# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208742Orig1s000

# 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

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|---|---|
| **NDA/BLA #:** | NDA208742 |
| **Drug Name:** | DEXTENZA (sustained release dexamethasone) 0.4 mg |
| **Indication(s):** | Treatment of ocular pain associated with ophthalmic surgery |
| **Applicant:** | Ocular Therapeutix |
| **Date(s):** | Stamp date: September 24, 2015 |
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| **Review Priority:** | Standard |
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**Keywords:** Pain, Inflammation, Dexamethasone, Ophthalmic surgery.

## Table of Contents



## LIST OF TABLES

## LIST OF FIGURES

# 1 EXECUTIVE SUMMARY

This NDA is submitted as a 505 (b) (2) application seeking approval of Dextenza (sustained release dexamethasone) 0.4 mg for the treatment of ocular pain associated with ophthalmic surgery. The primary evidence for the safety and efficacy of Dextenza comes from two prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled Phase 3 studies (oxt-13-002 & oxt-14-003). The two primary efficacy endpoints were the proportion of subjects with absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 14 and the proportion of subjects with absence of pain (i.e., score of '0') in the study eye at Day 8.

The primary efficacy analyses were conducted based on all randomized subjects (ITT) using a Pearson's chi-square test. A fixed sequence hierarchical testing procedure was used to control the type-I error rate due to the test of two primary efficacy endpoints. The difference in the proportion of subjects with absence of pain at Day 8 was tested only after the difference in the proportion of subjects with absence of anterior chamber cells at Day 14 was statistically significant in favor of Dextenza. The last observation carried forward (LOCF) method was used to impute missing data. Subjects who received a rescue medication prior to the evaluation of the primary efficacy endpoints were set as treatment failures.

Study oxt-13-002 provided statistically significant evidence in favor of Dextenza for both primary efficacy endpoints. The proportion of subjects with absence of pain at Day 8 (Dextenza vs Vehicle) was [80% vs 43%; diff (95% CI): 37% (24%, 49%)]. Study oxt-14-003 however did not demonstrate the superiority of Dextenza over Vehicle for the proportion of subjects with absence of cells at Day 14. Consequently, because of the pre-specified fixed sequence hierarchical testing procedure, no formal statistical conclusion could be made for the pain outcome in this study. However, in this study, the proportion of subjects with absence of pain at Day 8 in the Dextenza arm was fairly consistent with the result seen in study oxt-13-002, and the treatment difference was numerically favorable to the Dextenza arm (Table 1).

With respect to safety, 28% of subjects who received Dextenza reported at least one ocular adverse event (AE) in the study eye compared to 40% subjects in the Vehicle arm. The most frequently reported AEs in the study eye for subjects who received Dextenza were increased intraocular pressure (6.0%), anterior chamber inflammation (5.2%) and iritis (3.5%). Except one ocular AE reported in the Vehicle arm, none of the other reported ocular AEs were serious. In summary, compared to Vehicle, the Dextenza arm had a higher proportion of subjects with absence of pain at Day 8 and exhibited a favorable risk-benefit profile.

**Table 1: Summary of primary efficacy analysis (ITT: LOCF)**

| | | **Proportion of subjects with absence of pain** | | |
|---|---|---|---|---|
| **Study** | **Visit** | **Dextenza** | **Vehicle** | **Difference (%) (Asymptotic 95% CI)** |
| Oxt-13-002 | Day 8 | 131/ 164 (80%) | 36/83 (43%) | 37% (24%, 49%) |
| Oxt-14-003 | Day 8 | 124/ 161 (77%) | 47/80 (59%) | 18% (6%, 31%) |
| **Proportion of subjects with absence of anterior chamber cells** | | | | |
| Oxt-13-002 | Day 14 | 54/ 164 (33%) | 12/83 (14%) | 18% (8%, 29%) |
| Oxt-14-003 | Day 14 | 63/ 161 (39%) | 25/80 (31%) | 8% (-5%, 21%) |

Source: Adapted from Table 11-2 of the study reports. Subjects who received a rescue therapy were set as treatment failures.

# 2 INTRODUCTION

This NDA included data from two Phase 3 studies (oxt-13-002 and oxt-14-003) to support the safety and efficacy of Dextenza for the treatment of post-surgical pain in subjects who have undergone cataract extraction with intraocular lens implantation. Supportive evidence from a similarly designed Phase 2 study (oxt-12-002) was also considered.

## 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

Dextenza is a sustained dexamethasone drug delivery vehicle developed for the treatment of post-surgical pain and inflammation in subjects who have undergone cataract extraction with intraocular lens implantation. It is designed to be placed in the vertical canaliculus for sustained and tapered release of the active ingredient. Dextenza contains 0.4 mg of dexamethasone, which is the active ingredient in Maxidex® 0.1% (dexamethasone ophthalmic suspension) (Alcon Laboratories Inc., Fort Worth, TX), which received commercial approval in the United States (NDA 013422).

### 2.1.2 History of Drug Development

The applicant had one End-of-Phase 2 meeting with the agency on September 13, 2013. During this meeting, the applicant discussed the design of the two pivotal Phase 3 studies. The applicant proposed to evaluate the absence of pain and absence of anterior chambers cells both at Day 14 as the two primary efficacy endpoints. The agency however advised the applicant to evaluate the pain outcome earlier than the proposed 14 days. The applicant agreed to evaluate the pain outcome at Day 1 and Day 8 with the outcome at Day 8 considered as the primary efficacy pain outcome. Note, the protocols and the statistical analyses plans for all studies considered in this NDA submission were reviewed under IND114720.

