 3=moderate and 4=strong) at each visit, and anterior chamber cell and flare (ACCF) clearing and grade (0: absent, >0: present) at each visit. Safety evaluation included assessment of adverse events (AEs), visual acuity, intraocular pressure (IOP) and corneal endothelial cell density (ECD).

The following is an excerpt from the applicant's clinical study reports regarding the use of rescue and prohibited medications:

"*Rescue treatment was allowed per pre-specified rescue criteria. Rescue medications were those treatments with ocular topical corticosteroids and/or ocular topical NSAIDs. They may have been administered in the study eye, if at a follow-up visit after the surgery day, pre-specified rescue criteria applied. The pre-specified rescue criteria were: ACC grade ≥ 3 and/or ACF grade ≥ 3 at a follow visit after the surgery day. If the rescue criteria were not met, the medications were considered prohibited medications."*

Subjects who received study drug but required rescue treatment in the study eye continued with follow-up visits for safety and efficacy assessments.

3.2.2 Statistical Methods

3.2.2.1 Analysis Populations

The statistical analysis plan and the study protocol defined the following analysis sets for the evaluation of efficacy, safety and pharmacokinetics in Study C13-04:

- Intent-to-treat (ITT) analysis set: All randomized subjects who received study drug. Subjects were included in their randomly assigned treatment group.

- Per-protocol (PP) analysis set: ITT subjects without clinically significant protocol deviations. Also, an ACC grade at POD 8 was required. Subjects were included in the treatment group to which they were randomized.

- Safety analysis set: Subjects who received any amount of study drug. Subjects were included in the treatment group corresponding to the actual treatment received.

- Pharmacokinetics (PK) analysis set: All subjects who received study drug and had at least one post-dose plasma concentration measurement. For analysis, subjects were included in the treatment group corresponding to the actual treatment received.

3.2.2.2 Analysis Methods

The protocol defined primary efficacy analysis compared the efficacy of the two doses of Dexycu against placebo for the treatment of inflammation following cataract surgery. The analysis was conducted on the ITT population using a continuity corrected chi-square test. A Bonferroni testing procedure was used to control the Type-I error rate for the comparison of the two Dexycu doses against placebo. Subjects who received a rescue medication based on the protocol-defined criteria on or before Day 8, and subjects with no post-treatment ACC outcomes were treated as treatment failures (score of >0) in the primary efficacy analysis. For missing data due to other reasons, the inflammation status was determined based on the last non-missing inflammation score from a prior visit. As supportive analysis, the analysis of the primary efficacy endpoint was also conducted on the per-protocol population (PP) with observed data. Here also, subjects who received a rescue medication on or prior to Day 8 were treated as treatment failures.

As sensitivity analyses, the applicant conducted the analysis of the primary efficacy endpoint with the LOCF and multiple imputation approaches used to impute missing ACC outcome. In these analyses, data after rescue medication was considered missing. The multiple imputation model included treatment, age, sex, and post-baseline ACC clearing values at days 1, 3, 8, 15, and 30. In this approach, missing data for a given visit was imputed using a logistic regression model with ACC clearing from a previous visit and the other covariates included in the model (see SAS code in the appendix). Additionally, the applicant used the generalized linear mixed model (GLMM) as supportive analysis of the primary efficacy endpoint. The GLMM model included ACC clearing values at days 1, 3, 8, 15, and 30 as dependent variable; time, treatment

and time by treatment interaction included as covariates. A variance component covariance matrix was assumed (See SAS codes in the Appendix).

The applicant used a chi-squares test for testing the statistical significance difference between Dexycu and placebo for the binary secondary efficacy endpoints (the clearing of anterior chamber flare and anterior chamber cell and flare). The applicant also used the same GLMM model discussed earlier for the analysis of binary secondary efficacy endpoints and provided proportions and 95% confidence intervals for treatment differences. In addition, the applicant used a GLMM model to analyze the ordinal ACC and ACF outcomes. In this model, the ordinal outcomes are used as dependent variables and treatment, time, and treatment by time interactions are included as fixed effects (See SAS codes in the Appendix). No multiple comparison or multiplicity adjustments were applied for the secondary efficacy analyses and only observed data was used (missing data were not imputed).

The reviewer conducted the analysis of the primary efficacy endpoint on the ITT population using all observed data regardless of whether the data was collected before or after rescue medication. In this analysis, subjects who had missing ACC data at Day 8 were treated as treatment failures. The reviewer also conducted the analysis of the primary efficacy endpoint on the ITT population by treating all subjects who received a rescue medication (regardless of whether they met the rescue criteria) as treatment failures. The LOCF approach was used for those with missing ACC data. In both analyses, the proportion of subjects with clearing of anterior chamber cell for each arm and a 97.5% confidence interval for the treatment differences was provided. The confidence intervals were computed using the normal approximation.

The reviewer conducted the analyses of the binary secondary efficacy endpoints using the same approach used for the primary efficacy analysis. In addition, the reviewer used a proportional odds logistic regression model to compare the odds of having higher ACC grades between placebo and the two Dexycu arms. The logistic model included the ordinal ACC grade (ACC score: 0, 1, 2, 3 and 4) as dependent variable and treatment as covariate. In this analysis, the ACC score for subjects who received a rescue medication were set to an ACC score of 3 (the maximum observed score in the data), while, the last non-missing inflammation score from a prior visit was used for those with missing ACC outcome. The summary of how different approaches handled missing ACC data and ACC data collected after rescue medication use (with and without meeting criteria) is presented in Table 3.

The reviewer also conducted a tipping point analysis to determine how many subjects in the placebo arm who received a rescue medication (and hence set as treatment failures) need to be set as treatment successes for the treatment difference to no longer be statistically significant.

Note: The applicant used the Bonferroni adjustment to control the type I error rate for the test of two hypotheses for the primary efficacy analysis (i.e. each test was conducted at 0.025 level of significance). However, for each treatment comparison, they provided the 95% confidence interval for the treatment differences. To align with the adjustment for the multiple comparison, the reviewer provided the 97.5% confidence interval for differences between each Dexycu dose and placebo for both the primary and secondary efficacy endpoints.

Table 3: Summary of How Different Approaches Handled Missing Data at Day 8 and Data Collected After Rescue use

Data Type	Applicant's Analysis			
	Primary	**LOCF**	**GLMM[3]**	**Multiple Imputation[4]**
Missing ACC data	Treated as failure if no prior post-baseline values; Otherwise imputed using the last available data from a prior visit	Excluded if no prior post-baseline values; Otherwise, imputed using the last available data from a prior visit	Left as missing (No imputation)	Set as missing and imputed using a multiple imputation approach
ACC data collected after rescue medication [1]	Treated as failure	Excluded if no prior post-baseline values; Otherwise, set as missing and imputed using the last available data prior to the use of rescue medication	Set as missing (No imputation) if the ACC=0; Otherwise, observed data used	Set as missing and imputed using a multiple imputation approach
ACC data collected after rescue medication [2]	Used as observed			

Data Type	Reviewer's Analysis		
	Primary	**Treatment Policy**	**Logistic Regression[5]**
Missing ACC data	Treated as failure if no post-baseline values; Otherwise, imputed using the last available data from a prior visit	Treated as failure	Treated as failure if no prior post-baseline values; Otherwise, imputed using the last available data from a prior visit
ACC data collected after rescue medication [1]	Treated as failure	Used as observed	Treated as failure
ACC data collected after rescue medication [2]	Treated as failure	Used as observed	Used as observed

[1] Rescue medication received after meeting the protocol-defined criteria
[2] Rescue medication received without meeting the protocol-defined criteria
[3] A GLMM model was used for both the binary (0/1) and ordinal (0,1,2,3,4) ACC and secondary outcomes
[4] The imputation model is a logistic regression model with ACC from prior visits, sex and age included as covariates
[5] Used for the ordinal ACC score (0,1,2,3,4). Treatment failure (ACC=3; the maximum score observed in the data)

This reviewer also conducted a risk-benefit analysis at the subject level. This analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best-case scenario is the case in which an inflammation score of zero at Day 8 was observed without incurring a treatment related adverse event (AE) during the study. The worst-case scenario is incurring an AE during the study without clearing of the anterior chamber cells at Day 8. The other two scenarios are clearing of the anterior chamber cells at Day 8 (benefit) with AE, and no benefit and no AE.

Note: (b) (4) *the applicant has accepted the FDA's recommendation that the primary efficacy analysis be first conducted on a simpler approach (chi-square test) with the GLMM approach used as supportive. The applicant acknowledges this in the study report section 9.8.2 and has conducted the primary efficacy and secondary analyses using the chi-square test.*

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

3.2.3.1 Subject Disposition

The summary of the subject disposition is presented in Table 4. In all arms, over 95% of the randomized and treated subjects completed the study through Day 90. There were few subjects with missing data in all the three arms.

Table 4: Subject Disposition (Randomized Subjects)

	Placebo	**DEX342**	**DEX 517**
Randomized	80	158	157
Treated	80	158	156
Completed the Study through Day 8 *	80 (100%)	157 (99.4%)	156 (98.7%)
Completed the Study through Day 30	77 (96.3%)	157 (99.4%)	154 (98.7%)
Completed the Study through Day 90	76 (95.0%)	156 (98.7%)	154 (98.7%)
Reason for Subject Withdrawal prior to Day 90			
Adverse Event(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Violation(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-Up	2 (2.5%)	1 (0.6%)	2 (1.3%)
Consent Withdrawn	2 (2.5%)	1 (0.0%)	0 (0.0%)

Source: Adapted from Table 14.1.2 of the applicant's study reports. *Produced by the reviewer.

The number of subjects included in the different analysis sets and the summary of subjects who were discontinued from the per-protocol population is summarized in Table 5 and Table 6 respectively. Ninety-one (23%) subjects are listed as having clinically significant protocol deviations. Of these, 49 (54%) received rescue medication without meeting the protocol defined rescue criteria (Table 6).

Table 5: Analysis Sets (All randomized Subjects)

Analysis set	**Treatments**			**Total N=395**
	Placebo N=80	**DEX342 N=158**	**DEX 517 N=157**	
ITT	80 (100%)	158 (100%)	156 (99.4%)	394 (99.7%)
Per-protocol	58 (72.5%)	122 (77.2%)	122 (77.7%)	302 (76.5%)
Safety	80 (100%)	158 (100%)	156 (99.4%)	394 (99.7%)
PK	4 (5.0%)	13 (8.2%)	8 (5.1%)	25 (6.3%)

Source: Table 6 of the applicant's study report.

Table 6: Summary of Protocol Deviations (ITT)

Protocol deviations	**Treatments**			**Total N=394**
	Placebo N=80	**DEX342 N=158**	**DEX517 N=156**	
No. (%) of patients with any clinically significant protocol deviations	22 (27.5%)	35 (22.2%)	34 (21.8%)	91 (23.1%)
Ocular topical corticosteroids and/or ocular topical NSAIDs used in the study eye before Day 30, and pre-specified rescue criteria not met	16 (20%)	16 (10.1%)	17 (10.9%)	49 (12.4%)
Prohibited concomitant medication used during cataract surgery	10 (12.5%)	18 (11.4%)	12 (7.7%)	40 (10.2%)
Dosing error (listed by patient in Table 5)	3 (3.8%)	6 (3.8%)	6 (3.8%)	15 (3.8%)
Ocular or periocular corticosteroids, oral	1 (1.3%)	3(1.9%)	5 (3.2%)	9 (2.3%)

or IV corticosteroids, systemic immunomodulators, or alkylating agents used prior to POD 30				
Patient used any ocular, topical, or oral corticosteroids within 7 days prior to Day 0 (the day of surgery) (exclusion criteria No.1)	2 (2.5%)	1 (0.6%)	6 (3.8%)	9 (2.3%)
Investigational/experiments/off-label use of drugs or Devices occurred during study period	1 (1.3%)	1 (0.6%)	0 (0.0%)	2 (0.5%)
Patient has evidence of corneal abnormality or dystrophy or inability to obtain an acceptable specular micrograph at Screening (exclusion criterion No. 2)	0 (0.0%)	2 (1.3%)	0 (0.0%)	2 (0.5%)

Source: Table 4 of the applicant's study report

The summary of subjects who received a rescue medication after meeting the protocol defined rescue criteria and those who received a rescue medication without meeting the criteria are listed in Table 7. As shown in Table 7, more placebo randomized subjects received rescue medication compared to those in the Dexycu arms, and most of them received the rescue medication on or prior to Day 8 (34%). In the two Dexycu arms, rescue use increased starting around Day 8. A similar pattern is observed in the placebo randomized subjects who received rescue medications without meeting the protocol defined criteria.