The applicant also had a pre-NDA meeting with the agency to discuss the results of the two Phase 3 studies. The results showed that the Dextenza arm did not establish statistical superiority over Vehicle for the proportion of subjects with absence of anterior chamber cells at Day 14 in one of the two Phase 3 studies (oxt-14-003). Consequently, the agency advised the applicant to conduct an additional Phase 3 study if they intend to request an indication for inflammation. The applicant agreed to conduct a third Phase 3 study but requested if the results for the pain endpoints from both Phase 3 clinical trials with supportive evidence from the Phase 2 study are appropriate to support an NDA approval for a pain-only indication. The agency stated that the pain endpoints from both Phase 3 trials with supportive evidence from the Phase 2 study could be used for a NDA filing for a pain-only indication and that approval is a review issue requiring submission and review of a NDA.

### 2.1.3 Studies Reviewed

This NDA review was conducted mainly based on data from two Phase 3, prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled studies (Study oxt-13-002 & Study oxt-14-003). Additionally, supportive evidence from a Phase 2 study (Study oxt-12-002) with a similar design was also included. Study oxt-13-002 and Study oxt-14-003 enrolled 241 and 247 subjects respectively each from a total of 16 sites located in the United States (US). Study oxt-12-002 enrolled 60 subjects across 4 sites in the US. The brief summaries for each of these studies are presented in Table 2. A brief summary of a Phase 1 study (oxt-14-009) involving 16 healthy subjects considered as part of the safety evaluation is presented in the appendix.

**Table 2: Brief summary of studies (oxt-13-002, oxt-14-003 and oxt-12-002)**

| Study | Design | Treatment/Sample size | Endpoint/Analysis | Applicant's findings |
|---|---|---|---|---|
| Oxt-13-002 | A Phase 3, Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain after Cataract Surgery | – Dextenza: N=164<br>– Vehicle: N=83 | Primary Endpoints:<br>– Absence of cells (score of zero) in the anterior chamber cell of the study eye at Day 14<br>– Absence of pain (score of zero) in the study eye at Day 8<br><br>The primary efficacy analysis of evaluating superiority of Dextenza against Vehicle was conducted using a chi-square test on the ITT population consisting of all randomized subjects. Fixed sequence testing was to be used for the analysis of the primary efficacy endpoints. Pearson chi-squared statistic with a two-sided alpha = 0.05 was used to test the difference in the proportion of subjects with absence of anterior chamber cells in the study eye between treatments at Day 14. If that test was statistically significant at the two-sided alpha = 0.05 level in favor of OTX-DP, then the study was to be considered a success and the inference in the proportion of subjects with absence of ocular pain between treatments at Day 8 was to be tested using the Pearson chi-squared statistic at the two-sided alpha = 0.05 level. | The study was successful in meeting its primary efficacy endpoints of demonstrating superiority of OTX-DP over PVPP in the proportion of subjects with absence of ocular inflammation in the study eye at the Day 14 Visit and the proportion of subjects with absence of pain at the Day 8 Visit. A significantly greater proportion of study eyes in the OTX-DP vs. PVPP treatment group 33.1% vs. 14.5%) had an absence of anterior chamber cells at the Day 14 Visit (p=0.0018, difference: 18.7%), and a significantly greater proportion of study eyes in the OTX-DP vs. PVPP treatment group (80.4% vs. 43.4%) had an absence of ocular pain at Day 8 p<0.0001, difference: 37.0%). |
| Oxt-14-003 | A Phase 3, Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain after Cataract Surgery | – Dextenza: N=161<br>– Vehicle: N=80 | Primary Endpoints:<br>– Absence of cells (score of zero) in the anterior chamber cell of the study eye at Day 14<br>– Absence of pain (score of zero) in the study eye at Day 8<br><br>The primary efficacy analysis of evaluating superiority of Dextenza against Vehicle was conducted using a chi-square test on the ITT population consisting of all randomized subjects. Fixed sequence testing was to be used for the analysis of the primary efficacy endpoints. Pearson chi-squared statistic with a two-sided alpha = 0.05 was used to test the difference in the proportion of subjects with absence of anterior chamber cells in the study eye between treatments at Day 14. If that test was statistically significant at the two-sided alpha = 0.05 level in favor of OTX-DP, then the study was to be considered a success and the inference in the proportion | The proportion of subjects with absence of anterior chamber cells in the study eye at the Day 14 Visit was similar p=0.2182) in the OTX-DP (39.4%) and PVPP (31.3%) treatment groups; therefore the study failed to demonstrate superiority of OTX-DP over PVPP for the inflammation endpoint. However, OTX-DP was superior to PVPP for the proportion of study eyes with absence of ocular pain at the Day 8 Visit (OTX-DP, 77 5%; PVPP, 58.8%; p=0.0025%). |

| Study | Design | Treatment/Sample size | Endpoint/Analysis | Applicant's findings |
|---|---|---|---|---|
| | | | of subjects with absence of ocular pain between treatments at Day 8 was to be tested using the Pearson chi-squared statistic at the two-sided alpha = 0.05 level. | |
| Oxt-12-002 | A Phase 2, Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase II Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain after Cataract Surgery | – Dextenza: N=30<br>– Vehicle: N=30<br><br>. | Primary Endpoints:<br>– Absence of cells (score of zero) in the anterior chamber cell of the study eye at Day 8<br>– Absence of pain (score of zero) in the study eye at Day 8<br><br>The primary efficacy analysis of evaluating superiority of Dextenza against Vehicle was conducted using a chi-square test on the ITT population consisting of all randomized subjects. Fixed sequence testing was to be used for the analysis of the primary efficacy endpoints. Pearson chi-squared statistic with a two-sided alpha = 0.1 was used to test the difference in the proportion of subjects with absence of anterior chamber cells in the study eye between treatments at Day 8. If that test was statistically significant at the two-sided alpha = 0.1 level in favor of OTX-DP, then the study was to be considered a success and the inference in the proportion of subjects with absence of ocular pain between treatments at Day 8 was to be tested using the Pearson chi-squared statistic at the two-sided alpha = 0.1 level. | The results of these analyses indicated that 20.7% of subjects in the OTX-DP treatment group vs. 10 0% in the PVPP treatment group had an absence of anterior chamber cells at Day 8 (p=0.1495, difference: 10.7%, 95 CI: -7.5%, 28.9%), and that 79.3% of subjects in the OTX-DP group vs. 30.0% in the PVPP group had an absence of ocular pain at Day 8 (p<0.0001, difference: 49.3%, 95 CI: 27.3%, 71.4%). |

Source: Applicant's submitted study reports.

## 2.2 Data Sources

The data sources for this review included the applicant's clinical study reports for all studies and the integrated safety and efficacy analysis reports. Additionally, the applicant electronically submitted SAS datasets both as SDTM and ADAM data formats. The data sets used in this review are located at: \\Cdsesub1\evsprod\NDA208742\0000\m5\datasets\. The pain and inflammation outcomes at screening and subsequent measurement times were included in the "adeff.xpt" dataset. An indicator variable (PARAMCD) was included to distinguish the different outcomes (pain, inflammation, flare). For the primary efficacy analysis of the pain outcome, the variable CRIT1FL which takes a value of "absence" if the pain score was zero or the subject received a rescue therapy prior to Day 8, or "presence" if the a pain score was greater than zero was used. A data type variable DTYPE was also included to distinguish between imputed and observed values and the type of imputation involved (LOCF and LOCF/FAILURE). The treatment variable, given both as numeric (TRT01P) and character (TRT01PN), was also included in the above dataset. The adverse events and treatment exposures were included in the "adae.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 data were generally of good quality. The final statistical analysis plan and the amended protocols were all submitted. In the original submission, the applicant did not submit the SAS codes used for efficacy analyses. As a result of an information request, the applicant submitted the SAS codes used to produce the study results. The SAS codes are located at \\Cdsesub1\evsprod\NDA208742\0013.

## 3.2 Evaluation of Efficacy

This section summarizes the design of the three studies and the corresponding efficacy results submitted by the applicant and the reviewer's analysis.

### 3.2.1 Study Design and Endpoints

Eligible subjects for the studies considered in this NDA underwent clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens. At the conclusion of the cataract surgery, subjects who remained eligible for the study were randomized and had the investigational product or Vehicle inserted into the inferior vertical canaliculus of their operated eye (study eye) at Day 1. Ocular pain assessments were conducted at post-surgery days 2, 4, 8, 14, 30 and 60. If the test article was no longer present in the canaliculus at a study visit prior to the Day 60 visit, subjects returned one week later (± 2 days) for a final study assessment per the Day 60 schedule. Subjects were exited at the completion of the Day 60 visit if the test article was confirmed to be no longer present using visual technique

via slit lamp. The investigator and the subject were masked to the treatment assignment throughout the subject's participation in the trial. Besides, Dextenza and the Vehicle were identical in appearance and were supplied in identical packages so that they could not be distinguished by the user.

The primary efficacy endpoints in the two Phase 3 studies were the proportion of subjects with absence of cells (i.e., score of '0') in the anterior chamber of the study eye at Day 14 and the proportion of subjects with absence of pain (i.e., score of '0') in the study eye at Day 8. For the Phase 2 study, the two primary efficacy endpoints, absence of pain and cells, were evaluated at Day 8. Absence of flare, cells and pain at the follow-up post-surgery visits were the secondary efficacy endpoints. Pain was measured using an 11-point subjective scale which was later categorized to 0=no pain, 1-3=mild, 4-6=moderate and 7-10=severe pain. Anterior chamber cells were graded using a 6-point scale with 0=no cells, 0.5+=1-5 cells, 1+=6-15 cells, 2+=16-25 cells, 3+=26-50 cells and 4+= >50 cells in the field. Similarly, anterior chamber flare was graded using a 6-point scale with 0=none, 1+=faint, 2+=moderate, 3+=marked, and 4+= intense.

According to the study protocols, investigators had the discretion to prescribe anti-inflammatory medication anytime during the follow-up period for subjects who returned for the Day 2 and later visits who exhibited ≥ Grade 2+ (≥16) anterior chamber cells, ≥ 3+ (Marked: iris and lens details hazy) flare, and/or ≥ 4 (moderate to severe) ocular pain. Note that, neither the protocols nor the statistical analysis plans clearly stated whether data would be collected after rescue medication. Based on the information in the analysis datasets however, it appears that data were not recorded after rescue medication.

### 3.2.2 Statistical Methods

The primary efficacy analyses of evaluating the superiority of Dextenza against Vehicle was conducted based on all randomized subjects (ITT) using the Pearson chi-squared statistic. Fixed sequence testing was employed to maintain the type I error rate. The primary analyses first tested the difference in the proportion of subjects with absence of anterior chamber cells at Day 14 in the study eye between treatments. If the test of the difference in the proportion of study eyes with absence of anterior chamber cells at Day 14 was statistically significant at the two-sided alpha = 0.05 level in favor of Dextenza, the difference in the proportion of subjects with absence of ocular pain at Day 8 between treatments was tested at the two-sided alpha = 0.05 level. Note, for the Phase 2 study, both primary efficacy endpoints were evaluated at Day 8 and the protocol defined level of significance for the test of the two endpoints was 0.1. A 95% confidence interval was constructed around the difference (Dextenza minus Vehicle) in proportions for each primary outcome using asymptotic normal approximations. The last non-missing data from a prior visit was carried forward for missing data (LOCF). Subjects in both arms who received a rescue therapy prior to the evaluation of the primary efficacy endpoints were set as treatment failures. The primary efficacy endpoints were also analyzed using the same approaches based on the per-protocol population (including all subjects with no major protocol violation) with observed data only and based on the ITT population using the multiple imputations approach.