Table 7: Cumulative Summary of Subjects who received a Rescue Medication (ITT)

Visit	Rescue Criteria Met[1]			Rescue Criteria Not Met[2]		
	Placebo N=80	**DEX342 N=158**	**DEX517 N=156**	**Placebo N=80**	**DEX342 N=158**	**DEX517 N=156**
Day 1	5 (6%)	0 (0%)	0 (0%)	6 (8%)	9 (6%)	7 (4%)
Day 3	20 (25%)	0 (0%)	4 (3%)	13(16%)	10 (6%)	9 (6%)
Day 8	27 (34%)	3 (2%)	4 (3%)	15 (19%)	10 (6%)	10 (6%)
Day 15	29 (36%)	7 (4%)	11 (7%)	16 (20%)	13 (8%)	14 (9%)
Day 30	29 (36%)	7 (4%)	13 (8%)	16 (20%)	16 (10%)	17 (11%)

Source: Reviewer's analysis.

The summary of subjects with observed and missing ACC measurements at each visit by treatment and rescue medication use is presented in Table 8. ACC data after rescue medication use on or prior to Day 8 was collected for 34% of placebo randomized subjects compared to 3% in each of the two Dexycu arms. Two subjects in the DEX342 arm had missing data at Day 8: one subject discontinued study after cataract surgery (Day 0) and the other subject missed Day 8 visit.

Table 8: Summary of Subjects by Data Type (ITT)

Visit	Data Category	Placebo N=80	DEX342 N=158	DEX517 N=156
Day 1	Missing	1(1%)	2(1%)	0(0%)
	Observed (On Treatment)	68(85%)	147(93%)	149(96%)
	Observed (Treatment+Rescue[1])	5(6%)	0(0%)	0(0%)
	Observed (Treatment+Rescue[2])	6(8%)	9(6%)	7(4%)
Day 3	Missing	1(1%)	3(2%)	2(1%)
	Observed (On Treatment)	47(59%)	145(92%)	141(90%)
	Observed (Treatment+Rescue[1])	20(25%)	0(0%)	4(3%)
	Observed (Treatment+Rescue[2])	12(15%)	10(6%)	9(6%)
Day 8	Missing	0(0%)	2(1%)	0(0%)
	Observed (On Treatment)	39(49%)	143(91%)	143(92%)

	Observed (Treatment+Rescue[1])	27(34%)	3(2%)	4(3%)
	Observed (Treatment+Rescue[2])	14(18%)	10(6%)	9(6%)
Day 16	Missing	1(1%)	7(4%)	4(3%)
	Observed (On Treatment)	35(44%)	137(87%)	130(83%)
	Observed (Treatment+Rescue[1])	29(36%)	6(4%)	11(7%)
	Observed (Treatment+Rescue[2])	15(19%)	8(5%)	11(7%)
Day 30	Missing	2(3%)	4(3%)	4(3%)
	Observed (On Treatment)	34(43%)	133(84%)	124(79%)
	Observed (Treatment+Rescue[1])	29(36%)	7(4%)	13(8%)
	Observed (Treatment+Rescue[2])	15(19%)	14(9%)	15(10%)

Source: Reviewer's Analysis. Observed (Treatment): data available without any rescue medication, observed (Treatment + Rescue[1]): data collected after rescue use meeting rescue criteria; Observed (Treatment + Rescue[2]): data collected after receiving rescue medication without meeting rescue criteria; Missing: no data available.

Table 9: Summary of Subjects by Data Type (Per-Protocol population)

Visit	Data Category	Placebo N=58	DEX342 N=122	DEX517 N=122
Day 1	Observed (On Treatment)	56(97%)	122(100%)	122(100%)
	Observed (Treatment+Rescue[1])	2(3%)	0(0%)	0(0%)
Day 3	Missing	1(2%)	2(2%)	1(1%)
	Observed (On Treatment)	41(71%)	120(98%)	118(97%)
	Observed (Treatment+Rescue[1])	16(28%)	0(0%)	3(2%)
Day 8	Observed (On Treatment)	35(60%)	119(98%)	119(98%)
	Observed (Treatment+Rescue[1])	23(40%)	3(2%)	3(2%)
Day 15	Missing	1(2%)	1(1%)	1(1%)
	Observed (On Treatment)	32(55%)	116(95%)	111(91%)
	Observed (Treatment+Rescue[1])	25(43%)	5(4%)	10(8%)
Day 30	Missing	2(3%)	1(1%)	2(2%)
	Observed (On Treatment)	31(53%)	115(94%)	108(89%)
	Observed (Treatment+Rescue[1])	25(43%)	6(5%)	12(10%)

Source: Reviewer's Analysis. Observed (Treatment): data available without any rescue medication, observed (Treatment + Rescue[1]): data collected after rescue use meeting rescue criteria. Subjects who received a rescue medication without meeting the rescue criteria were excluded from the per-protocol population.

3.2.3.1 Demographic and Baseline Characteristics

Table 10 shows that there was no major imbalance among the three arms with respect to baseline and demographic characteristics. The majority of subjects were white (>79%), female (>51%) and over the age of 65 years (>73%). Subjects' age ranged between 43 and 90, with the average age of around 71 years.

Table 10: Baseline and Demographic Characteristics (ITT)

	Treatments		
	Placebo N=80	DEX342 N=158	DEX517 N=156
Study Eye			
OD	37 (46.3%)	87 (55.1%)	75 (48.1%)
OS	43 (53.8%)	71 (44.9%)	81 (51.9%)
Sex			
Male	39 (48.8%)	75 (47.5%)	69 (44.2%)
Female	41 (51.3%)	83 (52.5%)	87 (55.8%)
Age			

Mean (SD)	70.7 (8.79)	69.7 (8.84)	70.1 (8.96)
Median	71.5	70.0	71.0
Min, Max	46, 90	43, 86	46, 90
Age Group			
<65 Years	17 (21.3%)	41 (25.9%)	41 (26.3%)
>=65 Years	63 (78.8%)	117 (74.1%)	115 (73.7%)
Race			
White	67 (83.8%)	129 (81.6%)	123 (78.8%)
Black or African American	11 (13.8%)	17 (10.8%)	21 (13.5%)
American Indian or Alaskan Native	0 (0.0%)	1 (0.6%)	3 (1.9%)
Asian	1 (1.3%)	4 (2.5%)	1 (0.6%)
Native Hawaiian or Pacific Islander	0 (0.0%)	2 (1.3%)	1 (0.6%)
Other	1 (1.3%)	5 (3.2%)	7 (4.5%)
Ethnicity			
Hispanic or Latino	14 (17.5%)	19 (12.0%)	23 (14.7%)
Not Hispanic or Latino	66 (82.5%)	139 (88.0%)	133 (85.3%)

Source: Table 14.1.3.1 and 14.1.3.3 of the applicant's study reports

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

This section summarizes the findings from the efficacy analyses in Study C13-04.

3.2.4.1.1 Primary Efficacy Analysis

The protocol defined primary efficacy analyses results are presented in Table 11. Study C13-04 demonstrated a statistically significant treatment effect for both doses of Dexycu (342 µg and 517 µg) against placebo (P<0.001). The proportion of subjects with clearing of anterior chamber cells (ACC) at postoperative Day 8 without rescue use was 63% for subjects in the DEX342 arm and 65% for subjects in the DEX517 arm, compared with 26% for subjects randomized to the placebo arm. The treatment differences (Dexycu minus placebo) were 36% (97.5% CI: 22%, 50%) and 39% (97.5% CI: 25%, 53%) for DEX342 and DEX517, respectively. Significantly higher proportion of subjects in the placebo arm received a rescue medication on or prior to Day 8 compared to subjects randomized to the two doses of Dexycu. In summary, Study C13-04 provided evidence that a single dose of Dexycu was efficacious for the treatment of inflammation following cataract surgery.

Table 11: Results of the Primary Efficacy Analysis (ITT)

	Treatment			**Difference (%) (Asymptotic 97.5% CI)**	
Outcomes	**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%)	39.1% (25%, 53%)
Received Rescue Medication[2]	27 (34%)	3 (2%)	4 (3%)	-32% (-42%, 21%)	-31% (-42%, 20%)

Source: Table 10 of the study report. [1]Subjects who received rescue medication after meeting the rescue criteria on or before POD 8 were set as failures. The two subjects in the DEX342 arm with missing data at Day 8 were imputed as failures. [2]Subjects who met the protocol defined rescue criteria on or before POD 8 and consequently received a rescue medication.

Note: Per the clinical reviewer, Dr. Jennifer Harris, the recent site inspections for Study C13-04 indicated that Dr. Lawrence Role's site has closed and the source documents are not

available. Since this data cannot be verified, it is requested that the efficacy data for Study C13-04 be reanalyzed omitting all data from Dr. Role's site. This site was the 5th largest site in the study enrolling a total of 22 subjects (5 in placebo, 9 in DEX342 and 8 in DEX517; Table 19). The treatment differences (Dexycu-placebo) excluding data from this site are 34% (20%, 49%) and 40% (26%, 55%) for DEX342 and DEX517 respectively.

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=75	DEX342 N=149	DEX517 N=148	DEX342vs Placebo	DEX517vs Placebo
Day 1	7 (9%)	17 (11%)	26 (18%)	2% (-7%, 12%)	8% (-2%, 19%)
Day 3	13 (17%)	60 (40%)	48 (32%)	23% (10%, 36%)	15% (2%, 28%)
Day 8	20 (27%)	91 (61%)	99 (67%)	34% (20%, 49%)	40% (26%, 55%)
Day 15	28 (37%)	83 (56%)	96 (65%)	18% (3%, 34%)	28% (12%, 43%)
Day 30	36(48%)	118 (79%)	115 (78%)	31% (16%, 46%)	30% (15%, 45%)

Source: Reviewer's Analysis. All data from Dr. Role's site is excluded in this analysis. Subjects who received rescue medication after meeting the rescue criteria at a given visit were treated as failures. The two subjects in the DEX342 arm with missing data were imputed as failures.

3.2.4.1.2 Sensitivity analyses

There were very few subjects who discontinued the study (Table 4). Additionally, because subjects in all arms received a single dose of their respective treatments, and because the primary efficacy analysis was conducted on the ITT population (randomized and treated), treatment discontinuation was not an issue either. On the other hand, rescue medication was given to 34% of placebo randomized subjects based on pre-specified rescue criteria, and an additional 19% despite not meeting the pre-specified criteria by Day 8. Consequently, as shown by the sensitivity analysis results in Table 12, rescue medication was the single intercurrent event of interest that could impact the evaluation of efficacy significantly. The results of the sensitivity analysis are all supportive of the results of the primary efficacy analysis.

As expected, because rescue users are subjects with higher inflammation (ACC and/or ACF grades ≥3), the results from the LOCF analysis and the primary efficacy analysis are very similar. Two placebo randomized subjects who received a rescue medication on Day 3 and 8 because their ACC score at these visits were 3, were set as treatment failures in the primary efficacy analysis. However, the LOCF approach used the ACC scores at Day 1 and Day 3, respectively (both of which were zero) to impute the ACC scores at Day 8 and resulted in success for these two subjects. Consequently, the results of the LOCF and the protocol defined primary efficacy analysis were slightly different.

In all arms, the proportions of subjects with ACC clearing at Day 8 were slightly lower when all rescue users (including those who did not meet the rescue criteria) were set as treatment failures. The treatment differences however are still favorable to the Dexycu arms (Table 12).