This reviewer 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 a pain score of zero at Day 8 was observed without incurring an adverse event (AE) during the study. The worst case scenario is incurring an AE during the study without achieving a zero pain score at Day 8. The other two scenarios are having no pain at Day 8 (benefit) with AE, and no benefit and no AE. The reviewer also conducted a tipping point analysis to determine how many subjects in the Vehicle arm who received a rescue therapy (and hence set as treatment failures) need to be set as treatment successes for the treatment difference to no longer be statistically significant.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

#### 3.2.3.1 Demographic and Baseline Characteristics

There were no significant baseline imbalances between the two arms in the demographics of age, gender, race or iris color. In all studies, there were more female participants in the Dextenza arm than male participants; and most of the study participants were white (Table 3).

**Table 3: Baseline and demographic characteristics (ITT)**

| | **Study oxt-13-002** | | **Study oxt-14-003** | | **Study oxt-12-002** | |
|---|---|---|---|---|---|---|
| | **Dextenza N=164** | **Vehicle N=83** | **Dextenza N=161** | **Vehicle N=80** | **Dextenza N=30** | **Vehicle N=30** |
| Sex | | | | | | |
| Male | 61 (37.2%) | 39 (47.0%) | 63 (39.1%) | 41 (51.3%) | 13 (43.3%) | 18 (60.0%) |
| Female | 103 (62.8%) | 44 (53.0%) | 98 (60.9%) | 39 (48.8%) | 17 (56.7%) | 12 (40.0%) |
| Age | | | | | | |
| Mean (SD) | 67.4 (8.24) | 69.9 (8.09) | 69.0 (8.32) | 68.3 (8.07) | 63.9 (9.69) | 65.9 (8.55) |
| Median | 67 | 71 | 70 | 68 | 65.5 | 67 |
| Min, Max | 47, 87 | 46, 93 | 43, 86 | 49, 84 | 38, 80 | 50, 84 |
| Age Group | | | | | | |
| <65 Years | 56 (34.1%) | 16 (19.3%) | 49 (30.4%) | 22 (27.5%) | 14 (46.7%) | 9 (0.3%) |
| >=65 to <75 Years | 76 (46.3%) | 44 (53.0%) | 66 (41.0%) | 39 (48.8%) | 12 (40.0%) | 14 (46.7%) |
| ≥ 75 Years | 32 (19.5%) | 23 (27.7%) | 46 (28.6%) | 19 (23.8%) | 4 (13.3%) | 7 (23.3%) |
| Race | | | | | | |
| White | 136 (82.9%) | 62(74.7%) | 135 (85.7%) | 71 (88.8%) | 27 (90.0%) | 27 (90.0%) |
| Black or African American | 22(13.4%) | 18(21.7%) | 20 (12.4%) | 8 (10.0%) | 2 (6.1%) | 1 (3.3%) |
| Asian | 3(1.8%) | 3(3.6%) | 1 (0.6%) | 1 (1.3%) | 2 (6.1%) | 1 (3.3%) |
| Other | 3(1.8%) | 0(0%) | 2 (1.2%) | (0.0%) | 1 (3.3%) | 2 (6.1%) |
| Iris Color | | | | | | |
| Blue | 58 (35.4%) | 26 (31.3%) | 45 (28.0%) | 18 (22.5%) | 9 (30.0%) | 11 (36.7%) |
| Brown | 75 (45.7%) | 40 (48.2%) | 78 (48.4%) | 40 (50.0%) | 8 (26.7%) | 12 (40.0%) |
| Hazel | 16 (9.8%) | 7 (8.4%) | 25 (15.5%) | 17 (21.3%) | 11 (36.7%) | 4 (13.3%) |
| Green | 15 (9.1%) | 8 (9.6%) | 11 (6.8%) | 4 (5.0%) | 2 (6.7%) | 3 (10.0%) |
| Gray | 0 | 2 (2.4%) | 2 (1.2%) | 1 (1.3%) | 0 (0.0%) | 0 (0.0%) |
| Ethnicity | | | | | | |
| Hispanic or Latino | 8 (4.9%) | 2 (2.4%) | 29 (18.0%) | 9 (11.3%) | 3 (10.0%) | 3 (10.0%) |
| Not Hispanic or Latino | 156 (95.1%) | 81 (97.6%) | 132 (82.0%) | 71 (88.8%) | 27 (90.0%) | 27 (90.0%) |

Source: Table 14.1.2 of the applicant's study reports

### 3.2.3.2 Patient Disposition

The summary of the patient disposition for the three studies is presented in Table 4. In all studies, over 93% of subjects in each arm completed the study.

**Table 4: Patient disposition (ITT)**

| | **Dextenza** | **Vehicle** | **Total** |
|---|---|---|---|
| **Study oxt-13-002** | | | |
| Randomized | 164 | 83 | 247 |
| Treated[1] | 163 | 83 | 246 |
| Completed the Study | 163 (99.4%) | 81 (97.6%) | 244 (98.8%) |
| Reason for Subject Withdrawal | | | |
| Adverse Event(s) | 0 (0.0%) | 1 (50.0%) | 1 (33.3%) |
| Protocol Violation(s) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lost to Follow-Up | 0 (0.0%) | 1 (50.0%) | 1 (33.3%) |
| Consent Withdrawn | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Sponsor Termination of Study | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Investigator Decision | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other | 1 (100.0%) | 0 (0.0%) | 1 (33.3%) |
| **Study oxt-14-003** | | | |
| | Dextenza | Vehicle | Total |
| Randomized | 161 | 80 | 241 |
| Treated | 160 | 80 | 240 |
| Completed the Study | 159 (98.8%) | 76 (95.0%) | 226 (93.8%) |
| Reason for Subject Withdrawal | | | |
| 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 | 0 (0.0%) | 2 (50.0%) | 2 (33.3%) |
| Consent Withdrawn | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Sponsor Termination of Study | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Investigator Decision | 1 (50.0%) | 1 (25.0%) | 2 (33.3%) |
| Other | 1 (50.0%) | 1 (25.0%) | 2 (33.3%) |
| **Study oxt-12-002** | | | |
| Randomized | 30 | 30 | 60 |
| Treated | 29 (96.7%) | 30 (100%) | 59 (98.3%) |
| Completed the Study | 28 (93.3%) | 29 (96.7%) | 57 (95.0%) |
| Reason for Subject Withdrawal | | | |
| Adverse Event(s) | 1 (50.0%) | 0 (0.0%) | 1 (33.3%) |
| Protocol Violation(s) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lost to Follow-Up | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Consent Withdrawn | 1 (50.0%) | 1 (100.0%) | 2 (66.7%) |
| Sponsor 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 10.1 of Applicant's submitted Study Reports. [1] one subject randomized to the Vehicle arm received Dextenza.

The summary of subjects with observed pain measurements at each visit (not carried forward), subjects with missing pain outcomes (imputed using LOCF) and subjects who received a rescue therapy at or prior to a giving visit (treated as treatment failures) is presented in Table 5. There were very few subjects who discontinued the studies altogether. However, some subjects who

completed the studies did not have observed pain measurements for some visits. For example, in Study oxt-13-002, on Day 8, only 151/164 (92%) and 58/83 (70%) subjects in the Dextenza and Vehicle arms respectively had observed pain measurements. One subject in the each of the two arms had missing pain outcome and hence was imputed using LOCF. Additionally, 12 (7%) and 24 (29%) subjects in the Dextenza and Vehicle arms respectively received rescue therapy at or prior to Day 8 and hence were set as treatment failures.

**Table 5: Summary of subjects by data type: (Randomized subjects)**

| Visit | Study oxt-13-002 | | Study oxt-14-003 | | Study oxt-12-002[1] | |
|---|---|---|---|---|---|---|
| | Dextenza N=164 | Vehicle N=83 | Dextenza N=161 | Vehicle N=80 | Dextenza N=30 | Vehicle N=30 |
| Day 2 | | | | | | |
| Observed | 162(99%) | 83(100%) | 158(98%) | 79(99%) | 29(97%) | 29(97%) |
| Rescue | 1(1%) | 0(0%) | 2(1%) | 1(1%) | 0(0%) | 1(3%) |
| LOCF | 1(1%) | 0(0%) | 1(1%) | 0(0%) | 0 (0.0%) | (0.0%) |
| Day 4 | | | | | | |
| Observed | 161(98%) | 78(94%) | 156(97%) | 77(96%) | 27(90%) | 17(57%) |
| Rescue | 2(1%) | 4(5%) | 3(2%) | 3(4%) | 2(7%) | 13(43%) |
| LOCF | 1(1%) | 1(1%) | 2(1%) | 0(0%) | 0 (0.0%) | (0.0%) |
| Day 8 | | | | | | |
| Observed | 151(92%) | 58(70%) | 149(93%) | 65(81%) | 24(80%) | 13(43%) |
| Rescue | 12(7%) | 24(29%) | 10(6%) | 15(19%) | 5(17%) | 16(53%) |
| LOCF | 1(1%) | 1(1%) | 2(1%) | 0(0%) | 0(0%) | 1(3%) |
| Day 14 | | | | | | |
| Observed | 138(84%) | 45(54%) | 132(82%) | 50(63%) | 23(77%) | 8(27%) |
| Rescue | 24(15%) | 38(46%) | 28(17%) | 30(38%) | 6(20%) | 21(70%) |
| LOCF | 2(1%) | 0(0%) | 1(1%) | 0(0%) | 0(0%) | 1(3%) |
| Day 30 | | | | | | |
| Observed | 138(84%) | 42(51%) | 130(81%) | 47(59%) | 23(77%) | 8(27%) |
| Rescue | 24(15%) | 39(47%) | 28(17%) | 30(38%) | 6(20%) | 21(70%) |
| LOCF | 2(1%) | 2(2%) | 3(2%) | 3(4%) | 0(0%) | 1(3%) |

Source: Reviewer's Analysis Rescue =subjects who received a rescue therapy LOCF=subjects who had missing data but imputed using the LOCF approach [1]One subject randomized to the Dextenza arm was not treated and had no post-randomization visit

## 3.2.4 Results and Conclusions

### 3.2.4.1 Efficacy Results

Unless otherwise indicated, tables and figures presented in this review are based on analyses conducted by this reviewer using the analysis datasets submitted by the applicant and confirm the results of those presented by the applicant in the study reports.

#### 3.2.4.1.1 *Primary Efficacy Analysis*

The primary efficacy analyses results are presented in Table 6. Study oxt-13-002 demonstrated superiority of Dextenza over Vehicle in both primary efficacy endpoints. The proportion of subjects with no anterior chamber cells at day 14 in the Dextenza arm was significantly higher compared with the Vehicle arm (33% vs 14%; diff (95% CI): 18 (8%, 29%]). Similarly, a significantly higher proportion of subjects in the Dextenza arm reported no pain at Day 8 compared with the Vehicle arm [80% vs 43%; diff (95% CI): 37% (24%, 49%)].