Table 12: Sensitivity Analysis Results for the Primary Efficacy Endpoint (ITT)

Approaches	Treatment			Difference (%) (Asymptotic 97.5% CI)	
	Placebo N=80	DEX342 N=158	DEX517 N=156	DEX342 vs Placebo	DEX517 vs Placebo
Treatment policy[1]	31 (39%)	99 (63%)	105(67%)	24% (9%, 39%)	29% (14%, 43%)

Per-protocol[2]	15 (26%)	75(62%)	81 (66%)	37% (19%, 52%)	40.5% (25%, 57%)
Multiple imputation[3]	31 (39%)	102 (65%)	104 (67%)	26% (10%, 41%)	28% (13%, 44%)
LOCF[4]	23 (29%)	99 (63%)	102 (65%)	34% (21%, 46%)	37% (24%, 49%)
Primary[5]	16 (20%)	91 (58%)	98 (63%)	38% (26%, 49%)	43% (31%, 54%)
Rescue Medication[6]	41(51%)	13(8%)	13(8%)	-43% (-55%, -31%)	-43% (-55%, -31%)

[1]Source: Reviewer's analysis. All data including data collected after receiving rescue medication was used in the analysis. Two subjects in the DEX342 (one discontinued study after Day 0 and one subject with missing data at Day 8) were treated as treatment failures.
[2] Source: Adapted from Table 14.2.1.2 of the study report. Only subjects with no major protocol deviations were included in this analysis (N=122 for the two Dexycu groups and N=58 for the Placebo group). Subjects who received rescue medication after meeting the rescue criteria on or before Day 8 were treated as treatment failures.
[3] Source: Adapted from Table 14.2.2.14. Multiple imputation was used to impute an ACC clearing value at a Day 8 if the corresponding ACC grade was missing or a subject received rescue medication on or before a given time point.
[4] Source: Adapted from Table 14.2.2.12 of the study report. The ACC clearing status for subjects with missing data and for subjects who received a rescue medication after meeting the rescue criterion was determined based on observed ACC prior to rescue medication use (LOCF). One subject who discontinued study after Day 0 (LOCF cannot be applied) was treated as failure (The applicant excluded this subject from the analysis).
[5] Source: Reviewer's Analysis: Subjects who received rescue medication on or before Day 8 regardless of whether the protocol-defined rescue criterion was met were set as failures. Data for two subjects with missing ACC data at Day 8 was imputed as failures.
[6]Subjects who received rescue medication regardless of whether a rescue criterion is met on or before Day 8.

Reviewer's remarks:

The primary and sensitivity analyses estimate different quantities of treatment effect. The protocol defined primary efficacy analysis estimates the *difference between Dexycu and placebo in the proportion of subjects in the ITT population with ACC clearing at Day 8 without a need for a rescue medication based on the protocol-defined criteria*.

The analysis listed as treatment-policy estimates *the difference in the proportion of subjects with ACC clearing at Day 8 in all subjects in the ITT population, regardless of receiving rescue medication.* The treatment difference from the per-protocol analysis could be viewed as t*he treatment difference in the proportion of subjects with ACC at Day 8 without a rescue medication (based on the protocol-defined criteria) among subjects who did not have any clinically meaningful protocol deviations*. Note that rescue use based on the pre-specified criteria was not considered as a protocol deviation.

The treatment difference in the LOCF approach could be interpreted in multiple ways. One such interpretation is *the difference in the proportion of subjects with ACC at the last time through Day 8 prior to receiving a rescue medication*. (b) (4)

The multiple imputation approach estimates *the treatment difference in the proportion of subjects with ACC clearing at Day 8 in a hypothetical scenario where all subjects had stayed in the study and did not receive a rescue medication based on the protocol-defined criteria*. This analysis assumes data after rescue medication as missing and relies on the missing at random assumption (MAR). Assuming data after rescue use as missing when in fact it is collected might not be a reasonable approach. In addition, the MAR assumption could not be verified from observed data and whether a hypothetical treatment effect is acceptable for regulatory approval should be further investigated.

In summary, except in the multiple imputation approach (where data after rescue use is set as missing), missing data was negligible, and the estimations were done with minimal statistical assumptions. However, the analysis based on the per-protocol population excludes nearly 23%

of randomized subjects, including some subjects who received medications that might impact the efficacy outcome. Thus, the results from this analysis should be interpreted with caution.

Tipping point Analysis

The reviewer's tipping point analysis shows that at least 17 and 19 placebo randomized subjects who received a rescue medication prior to Day 8, had to be set as treatment successes for the treatment effect for DEX342 and DEX517, respectively, to no longer be statistically significant. Additionally, even if all placebo randomized subjects who received the rescue medication were treated as treatment successes, the observed treatment difference will still be numerically favorable to Dexycu (Figure 1). This reviewer defers the determination of whether subjects rightly received rescue medication and thus were indeed treatment failures for the primary efficacy outcome to the clinical review team.

3.2.4.1.3 Secondary Efficacy Endpoints

The results of the secondary efficacy endpoints are supportive of the primary efficacy analysis results. The proportion of subjects with ACC clearing was consistently higher in the Dexycu arms compared to placebo at all visits (Table 13 and Figure 2). Similarly, positive results for both Dexycu arms were also shown for the endpoints of ACF clearing (Figure 3) and the endpoints of ACC and ACF clearing (Figure 4).

The summary of the inflammation categories by visit is presented in Figure 5. In the placebo arm, more than 78% of subjects had at least one anterior chamber cell in the study eye at Day 8; with almost half having at least 6 anterior chamber cells. The odds of having higher inflammation category (higher number of cells in the anterior chamber) versus a lower category for subjects in the placebo arm was about 3 times higher compared to those in the DEX517 arm [Odds Ratio (95% CI): 0.29 (0.17, 0.49)]. The corresponding figure for DEX342 was [Odds Ratio (95% CI): 0.26 (0.15, 0.44)]. These results agree with the applicant's analysis of the ordinal ACC data conducted using a GLMM model.

Table 13: Proportion of Subjects with Clearing of the Anterior Chamber Cell by Visit (ITT)

Visits	Treatments			Difference and 97.5% CI	
	Placebo N=80	**DEX342 N=158**	**DEX517 N=156**	**DEX342vs Placebo**	**DEX517vs Placebo**
Day 1	7 (9%)	18 (11%)	30 (19%)	3% (-6%, 12%)	10% (0%, 20%)
Day 3	14 (18%)	63 (40%)	51 (33%)	22% (9%, 35%)	15% (2%, 28%)
Day 8	21(26%)	99 (63%)	102 (65%)	36% (22%, 50%)	39% (25%, 53%)
Day 15	31 (39%)	91 (58%)	99 (63%)	19% (4%, 34%)	25% (10%, 40%)
Day 30	40 (50%)	127 (80%)	122 (78%)	30% (16%, 45%)	28% (14%, 43%)

Source: Adapted from Table 10 of the study report. One subject in DEX342 with on post-treatment ACC data at all timepoints and subjects who received rescue medication prior to the evaluation of efficacy after meeting the protocol-defined criteria were treated as treatment failures. Data from a prior visit was used for subjects with missing outcomes at a given visit.

Note: The reviewer's results for the secondary efficacy endpoints are slightly different from the applicant's results presented in Tables 11-13 in the study reports. The applicant conducted the analysis using a GLMM model on the ITT population with observed data only (including data collected after rescue use). The analysis excluded subjects with missing data. The reviewer

however followed the same approach used in the protocol defined primary efficacy analysis (rescue use as failure and LOCF for missing data). This enables the interpretation of the results of the secondary endpoints in the same manner as the primary efficacy analysis. Similar conclusions of a positive treatment effect are however observed in both the applicant's and the reviewer's analyses.

3.3 Evaluation of Safety

This section summarizes the safety findings for Dexycu from Study C13-04 and two additional studies included in this NDA submission. Based on the overall safety evaluation from the three studies, it appears that increase in the intraocular pressure, corneal endothelial, eye pain, dry eye, cell loss and iritis were the most frequently reported adverse events for Dexycu. The safety results are summarized in Sections 3.3.1-3.3.3 for each of the three studies separately.

3.3.1 Safety summary: Study C13-04

As shown in Table 14, a total of 79 (50%) and 72 (46.2%) subjects who received DEX342 and DEX517 respectively reported at least one ocular adverse event in the study or both eyes compared to 51 (63.8%) subjects randomized to the placebo arm. The most frequently reported AEs in the study eye among subjects who received the two Dexycu doses (DEX342 and DEX517) were increased intraocular pressure (11.7%, 13.5%), eye pain (10.1%, 2.6%), dry eye (7.6%, 3.8%), and corneal oedema (6.3%, 7.7%). The higher dose (DEX517) appears to have slightly lower ocular adverse event incidences. Only one reported ocular AE in the DEX342 arm was serious (corneal decomposition). At least one systemic AE was reported in 6 (7.5%) subjects in the placebo arm compared to 18 (11.4%) and 17 (10.9%) subjects in the DEX342 and DEX517arms respectively.

Recall that, one of the most frequently reported adverse events was increase in intraocular pressure. The summary results for the change from screening IOP analyzed using an analysis of covariance (ANCOVA) model with screening IOP and treatment as covariates is presented in Figure 6. A reduction in IOP of about 1-2 mm Hg was observed in all the three arms starting at post-operative Day 3; with slightly lower reduction observed in the Dexycu arms compared to placebo.

Additional safety evaluation was assessed using change in visual acuity and endothelial cell density. The visual acuity was reported as the logarithm of the minimum angle of resolution (logMAR) score which could be computed from the Snellen chart as -log (20/SNELLD). For example, for a subject with a visual acuity of 20/60, the VA value will be (-log (20/50)) which is about 0.48; and similarly, the logMAR value for a subject with a 20/30 vision will be around 0.18. Thus, higher values of logMAR imply lower vision. The two Dexycu arms were compared to placebo with respect to the mean change from baseline visual acuity at each time point. The summary results are presented in Figure 7. In all arms, the mean change from baseline values are negative, implying that, on average, visual acuity has improved in all arms. The improvements are comparable across the three arms.

The mean endothelial density at screening was 2506, 2561, 2571 cells/mm^2 in the placebo, DEX342 and DEX517 arms respectively. The change from baseline (screening) in the mean endothelial density at Day 90 was comparable among the three arms, with slightly higher decline observed in the DEX517 arm (383, 390 and 449 cells/mm^2 in the placebo, DEX342 and DEX517 arms respectively; Table 18).

Table 14: Summary of Adverse Events in the Study Eye (Safety Analysis Set: Study C13-04)

Adverse event	Treatments			Total N=394
	Placebo N=80	DEX342 N=158	DEX517 N=156	
At least on AE in study eye or both eyes	51 (63.8%)	79 (50.0%)	72 (46.2%)	202 (51.3%)
At least one Serious AE	0(0.0%)	1 (0.6%)	0 (0.0%)	1 (0.3%)
Intraocular pressure increased	7 (8.8%)	18 (11.4%)	21 (13.5%)	46 (11.7%)
Corneal oedema	8 (10.0%)	10 (6.3%)	12 (7.7%)	30 (7.6%)
Eye pain	7 (8.8%)	16 (10.1%)	4 (2.6%)	27 (6.9%)
Anterior chamber inflammation	10 (12.5%)	2 (1.3%)	8 (5.1%)	20 (5.1%)
Iritis	11 (13.8%)	4 (2.5%)	5 (3.2%)	20 (5.1%)
Dry eye	0 (0.0%)	12 (7.6%)	6 (3.8%)	18 (4.6%)
Anterior chamber cell	8 (10.0%)	6 (3.8%)	2 (1.3%)	16 (4.1%)
Cystoid macular oedema	3 (3.8%)	6 (3.8%)	5 (3.2%)	14 (3.6%)
Eye inflammation	6 (7.5%)	4 (2.5%)	3 (1.9%)	13 (3.3%)
Posterior capsule opacification	2 (2.5%)	3 (1.9%)	6 (3.8%)	11 (2.8%)
Visual acuity reduced	2 (2.5%)	4 (2.5%)	4 (2.6%)	10 (2.5%)
Foreign body sensation in eyes	0 (0.0%)	3 (1.9%)	4 (2.6%)	7 (1.8%)
Vitreous floaters	0 (0.0%)	3 (1.9%)	4 (2.6%)	7 (1.8%)
Photophobia	3 (3.8%)	3 (1.9%)	0 (0.0%)	6 (1.5%)
Macular oedema	2 (2.5%)	2 (1.3%)	1 (0.6%)	5 (1.3%)
Vitreous detachment	1 (1.3%)	1 (0.6%)	2 (1.3%)	4 (1.0%)
Anterior chamber flare	1 (1.3%)	2 (1.3%)	0 (0.0%)	3 (0.8%)
Blepharitis	0 (0.0%)	1 (0.6%)	2 (1.3%)	3 (0.8%)
Conjunctival oedema	1 (1.3%)	1 (0.6%)	1 (0.6%)	3 (0.8%)
Conjunctivitis allergic	0 (0.0%)	1 (0.6%)	2 (1.3%)	3 (0.8%)
Conjunctivitis viral	0 (0.0%)	2 (1.3%)	1 (0.6%)	3 (0.8%)
Iridocyclitis	0 (0.0%)	3 (1.9%)	0 (0.0%)	3 (0.8%)
Macular fibrosis	0 (0.0%)	1 (0.6%)	2 (1.3%)	3 (0.8%)
Photopsia	0 (0.0%)	2 (1.3%)	1 (0.6%)	3 (0.8%)
Vision blurred	1 (1.3%)	2 (1.3%)	0 (0.0%)	3 (0.8%)
Corneal endothelial cell loss	1 (1.3%)	1 (0.6%)	0 (0.0%)	2 (0.5%)
Diabetic retinal oedema	1 (1.3%)	1 (0.6%)	0 (0.0%)	2 (0.5%)
Lacrimation increased	0 (0.0%)	1 (0.6%)	1 (0.6%)	2 (0.5%)

Source: Table 14.3.3.4 of the study report

3.3.2 Safety summary: Study C15-01

The safety of DEX517 was further evaluated in Study C15-01, a prospective, randomized, open-label, parallel-design, active-controlled (prednisolone), multicenter safety study. In this study, 194 subjects who were undergoing cataract surgery were randomized in a 1:1 ratio to receive either DEX517 (N=130) or 1% prednisolone (N=64). Of these, 126 subjects in the DEX517 and 55 subjects in the prednisolone arm received their respective treatments. The summary of adverse events reported in this study are presented in Table 15. A total of 53(42.1%) subjects in the DEX517 group and 12(23.6%) subjects in the prednisolone reported at least one AE in the study eye. The most frequently reported AEs in the DEX517group were

increased IOP (11.1%) and iritis (6.3%). In comparison, the incidence of these two events in the prednisolone group were 3.6% (2/55 subjects) and 0%, respectively. The study reported that no treatment emergent AEs of corneal endothelial cell loss were observed. A detailed summary of the design of this study is presented in the Appendix.