Study oxt-14-003 did not demonstrate the superiority of Dextenza over Vehicle for the proportion of subjects with absence of anterior chamber cells at Day 14 [39% vs 31%; diff (95% CI): 8% (-5%, 21%]. The proportion of subjects with no pain at Day 8 was higher in the Dextenza arm compared to the Vehicle arm [77% vs 59%; diff (95% CI): 18% (6%, 31%)]. However, because of the pre-specified fixed-sequence hierarchical testing procedure, conclusive inferential claim concerning the pain outcome could not be made in this study.

Similarly, the Phase 2 study (oxt-12-002) did not result in statistically significant difference in the proportion of subjects with no anterior chamber cells at day 8 [20% vs 10%; diff (95% CI): 10% (-10%, 30%]. Note that, for this study, both primary efficacy endpoints were evaluated at Day 8 and the protocol defined significance level for the test of the two primary efficacy endpoints was 10%.

**Table 6: Summary of primary efficacy analysis (ITT: LOCF)**

| | | **Proportion of subjects with absence of pain** | | |
|---|---|---|---|---|
| **Study** | **Visit** | **Dextenza** | **Vehicle** | **Difference (%) (Asymptotic 95% CI)** |
| Oxt-13-002 | Day 8 | 131/ 164 (80%) | 36/83 (43%) | 37% (24%, 49%) |
| Oxt-14-003[1] | Day 8 | 124/ 161 (77%) | 47/80 (59%) | 18% (6%, 31%) |
| Oxt-12-002[1] | Day 8 | 23/30 (77%) | 9/30 (30%) | 47% (20%, 70%) |
| **Proportion of subjects with absence of anterior chamber cells** | | | | |
| Oxt-13-002 | Day 14 | 54/ 164 (33%) | 12/83 (14%) | 18% (8%, 29%) |
| Oxt-14-003 | Day 14 | 63/ 161 (39%) | 25/80 (31%) | 8% (-5%, 21%) |
| Oxt-12-002[2] | Day 8 | 6/30 (20%) | 3/30 (10%) | 10% (-10%, 30%) |

Source: Adapted from Table 11-2 of the study reports. Subjects who received a rescue therapy were set as treatment failures. [1] In these two studies, formal statistical testing for this endpoint could not be made due to the fixed sequence testing procedure. [2] In study oxt-12-002, Day 8 was the protocol defined time point for the evaluation of this endpoint.

Neither the protocols nor the statistical analysis plans specified the estimand of interest. In the absence of an explicitly pre specified, justified, and accepted primary estimand of interest, one must evaluate whether each possible estimand is "meaningful for all study participants, and estimable with minimal assumptions," as recommended in the National Research Council (NRC) report. For example, the primary efficacy analysis with LOCF could be interpreted as an evaluation of the "last available observation" (LAO) estimand, that is, the difference in the proportion of subjects with a zero pain score until each time point at which patients adhere to the assigned treatment. Although this estimand is likely a reasonable measure of drug activity, it may not provide a meaningful measure of effectiveness for all patients. Therefore, an evaluation of the effectiveness of Dextenza should not be based solely on the primary analysis of the LAO estimand. To this end, supportive evidence from several secondary efficacy endpoints was considered. The results of these analyses were supportive of the primary efficacy analysis results (see Section 3.2.4.1.3).

One other estimand that could provide a measure of effectiveness is the difference in proportion of subjects with a zero pain score at Day 8 in all randomized patients, regardless of adherence to the assigned treatment. However, because pain outcomes after subjects discontinued the study treatment or after they received a rescue therapy were not recorded, this estimation relies on some untested assumption. A potentially conservative estimate for this estimand could be

obtained by imputing all missing pain outcomes at Day 8 for the Dextenza arm as failures while those in the Vehicle arm set as successes. However, since there were very few subjects with missing pain outcomes (See Section 3.2.3.2); and that the LOCF has already imputed failure for most of those few subjects with missing data, this approach provided results that were similar with the protocol defined primary efficacy analysis. This provides a reasonable credence to the primary efficacy analysis to provide a conservative estimate for the effectiveness of the drug product (Table 7).

**Table 7: Proportion of subjects with absence of pain at day 8 (ITT: LOCF)**

| | Treatment | | Difference (%) |
|---|---|---|---|
| **Study** | **Dextenza** | **Vehicle** | **(Asymptotic 95% CI)** |
| Oxt-13-002 | 131/ 164 (80%) | 36/83 (43%) | 37% (24%, 49%) |
| Oxt-14-003 | 123/ 161 (76%) | 47/80 (59%) | 18% (5%, 30%) |
| Oxt-12-002 | 23/30 (77%) | 10/30 (33%) | 44% (24%, 68%) |

Source: Reviewer's analysis. Subjects in both arms who received a rescue therapy and those with missing data in the Dextenza arm were set as treatment failures regardless of the LOCF value while subjects in the Vehicle arm with missing data were set as treatment success regardless of the LOCF value.

#### 3.2.4.1.2 *Sensitivity Analysis*

The agency's recommended sensitivity analyses included the analysis of the primary efficacy endpoint on the per-protocol population with observed data only and the analysis of the primary efficacy analysis on the ITT population with multiple imputations. The reviewer included a tipping point analysis to evaluate the impact of treating subjects who received a rescue therapy as treatment failures. The results of the analysis on the per-protocol population with observed data only and the analysis on the ITT population with multiple imputations were consistent with the primary efficacy analysis results. The major reasons cited for the exclusion of subjects from the per-protocol population include (more frequent to less frequent): missed primary efficacy variable assessment or assessment made outside the pre-specified window, cataract surgery in the fellow eye prior to Day 14, use of excluded concomitant ocular medication and randomization error.

**Table 8: Summary of efficacy endpoints (Per-Protocol: Observed data only)**

| | | Proportion of subjects with absence of pain | | |
|---|---|---|---|---|
| **Study** | **Visit** | **Dextenza** | **Vehicle** | **Difference (%) (Asymptotic 95% CI)** |
| Oxt-13-002 | Day 8 | 119/ 149 (80%) | 31/74 (42%) | 37% (24%, 50%) |
| Oxt-14-003 | Day 8 | 114/ 148 (77%) | 47/78 (60%) | 18% (5%, 31%) |
| Oxt-12-002 | Day 8 | 23/29 (79%) | 9/28 (32%) | 47% (20%, 70%) |
| **Proportion of subjects with absence of anterior chamber cells** | | | | |
| Oxt-13-002 | Day 14 | 49/ 149 (33%) | 12/73 (16%) | 17% (5%, 28%) |
| Oxt-14-003 | Day 14 | 59/ 148 (40%) | 25/78 (32%) | 8% (-5%, 21%) |
| Oxt-12-002[1] | Day 8 | 10/29 (34%) | 1/30 (3%) | 31% (13%, 50%) |

Source: Adapted from Table 11-2 of the study reports. Subjects who received a rescue therapy were set as treatment failures. [1] For this study, Day 8 was the protocol defined time point for the evaluation of this endpoint.

**Table 9: Summary of efficacy endpoints (ITT: Multiple imputations)**

| | | Proportion of subjects with absence of pain | | |
|---|---|---|---|---|
| **Study** | **Visit** | **Dextenza** | **Vehicle** | **Difference (%) (Asymptotic 95% CI)** |
| Oxt-13-002 | Day 8 | 132/ 164 (80%) | 36/83 (43%) | 37% (25%, 50%) |

| | | | | |
|---|---|---|---|---|
| Oxt-14-003 | Day 8 | 125/ 161 (78%) | 47/80 (59%) | 19% (6%, 31%) |
| Oxt-12-002 | Day 8 | 24/30 (80%) | 9/30 (30%) | 50% (28%, 72%) |
| **Proportion of subjects with absence of anterior chamber cells** | | | | |
| Oxt-13-002 | Day 14 | 55/ 164 (33%) | 12/83 (14%) | 19% (8%, 29%) |
| Oxt-14-003 | Day 14 | 63/ 161 (39%) | 25/80 (31%) | 8% (-5%, 21%) |
| Oxt-12-002[1] | Day 8 | 10/30 (33%) | 4/30 (13%) | 20% (-1%, 41%) |

Source: Adapted from Table 11-2 of the study reports. Subjects who received a rescue therapy were set as treatment failures. [1] For this study, Day 8 was the protocol defined time point for the evaluation of this endpoint.

A relatively higher proportion of subjects randomized to the vehicle arm received a rescue medication at or prior to Day 8 compared to subjects randomized to the Dextenza arm. This in itself could be considered as evidence that Dextenza had a pain control effect. However, according to the protocols, investigators were expected to consider prescribing anti-inflammatory medications for subjects who returned for the Day 2 and later visits who exhibited ≥ Grade 2+ (≥16) anterior chamber cells, ≥ 3+ (Marked: iris and lens details hazy) flare, **and/or** ≥ 4 (moderate to severe) ocular pain. From this, it appears that the man criterion for a rescue therapy was the absence of cells and flare. For example, in Study oxt-13-002, only 5 of the 24 subjects in the Vehicle arm satisfied the pain criteria for rescue therapy (>=4 pains score) at any time during the study. Additionally, 9 of the 24 subjects who received a rescue therapy in the Vehicle arm had a zero pain score at Day 8 but were set as treatment failures because they received a rescue therapy based on the flare or cell criteria.

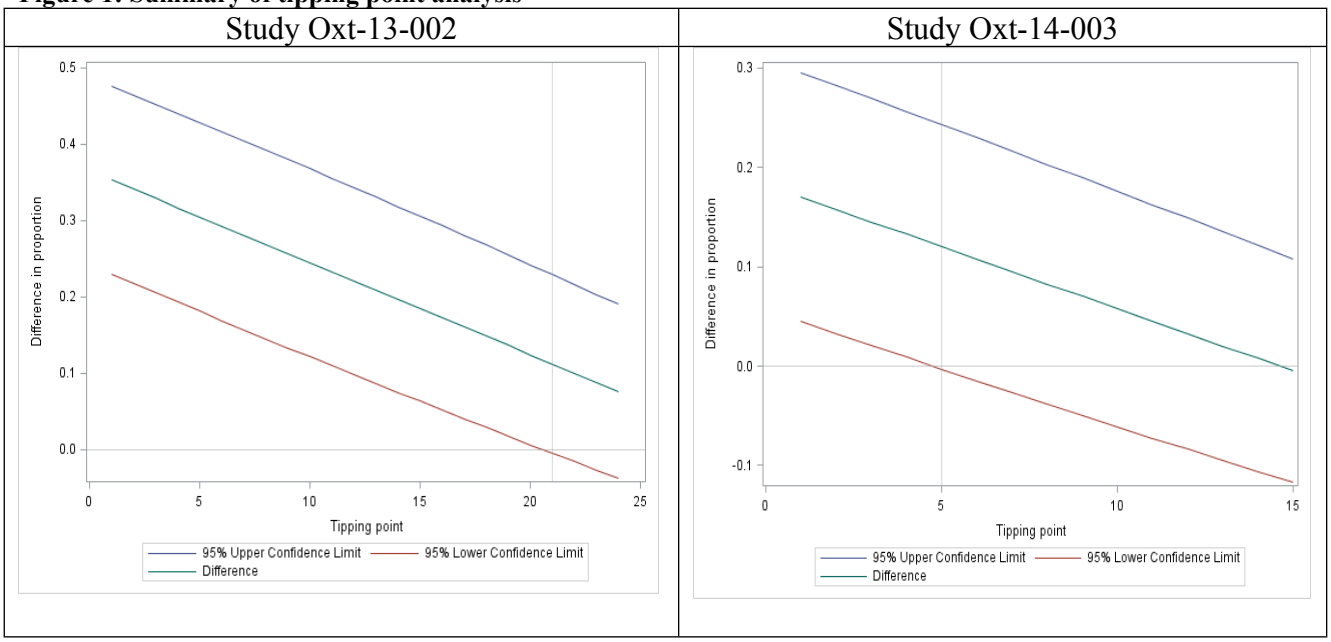
This reviewer thus conducted a tipping point analysis to determine the number of subjects in the Vehicle arm who received a rescue therapy (and thus set as treatment failures) that need to be set as treatment successes for the treatment difference for the pain outcome to be statistically non-significant. A larger tipping point implies that the result was only minimally impacted by subjects in the Vehicle arm who received a rescue medication and set as treatment failures. In study oxt-13-002, 21 or more of the 24 subjects who received a rescue therapy prior to Day 8 had to be set as treatment successes in order for the treatment effect to no longer be statistically significant. Additionally, even if all 24 subjects were treated as treatment successes, the observed treatment difference will still be numerically favorable to Dextenza. In Study oxt-14-003, if 5 or more of the 15 subjects who received a rescue therapy and hence were treated as treatment failures were set as treatment successes, the treatment effect would no longer be statistically significant (Figure 1). This reviewer defers the determination of whether subjects rightly received rescue therapy and thus were indeed treatment failures for the pain outcome to the clinical review team.