Table 15: Summary of Adverse Events (Safety Analysis Set: Study C15-01)

Adverse event	Treatments		Total N=181
	DEX517 N=126	Prednisolone N=55	
Intraocular pressure increased	14 (11.1%)	2 (3.6%)	16 (8.8%)
Foreign body sensation in eyes	6 (4.8%)	2 (3.6%)	8 (4.4%)
Glare	0 (0.0%)	1 (1.8%)	1 (0.5%)
Iritis	8 (6.3%)	0 (0.0%)	8 (4.4%)
Lacrimation increased	1 (0.8%)	2 (3.6%)	3 (1.6%)
Macular oedema	2 (1.6%)	0 (0.0%)	2 (1.1%)
Meibomian gland dysfunction	0 (0.0%)	1 (1.8%)	1 (0.5%)
Optic disc haemorrhage	1 (0.8%)	0 (0.0%)	1 (0.5%)
Photophobia	2 (1.6%)	1 (1.8%)	3 (1.6%)
Pinguecula	1 (0.8%)	0 (0.0%)	1 (0.5%)
Posterior capsule opacification	5 (4.0%)	0 (0.0%)	5 (2.8%)
Punctate keratitis	0 (0.0%)	1 (1.8%)	1 (0.5%)
Retinal pigment epitheliopathy	1 (0.8%)	0 (0.0%)	1 (0.5%)
Retinopathy	0 (0.0%)	1 (1.8%)	1 (0.5%)
Vision blurred	1 (0.8%)	1 (1.8%)	2 (1.1%)
Vitreous detachment	2 (1.6%)	0 (0.0%)	2 (1.1%)
Vitreous floaters	1 (0.8%)	1 (1.8%)	2 (1.1%)
Foreign body sensation in eyes	6 (4.8%)	2 (3.6%)	8 (4.4%)
Glare	0 (0.0%)	1 (1.8%)	1 (0.5%)
Iritis	8 (6.3%)	0 (0.0%)	8 (4.4%)
Lacrimation increased	1 (0.8%)	2 (3.6%)	3 (1.6%)
Macular oedema	2 (1.6%)	0 (0.0%)	2 (1.1%)

Source: Table 10 of the study report

3.3.3 Safety Summary: Study C11-01

In addition to the two Phase 3 studies, the applicant conducted a prospective, randomized, double-masked, dose-ranging, parallel-group, multicenter study. Per the applicant, the study failed to enroll the originally planned 228 subjects. The study ended up enrolling 172 subjects who were then randomized in a 1:1:1 ratio to receive a single dose of one of three Dexycu doses (342, 517 or 697 µg; hereafter referred to as DEX342 DEX517 and DEX697). Consequently, the applicant deemed the efficacy results from this study as exploratory only. This section summarizes the safety results as presented in the applicant's study reports. A detailed description of the design of this study and the exploratory efficacy results are presented in the Section 8. As shown in Table 16, a total of 87 subjects, 29 (49.1%), 30 (52.6%) and 29 (50.0%) in the DEX342, DEX517 and DEX697 reported at least one ocular adverse event in the study eye. The most frequently reported ocular adverse events in the study eye were corneal endothelial cell loss (11.0%), iritis (9.3%), and corneal edema (8.7%). Twelve serious adverse events (SAEs) were reported for 11 subjects; six subjects in the DEX342, 2 in the DEX517 group, and three in the DEX697 group. The most frequently reported SAE was corneal

endothelial cell loss (7 subjects). Other SAEs were corneal edema (2 subjects), cervix carcinoma, endophthalmitis, and influenza (1 subject each).

Table 16: Summary of Adverse Events (Safety Analysis Set: Study C11-01)

Adverse event	Treatments			Total N=172
	DEX342 N=57	DEX517 N=57	DEX697 N=58	
At least on AE in study eye or both eyes	29 (49.1%)	30 (52.6%)	29 (50.0%)	87 (50.6%)
At least one Serious AE	6(10.5%)	2 (3.5%)	3 (5.2%)	12 (7.0%)
Corneal endothelial cell lossa	5 (8.8%)	5 (8.8%)	9 (15.5%)	19 (11.0%)
Iritis	5 (8.8%)	4 (7.0%)	7 (12.1%)	16 (9.3%)
Corneal oedema	4 (7.0%)	8 (14.0%)	3 (5.2%)	15 (8.7%)
Eye pain	5 (8.8%)	0 (0.0%)	2 (3.4%)	7 (4.1%)
Photophobia	2 (3.5%)	2 (3.5%)	2 (3.4%)	6 (3.5%)
Ocular hypertension	1 (1.8%)	2 (3.5%)	2 (3.4%)	5 (2.9%)
Vision blurred	0 (0.0%)	3 (5.3%)	2 (3.4%)	5 (2.9%)
Foreign body sensation in eyes	2 (3.5%)	1 (1.8%)	1 (1.7%)	4 (2.3%)
Abnormal sensation in eye	1 (1.8%)	2 (3.5%)	0 (0.0%)	3 (1.7%)
Eye swelling	2 (3.5%)	0 (0.0%)	1 (1.7%)	3 (1.7%)
Ocular discomfort	0 (0.0%)	2 (3.5%)	1 (1.7%)	3 (1.7%)
Conjunctival haemorrhage	2 (3.5%)	0 (0.0%)	0 (0.0%)	2 (1.2%)
Vitreous detachment	2 (3.5%)	0 (0.0%)	0 (0.0%)	2 (1.2%)
Eye irritation	0 (0.0%)	0 (0.0%)	2 (3.4%)	2 (1.2%)
Intraocular pressure increased	1 (1.8%)	4 (7.0%)	3 (5.2%)	8 (4.7%)

Source Table 21 of the study report

4 Risk-benefit analysis

The risk benefit analysis presented in this section is conducted based on the efficacy and safety data from study C13-04. Compared to placebo, higher proportion of subjects in the Dexycu arms achieved clearing of the anterior chamber cell at Day 8 (benefit) without reported increase in intraocular pressure, ocular oedema or reporting any ocular adverse events (risks).

In the placebo arm, more than half of the subjects did not achieve clearing of the anterior chamber cell at Day 8 and did not experience any of the commonly reported adverse events. A relatively lower percentage of the subjects in the Dexycu arms reported one of the commonly reported adverse events without achieving a clearing of the anterior chamber cell at Day 8. Overall, Dexycu appears to have a favorable risk-benefit profile with respect to the frequently reported adverse events in this study (Figure 8-Figure 10).

5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses presented in this section are based on the data from Study C13-04. The subgroup analyses results presented in this section are considered descriptive and should only be used to characterize the observed treatment differences between subgroups. Overall, the subgroup analyses results were consistent with the primary efficacy analysis results (Figure 11).

6 SUMMARY AND CONCLUSIONS

6.1 Statistical Issues

No major statistical issues were encountered in this review.

6.2 Collective evidence

This review evaluated the efficacy of Dexycu in one Phase 3 study, namely, Study C13-04. The efficacy results from Study C13-04 demonstrated that Dexycu (342 µg and 517 µg) is efficacious in clearing anterior chamber cells at Day 8. The observed treatment effect appears to be sustained at later time points evaluated.

A further evaluation of efficacy based on the secondary endpoints of anterior chamber flare clearing and anterior chamber flare and cell clearing and several subgroup analyses provided further evidence in support of the primary efficacy analysis findings. Evaluations of efficacy using different methods to handle intercurrent events (rescue use and study discontinuation) also pointed to the same direction, providing further evidence of the robustness of the results of the primary efficacy analysis. Additionally, Dexycu appears to have a positive risk-benefit profile compared to placebo.

6.3 Conclusions and Recommendations

The findings from the analyses presented in this statistical review provide evidence that the two doses of Dexycu are effective for the treatment inflammation following cataract surgery. The overall-risk benefits evaluation and the subsequent determination for approval for this product is deferred to the clinical review team.

6.4 Labeling recommendation (if approved)

Based on the review of the study results and the text presented in Section 14 of the current version of the drug labeling, this reviewer has the following comments:

a) (b) (4)

b) Subjects who received a rescue medication based on the protocol-defined rescue criteria were treated as treatment failures for the primary efficacy analysis. However, there were additional set of subjects who received a rescue medication without meeting the rescue criteria (prohibited medications). These subjects need to be treated as treatment failures in the primary efficacy analysis as well.

c) The applicant used the Bonferroni adjustment to control the Type I error rate due to the test of two hypotheses for the primary efficacy analysis (i.e. each test was conducted at 0.025 level of significance). However, for each treatment comparison, they provided the 95% confidence interval for the treatment differences. To align with the adjustment for the multiple comparison, the reviewer provided the 97.5% confidence interval for differences between each Dexycu dose and placebo.

d) (b) (4) We acknowledge that the drug is efficacious based on the efficacy findings in the placebo controlled study (Study C13-04). (b) (4)

This reviewer thus recommends the following text and efficacy summary table for Section 14 (Clinical studies) of the drug labeling:

In a randomized, multicenter, double-masked, parallel group, vehicle-controlled trial, subjects received Dexycu or its non-drug delivery vehicle immediately upon completion of cataract surgery. In this trial, Dexycu had a higher percentage of subjects who achieved clearing of the anterior chamber cell without receiving a rescue medication. Results are shown in Table xx.

Table xx: 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	DEX342vs Placebo	DEX517vs Placebo
Day 1	7 (9%)	17 (11%)	26 (17%)	2% (-6%, 10%)	8% (-1%, 16%)
Day 3	13 (16%)	60 (38%)	47 (30%)	22% (11%, 33%)	14% (3%, 25%)
Day 8	16 (20%)	91 (58%)	98 (63%)	38% (26%, 49%)	43% (31%, 54%)
Day 15	21 (26%)	83 (53%)	95 (61%)	26% (14%, 39%)	35% (22%, 47%)
Day 30	28 (35%)	116 (73%)	113 (72%)	38% (26%, 51%)	37% (25%, 50%)

Subjects who received rescue medication were treated as failure.

Applicant's text in Clinical section

(b) (4)

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

Table 17: Schedule of Procedures and Assessments and Analysis visit Windows

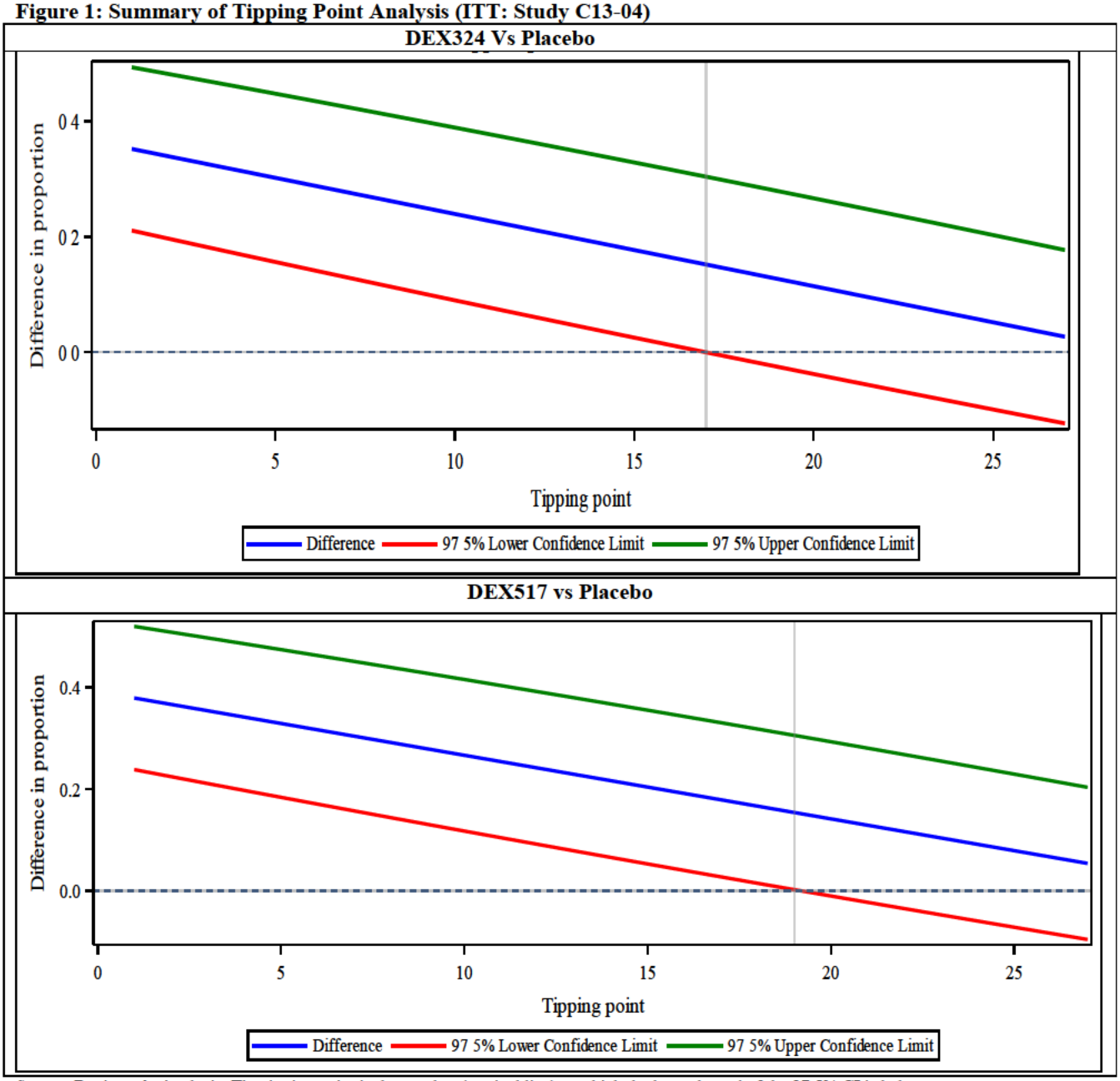
	Pre-operative Screening	Surgery and Postoperative Study Visits							
		Surgery	Postoperative Day (POD)						
	(Day -45 to -3)	Day 0	Day 1	Day 3 (+ 2 days)	Day 8 (+ 1 day)	Day 15 (± 3 days)	Day 30 (± 3 days)	Day 90 (End of Study) (± 7 days)	Early Termi-nation
Study Drug Injection		X							
Informed Consent	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
IOP	X		X	X	X	X	X	X	X
Dilated Ophthalmoscopy	X						X		X
Corneal Endothelial Cell Density	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
Optional Plasma PK Sample[a]		X	X	X	X	X			

Protocol Time Point	Target Study Day	Analysis Windows in Study Day
Screening Day -45 to -3	-3	[-45, -2]
Surgery (Day 0)	1	1
POD 1	2	2
POD 3	4	[3, 5]
POD 8	9	[7, 11]
POD 15	16	[13, 20]
POD 30	31	[21, 40]
POD 90	91	≥ 41

Source: Table 1 of the study reports (schedule of events) and Table 3 of the statistical analysis plan (analysis windows)

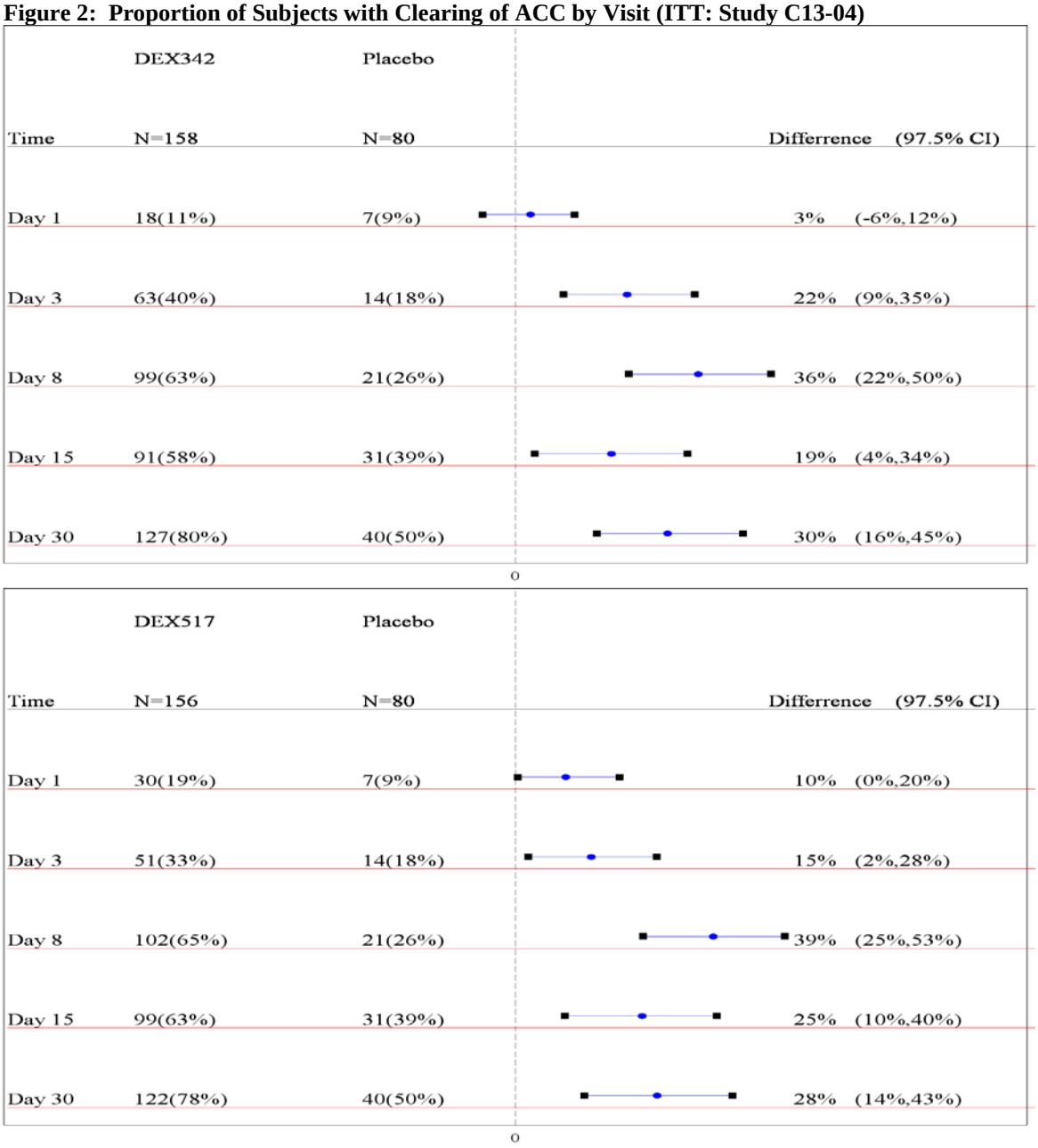
7 Appendix: Summary Results

Figure 1: Summary of Tipping Point Analysis (ITT: Study C13-04)



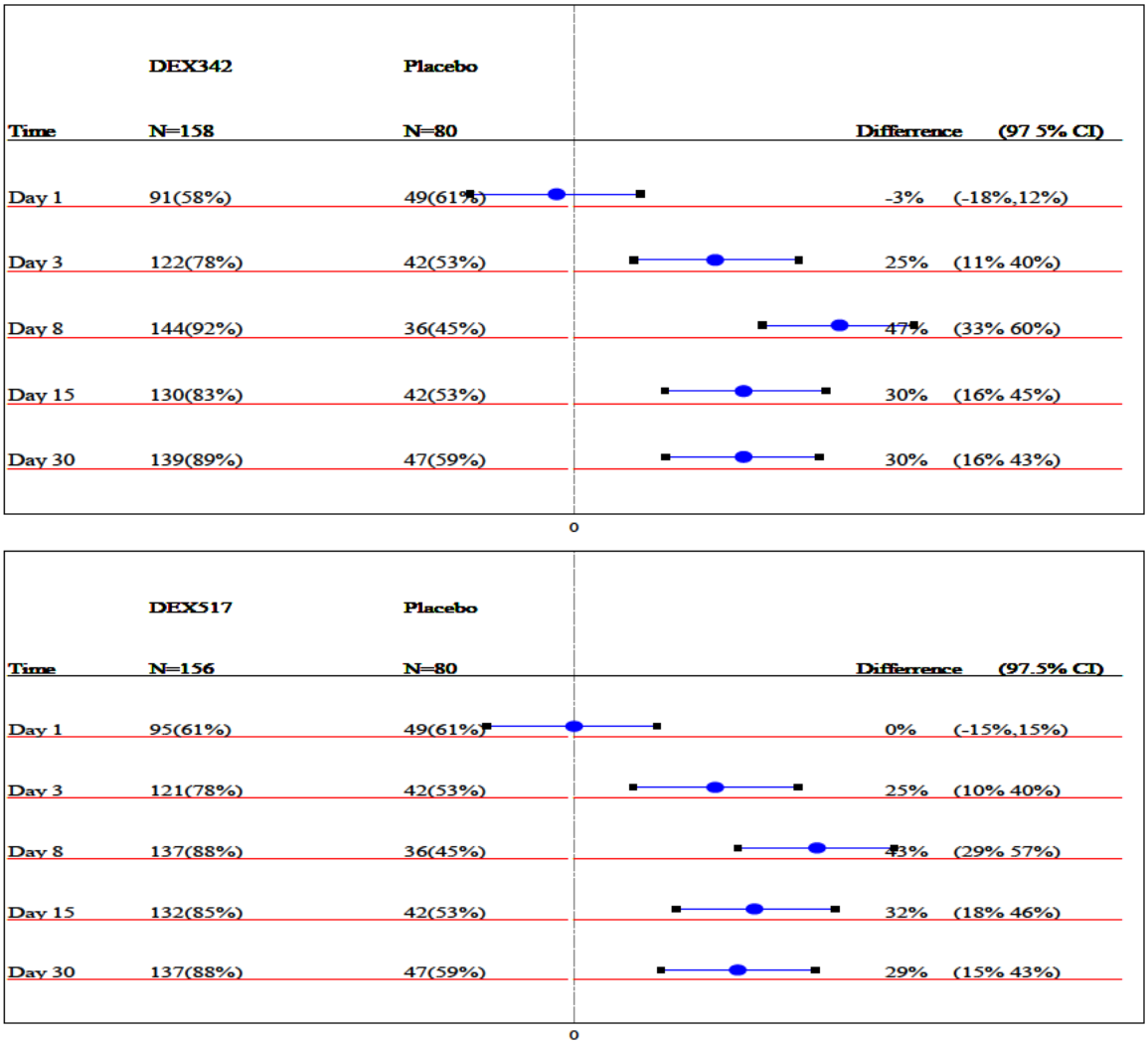
Source: Reviewer's Analysis. The tipping point is the number (vertical line) at which the lower bound of the 97.5% CI is below zero.

Figure 2: Proportion of Subjects with Clearing of ACC by Visit (ITT: Study C13-04)



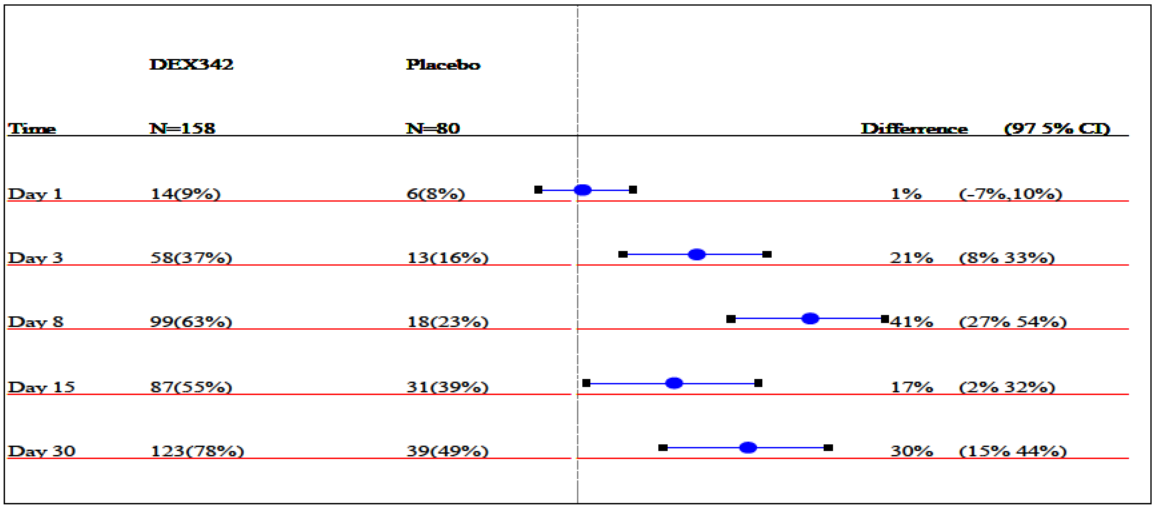
Source: Reviewer's analysis. Adapted from Table 10 of the study report. Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACC outcomes were set as treatment failures. For subjects with missing ACC, the ACC clearing was determined using ACC outcome from the previous visit.

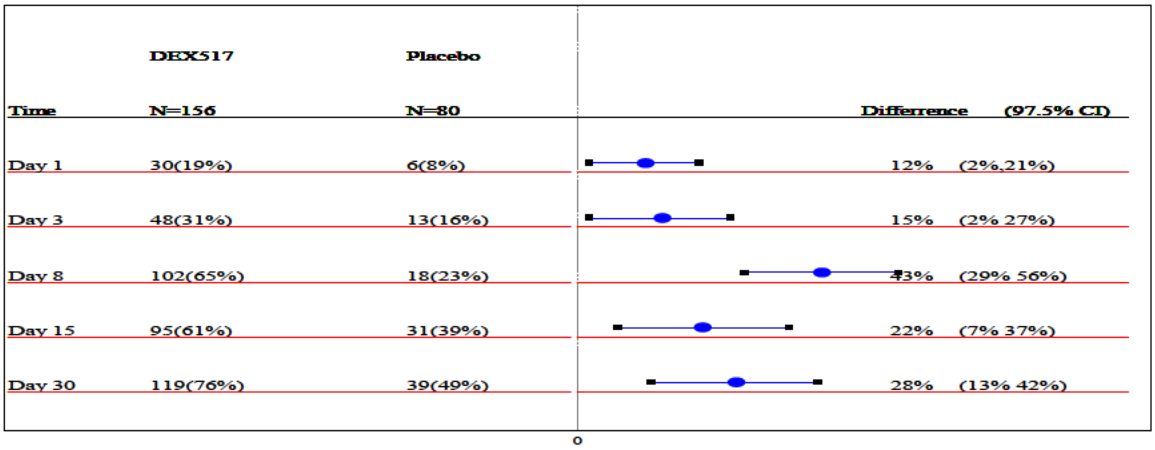
Figure 3: Proportion of Subjects with Clearing of ACF by Visit (ITT: Study C13-04)



Source: Reviewer's analysis. Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACF outcomes were set as treatment failures. For subjects with missing ACF, the ACF clearing was determined using ACF outcome from the previous visit.

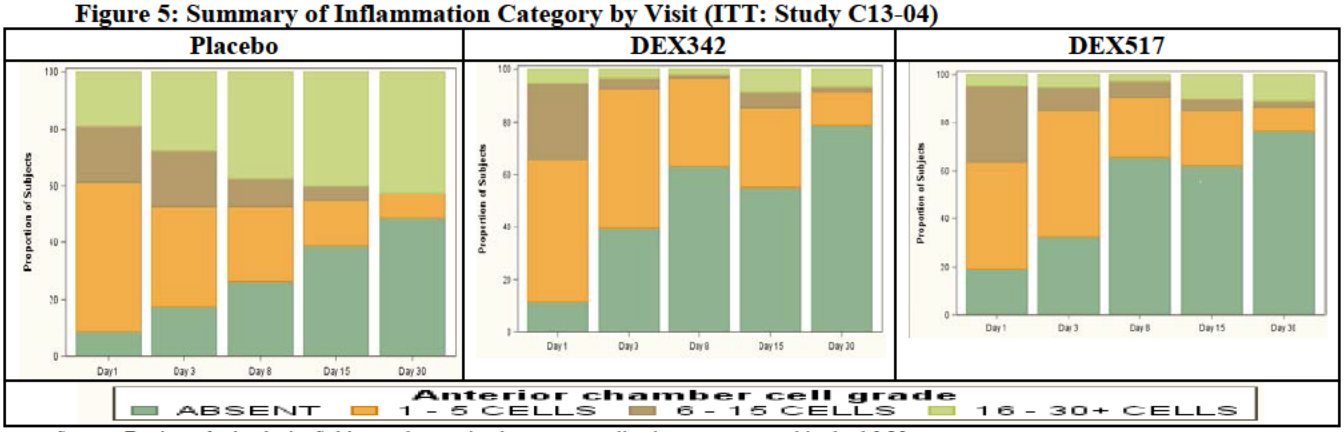
Figure 4: Proportion of Subjects with Clearing of ACC and ACF by Visit (ITT: Study C13-04)





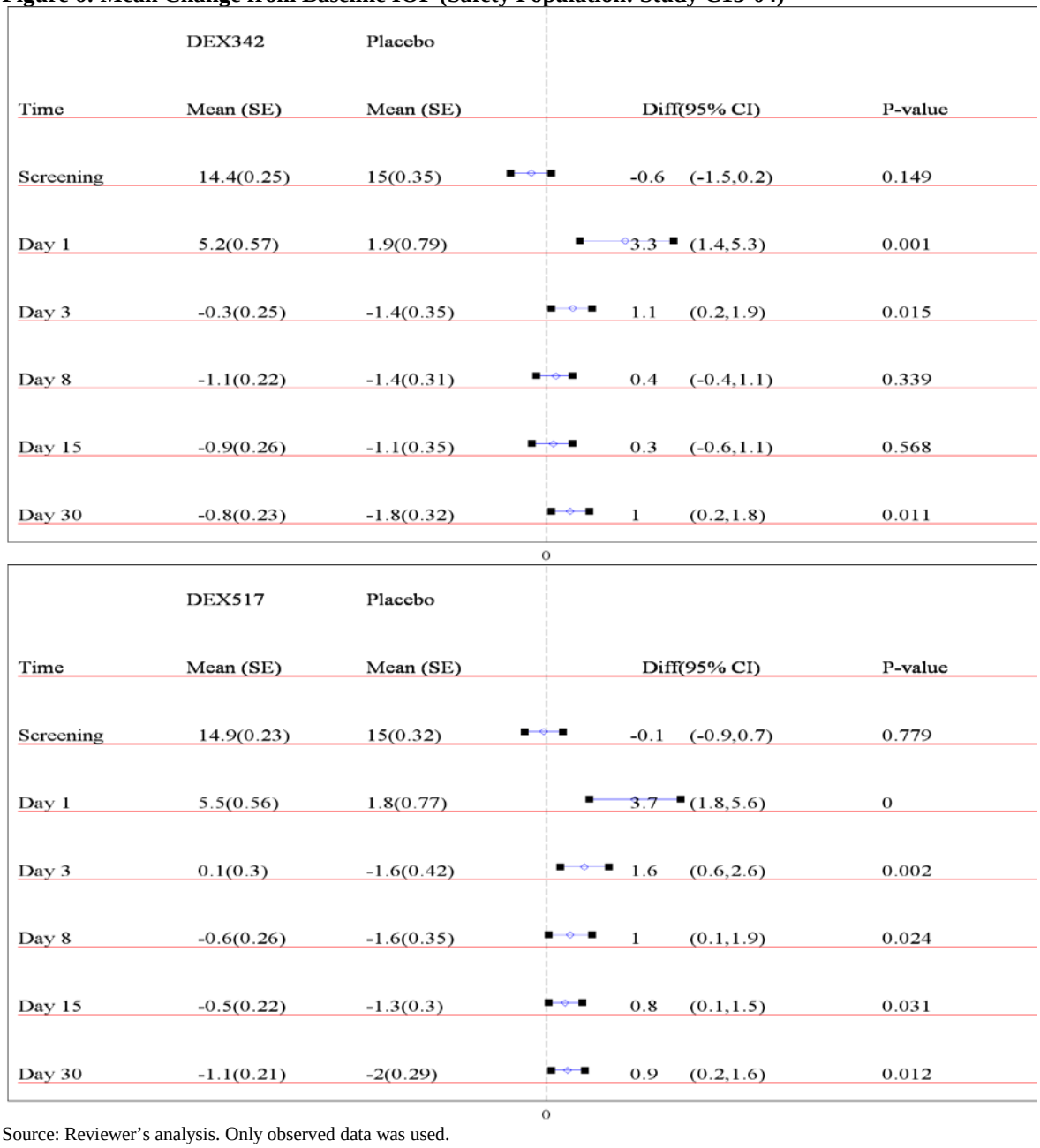
Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACC&ACF outcomes were set as treatment failures. For subjects with missing ACC&ACF, the ACC&ACF clearing was determined using ACC&ACF outcome from the previous visit.

Figure 5: Summary of Inflammation Category by Visit (ITT: Study C13-04)



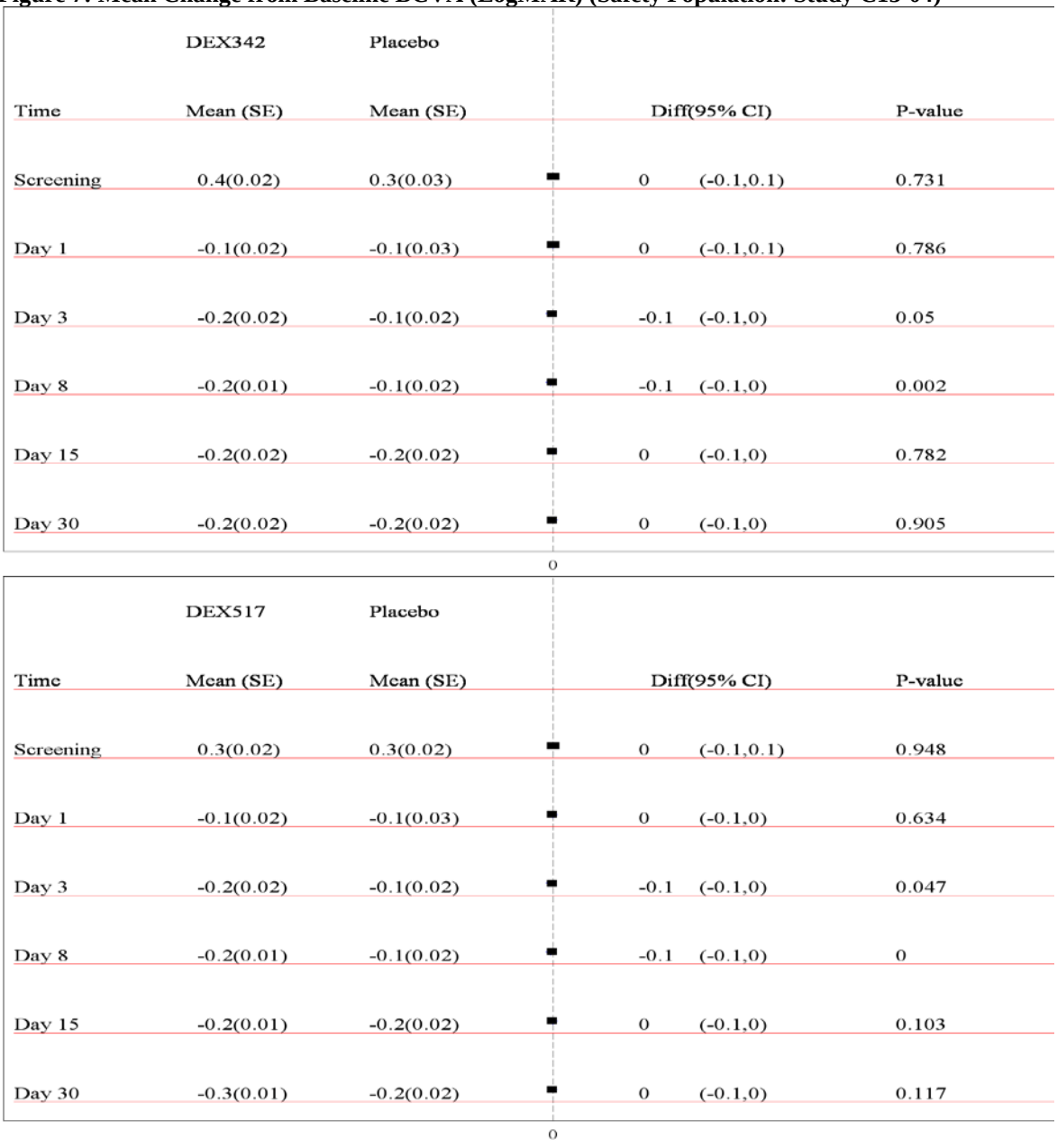
Source: Reviewer's Analysis. Subjects who received a rescue medication were counted in the 16-30+ category.

Figure 6: Mean Change from Baseline IOP (Safety Population: Study C13-04)



Source: Reviewer's analysis. Only observed data was used.

Figure 7: Mean Change from Baseline BCVA (LogMAR) (Safety Population: Study C13-04)



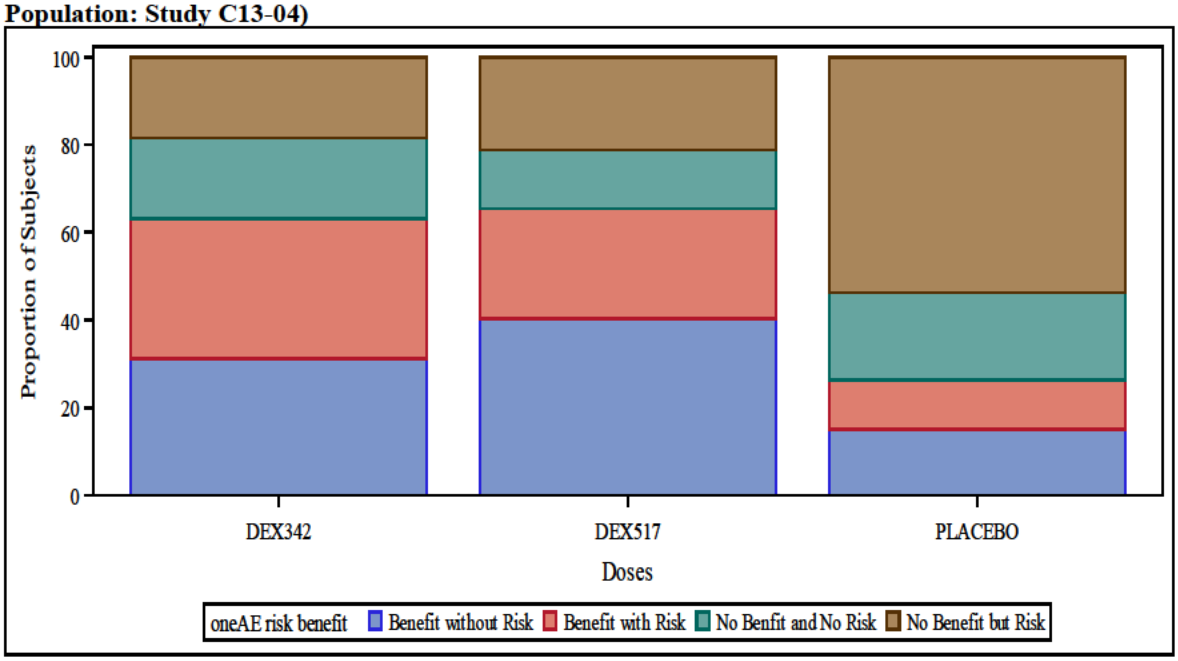
Source: Reviewer's Analysis. Only observed data was used.

Table 18: Mean Endothelial Cell Density (cell/ mm^2) by Visit (Safety Population: Study C13-04)

	Treatment		
Time	**Placebo Mean (SD)**	**DEX342 Mean (SD)**	**DEX517 Mean (SD)**
Screening	2506 (263)	2561 (295)	2571(310)
Day 90	2123 (564)	2171 (520)	2122 (577)

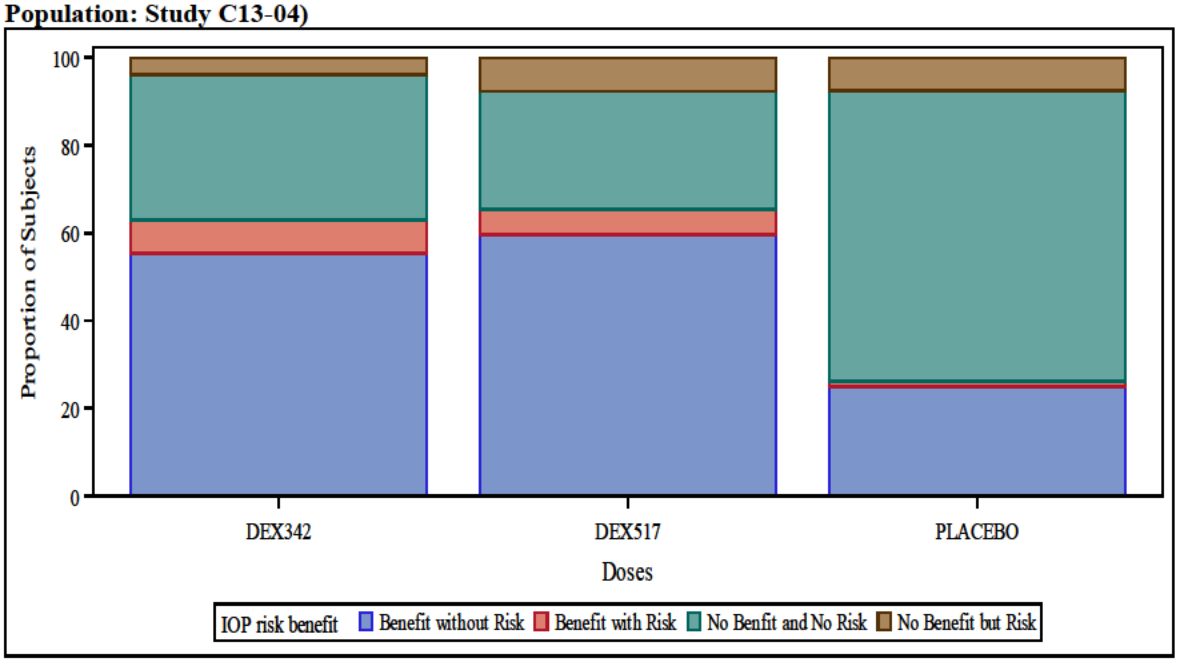
Source: Reviewer's Analysis. SD: Standard deviation. Only observed data was used.

Figure 8: Risk Benefit: At least One Ocular AE versus Inflammation Score of Zero at Day 8 (Safety Population: Study C13-04)



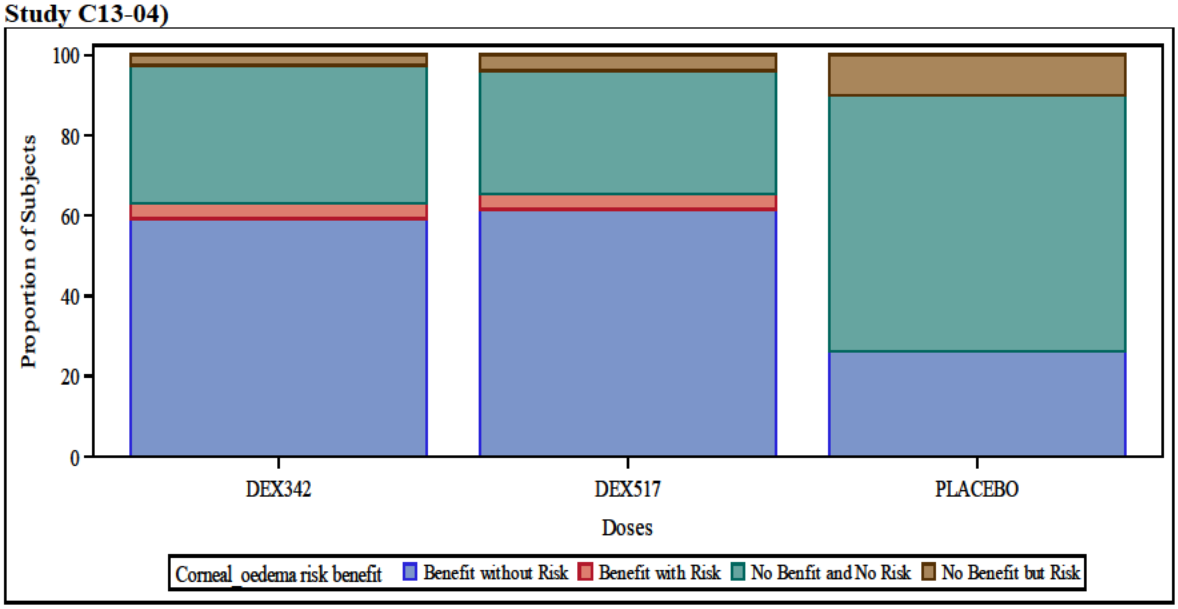
Source: Reviewer's Analysis. Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACC outcomes were set as treatment failures. For subjects with missing ACC, the ACC clearing was determined using ACC outcome from the previous visit.

Figure 9: Risk Benefit: IOP Increase from Screening versus Inflammation Score of Zero at Day 8 (Safety Population: Study C13-04)



Source: Reviewer's Analysis. Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACC outcomes were set as treatment failures. For subjects with missing ACC, the ACC clearing was determined using ACC outcome from the previous visit.

Figure 10: Risk benefit: Corneal Oedema versus Inflammation Score of Zero at Day 8 (Safety Population: Study C13-04)



Source: Reviewer's Analysis. Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACC outcomes were set as treatment failures. For subjects with missing ACC, the ACC clearing was determined using ACC outcome from the previous visit.

Figure 11: Subgroup Analysis: Proportion of Subjects with Clearing of ACC at Day 8 (ITT: Study C13-04)

Subgroups	DEX517 N (%)	Placebo N (%)	Difference(97.5% CI)	
Overall	102(65%)	21(26%)	39%	(25%,53%)
Sex: F	52(60%)	11(27%)	33%	(13%,52%)
Sex: M	50(72%)	10(26%)	47%	(27%,67%)
Age: <65 years	23(56%)	3(18%)	38%	(11%,65%)
Age: >=65 years	79(69%)	18(29%)	40%	(24%,56%)
Race: Black	14(67%)	3(27%)	39%	(1%,77%)
Race: OTHER	8(67%)	0(0%)	67%	(36%,97%)
Race: WHITE	80(65%)	18(27%)	38%	(23%,54%)

Subgroups	DEX342 N (%)	Placebo N (%)	Difference(97.5% CI)	
Overall	99(63%)	21(26%)	36%	(22%,50%)
Sex: F	56(67%)	11(27%)	41%	(21%,60%)
Sex: M	43(57%)	10(26%)	32%	(11%,52%)
Age: <65 years	20(49%)	3(18%)	31%	(4%,58%)
Age: >=65 years	79(68%)	18(29%)	39%	(23%,55%)
Race: Black	12(71%)	3(27%)	43%	(4%,82%)
Race: OTHER	7(58%)	0(0%)	58%	(26%,90%)
Race: WHITE	80(62%)	18(27%)	35%	(20%,51%)

Source: Reviewer's Analysis. Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACC outcomes were set as treatment failures. For subjects with missing ACC, the ACC clearing was determined using ACC outcome from the previous visit.

Table 19: Number of Randomized Subjects and Treatment Differences by Investigational Sites (ITT: Study C13-04)

Investigator Name		Number Randomized			Difference vs Placebo	
	Placebo N=80	DEX342 N=158	DEX517 N=157	Total N=395	DEX342	DEX517
Matossian	0	0	1	1	NA	NA
Linn	1	1	2	4	100%	50%
Whitman	0	2	2	4	NA	NA
Nhu	1	1	3	5	100%	67%
Haq	2	3	3	8	67%	NA
Sadri	1	3	4	8	-33%	-25%
Feinerman	2	4	3	9	100%	100%
Logan	2	4	3	9	25%	50%
Segal	2	4	3	9	50%	17%
Gollamudi	2	4	4	10	-50%	-25%
Unzueta	2	4	4	10	50%	50%
Mellgren	3	5	4	12	20%	25%
Milauskas	3	4	5	12	42%	7%
Modi	2	6	4	12	33%	25%
Tyson	3	5	5	13	NA	NA
Khachikian	3	5	6	14	27%	50%
Blase	3	6	6	15	17%	83%
Pai	3	8	7	18	-4%	-10%
Sorenson	4	8	7	19	38%	14%
Hartman	4	8	9	21	13%	44%
Johnson	4	9	8	21	78%	38%
Roel	**5**	**9**	**8**	**22**	69%	18%
Bylsma	5	8	10	23	38%	80%
LoBue	4	10	9	23	45%	75%
Nordlund	5	9	10	24	24%	36%
Savetsky	7	14	13	34	43%	56%
Sampson	7	14	14	35	29%	50%

Source: Reviewer's Analysis. Treatment differences (Dexycu-placebo) are based on analysis of the primary efficacy endpoint for each site. Subjects who received a rescue medication prior to the evaluation of efficacy and subjects with no post-treatment ACC outcomes were set as treatment failures. For subjects with missing ACC, the ACC clearing was determined using ACC outcome from the previous visit.

8 Appendix: Summary of Additional Studies considered

8.1 Study C15-01

This was a prospective, randomized, open-label, parallel-design, multicenter study. In this study, 194 subjects who were 40 years of age or older undergoing cataract surgery were enrolled. Subjects who met all inclusion and no exclusion criteria were randomized to receive either a single 5-mcl anterior chamber intraocular dose of 517 µg of Dexycu after cataract surgery, or three weeks of treatment with prednisolone acetate ophthalmic suspension 1% eye drops (one drop, four times daily [QID] for three weeks). The primary objective of this study was to evaluate the safety of Dexycu in the treatment of inflammation associated with cataract surgery.

Subjects were followed for 90 days after the day of surgery for evaluation of safety. Safety was assessed by evaluating adverse events, ophthalmic examinations in the study eye, fundus

examination by dilated ophthalmoscopy, intraocular pressure [IOP] by Goldmann applanation tonometry, visual acuity (assessed using standard Snellen charts), endothelial cell density [ECD] by specular microscopy) and use of concomitant medications and concurrent procedures.

The study prohibited the use of ocular topical corticosteroids in the study eye through Day 30, unless the pre-specified rescue criteria were met. A rescue treatment with ocular topical corticosteroids and/or ocular topical non-steroidal anti-inflammatories would be administered in the study eye, if at a follow-up visit anterior chamber cell grade is ≥3 (grade 3= 16-30+ cells) and/or the anterior chamber flare grade is ≥3 (grade 3= moderate intensity) or higher.

Of the 194 subjects who were randomized to the two study arms, 181subjects (126 in DEX517 and 55 in Prednisolone) received their respective treatments and 174 completed the study. There was no major difference between the two arms with respect to baseline and demographic characteristics. In both arms, more female subjects and subjects over the age of 65 were randomized. There were very few subjects who discontinued the study in both arms (Table 20 and Table 21).

Table 20: Subject Disposition (Study C15-01)

Study C15-01			
	DEX517	**Prednisolone**	**Total**
Randomized	130	64	194
Treated	126	55	181
Completed the Study	122 (96.8)	52 (94.5)	174 (96.1)
Reason for Subject Withdrawal			
Adverse Event(s)	1 (0.8%)	1 (1.8%)	2 (1.1%)
Protocol Violation(s)	1 (0.8%)	0 (0.0%)	1 (0.6%)
Lost to Follow-Up	1 (0.8%)	2 (3.6%)	3 (1.7%)
Consent Withdrawn	1 (0.8%)	0 (0.0%)	1 (0.6%)
Applicant Termination of Study	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigator Decision	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Table 2 of the study reports

Table 21: Baseline and Demographic Characteristics (Safety Population: Study C15-01)

Subgroup	**Treatment**		**Total N=181**
	DEX517 N=126	**Prednisolone N=64**	
Sex			
Male	59 (46.8%)	24 (43.6%)	83 (45.9%)
Female	67 (53.2%)	31 (56.4%)	98 (54.1%)
Age			
Mean (SD)	67.7 (8.95)	68.6 (10.24)	68.0 (9.34)
Median	69.0	68.0	69.0
Min, Max	39, 97	41, 98	39, 98
Age Group			
<65 Years	34 (27.0%)	17 (30.9%)	41 (28.2%)
>=65 Years	92 (73.0%)	38 (69.1%)	130 (71.8%)
Race			
White	111 (88.1%)	52 (94.5%)	163 (90.1%)
Black or African American	11 (8.7%)	1 (1.8%)	12 (6.6%)
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)

Asian	1 (0.8%)	2 (3.6%)	3 (1.7%)
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	3 (2.4%)	0 (0.0%)	3 (1.7%)
Ethnicity			
Hispanic or Latino	9 (7.1%)	1 (1.8%)	10 (5.5%)
Not Hispanic or Latino	117 (92.9)	54 (98.2)	171 (94.5%)

Source: Table 4 of the study reports

Per the study reports, because the objective of this study was to generate additional safety data in support of Dexycu; no formal statistical testing was performed. Consequently, the primary efficacy analysis which compared the two arms with respect to proportion of subjects with ACC clearing on POD 8 is purely exploratory. (b) (4)

(b) (4)

(b) (4)

(b) (4)

[redacted]

8.2 Study C11-01

This was a prospective, randomized, double-masked, dose-ranging, parallel-group, multicenter study. Subjects who met all eligibility criteria were randomized in a 1:1:1 ratio on the day of surgery to receive a single 5 mcl dose of one of three Dexycu concentrations (342, 517 or 697 µg; hereafter referred to as DEX342 DEX517 and DEX697). The primary objective was to evaluate the efficacy of two dose levels of Dexycu compared to the Dexycu low dose in the treatment of inflammation associated with ocular surgery. The secondary objective was to evaluate the safety and tolerability of Dexycu used for the treatment of inflammation associated with ocular surgery. The study planned to enroll 238 subjects aged 40 years or older undergoing cataract surgery. The study however fell short of the targeted number of subjects and enrolled a total of 172 subjects. Consequently, the study was deemed exploratory only by the applicant.

The total duration of the study was 90 days with follow-up visits to evaluate efficacy and safety outcomes performed at postoperative days (POD) 1, 3, 8, 15, and 30, with a final safety visit at POD 90. Evaluations of the study eye were performed at all study visits by performing slit lamp assessment for anterior chamber cells (ACC), anterior chamber flare (ACF) and corneal status. Adverse events (AEs), use of concomitant medications, and concurrent procedures were assessed at each visit after screening. Other safety assessments conducted at specified visits were visual acuity, intraocular pressure (IOP), corneal endothelial cell density (ECD), and dilated ophthalmoscopy. There were few subjects with missing data in all the three arms. There was also no major difference among the three arms with respect to baseline and demographic characteristics (Table 23 and Table 24).

The majority of subjects were white, female and over the age of 65 years. The primary efficacy analysis was conducted on the ITT population defined as all randomized subjects who received the study drug. Missing data were imputed using the LOCF approach. (b) (4)

[redacted]

Table 23: Subject Disposition (Study C11-01)

	DEX342	DEX517	DEX697	Total
Randomized	58 (100%)	56 (100%)	58 (100%)	172 (100%)
Completed the Study	56 (96.5%)	55 (96.5%)	58 (100%)	168 (97.7%)
Reason for Subject Withdrawal				
Lost to follow-up	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (0.6%)
Withdrawal by subject	2 (3.5%)	1 (1.8%)	0 (0.0%)	3 (1.7%)

Source: Table 6 of the study reports

Table 24: Baseline and Demographic Characteristics (Safety Population: Study C11-01)

Characteristic	DEX342 (n = 58)	DEX517 (n = 56)	DEX697 (n = 58)	Total (N = 72)
Age (years)				
< 65	17 (29.3%)	9 (16.1%)	15 (25.9%)	41 (23.8%)
≥ 65	41 (70.7%)	47 (83.9%)	43 (74.1%)	131 (76.2%)
Mean (SD)	68.0 (8.9)	71.8 (8.3)	70.7 (10.0)	70.1 (9.2)
Min, Max	(46.0, 88.0)	(50.0, 87.0)	(48.0, 85.0)	(46.0, 88.0)
Sex				
Male	23 (39.7%)	17 (30.4%)	27 (46.6%)	67 (39.0%)
Female	35 (60.3%)	39 (69.6%)	31 (53.4%)	105 (61.0%)
Race				
American Indian or Alaska Native	2 (3.4%)	1 (1.8%)	0(0.0%)	3 (1.7%)
Asian	2 (3.4%)	2 (3.6%)	6 (10.3%)	10 (5.8%)
Black or African American	1 (1.7%)	1 (1.8%)	5 (8.6%)	7 (4.1%)
Native Hawaiian or Other Pacific Islander	0(0.0%)	0(0.0%)	1 (1.7%)	1 (0.6%)
White	50 (86.2%)	51 (91.1%)	45 (77.6%)	146 (84.9%)
Other	3 (5.2%)	1 (1.8%)	1 (1.7%)	5 (2.9%)
Study Eye				
Right	32 (55.2%)	29 (51.8%)	29 (50.0%)	90 (52.3%)
Left	26 (44.8%)	27 (48.2%)	29 (50.0%)	82 (47.7%)

Source: Table 8 of the study report

(b) (4)

8.3 Studies C09-01 and C10-01

(b) (4)


(b) (4)

Description of the Applicant's Multiple Imputation and sample SAS codes:

14.4.4 Multiple Imputation

Multiple imputation will be used to impute an ACC clearing value at a post-baseline time point if the corresponding ACC grade is missing or a patient received rescue medication on or before a given time point. The multiple imputation requires that the data are missing at random and that the sample size is large. SAS® procedure PROC MI with default parameters for the multiple imputation will be used. The multiple imputation model will include the following variables for imputing a post-baseline ACC clearing value at Day 8:

- Treatment group (categorical variable)
- ACC clearing values at POD # 1, 3, 8, 15, and 30
- Sex
- Age
- Non-missing post-baseline ACC clearing results measured prior to the time point being imputed (binary variables)

Non-missing post-baseline ACC clearing referred to above are the ACC clearing results at the time points prior to the time point being imputed:

- The observed (i.e., not imputed) ACC clearing results
- The ACC clearing results imputed using multiple imputation conducted at time points prior to the current time point being imputed.

Sample SAS code:

Description of the Applicant's GLMM model for binary outcomes and Sample SAS codes:

14.5 EVALUATION OF COVARIATES

As another exploratory analysis, we examine the potential effect of age and sex on the rate of anterior chamber cell clearing of study eye at POD # 8. The GLMM model will include values of clearing (0) or not clearing (1) on POD #1, 3, 8, 15, and 30 as the dependent variable; treatment group, time, treatment by time interaction as fixed effects; and age and sex as covariates. Time ordering will be treated as a repeated measure within subjects. A variance component covariance matrix is assumed. The odds of having a clearing is $\frac{p_{ijk}}{1-p_{ijk}}$ for subject j assigned to treatment i at time, where p_{ijk} is the probability that a subject having a clearing ($Y_{ijk} = 0$). The GLMM model is:

$$\log(p_{ijk}/(1-p_{ijk})) = \mu + \alpha_i + \beta_1 Age_{ij} + \beta_2 Sex_{ij} + \gamma_k + (\alpha\gamma)_{ik}$$

Where α_i is the treatment effect; β_1 is the coefficient of Age; β_2 is the coefficient of Sex; γ_k is time effect; $(\alpha\gamma)_{ik}$ is the treatment by time interaction; $\mu + \alpha_i + \beta_1 Age_{ij} + \beta_2 Sex_{ij} + \gamma_k + (\alpha\gamma)_{ik}$ is the mean for treatment i at time k, containing effects for treatment, time, treatment by time interaction and effects of covariates (Age and Sex). Time ordering is a repeated measure within subjects. SAS PROC GLIMMIX procedure will be used. A sample SAS code for the model is shown below. The SAS GLIMMIX procedure is modeling the probability without clearing variable = '1' (i.e. without clearing as the reference level).

Where TRT01PN = planned treatment group in numeric (1 = placebo/vehicle, 0 mcg dexamethasone; 2 = IBI-10090, 342 mcg dexamethasone; 3 = IBI-10090, 517 mcg

Sample SAS codes for the Applicant's GLMM model for Ordinal Outcomes:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABEL T ESHETE
12/21/2017

YAN WANG
12/21/2017
I concur with the overall efficacy conclusions.