**Table 10: Summary of subjects who received a rescue therapy at or prior to a given visit**

| | Study | | | | | |
|---|---|---|---|---|---|---|
| | Oxt-13-002 | | Oxt-14-003 | | Oxt-12-002 | |
| Visit | Dextenza N=164 | Vehicle N=83 | Dextenza N=161 | Vehicle N=80 | Dextenza N=30 | Vehicle N=30 |
| Day 1 | 1(0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (3.3%) |
| Day 2 | 1 (0.6%) | 0 (0.0%) | 2 (1.2%) | 1 (1.2%) | 0 (0.0%) | 1 (3.3%) |
| Day 4 | 2 (1.2%) | 4 (4.8%) | 3 (1.9%) | 3 (3.8%) | 2 (6.7%) | 13 (43.3%) |
| Day 8 | 12 7.3%) | 24 (28.9%) | 10 (6.2%) | 15 (18.8%) | 5 (16.7%) | 16 (53.3%) |
| Day 14 | 24 14.0%) | 38 (45.8%) | 28 (17.4%) | 30 (37.5%) | 6 (20.0%) | 21 (70.0%) |

Source: Adapted from Table 11-1 of the study reports.

**Figure 1: Summary of tipping point analysis**




Source: Reviewer's Analysis. The tipping point is the number (vertical line) at which the lower bound of the 95% CI is below zero.

The applicant stated that some subjects in the Vehicle arm did not receive rescue medication at the earlier study visits despite meeting the criteria for rescue. The applicant cited this issue as one of the reasons that the treatment difference for the inflammation outcome in study oxt-14-003 was not statistically significant. The reviewer's tipping point analysis for this outcome showed that, if at least 5 additional subjects in the Vehicle arm were given a rescue therapy, thereby rendering them as treatment failures in this primary efficacy endpoint, the treatment difference for the inflammation outcome would have been statistically significant [39% vs 26%; diff (95% CI): 13% (2.7%, 25%)].

#### 3.2.4.1.3 *Secondary Efficacy Endpoints*

Absence of flare, cells and pain at subsequent study visits (Days 1, 2, 4, 8, 14, 30 and 60) were the secondary efficacy endpoints. In all studies, the proportion of subjects with absence of pain, cells and flare was consistently higher in the Dextenza arm at all of the efficacy evaluation visits (except on Day 2 in Study oxt-14-003) with treatment differences ranging between 0% and 53%. The summary results are presented in Figure 2-Figure 10 in the appendix.

The summary of the mean pain scores for each visit is presented in Figure 11 and Figure 12. The Dextenza arm had consistently lower mean pain scores for all study visits. The summary of the pain categories at Day 8 for the two Phase 3 studies is presented in Table 11. The reviewer fitted a proportional odds logistic regression with treatment as the covariate and the four pain categories (none, mild, moderate, severe) as response. The results showed that in Study oxt-13-002, the odds of a having higher pain category versus a lower pain category for subjects in the Vehicle arm was at least three times higher compared to those in the Dextenza arm [OR (95% CI): 5.1 (2.9, 8.9)]. The corresponding figure for Study oxt-14- 002 was [OR (95% CI): 2.5 (1.4, 4.4)].

**Table 11: Summary of pain category at Day 8 (ITT, LOCF)**

| | Study Oxt-13-002 | | Study Oxt-14-003 | |
|---|---|---|---|---|
| Pain Category | Dextenza N=164 | Vehicle N=83 | Dextenza N=161 | Vehicle N=80 |
| None | 131(80%) | 36 (43%) | 124 (77%) | 47 (59%) |
| Mild | 19 (12%) | 20 (24%) | 21 (13%) | 14 (17%) |
| Moderate | 1 (0.6%) | 3 (4%) | 5 (3%) | 3 (4%) |
| Severe | 13 (8%) | 24 (29%) | 11 (6%) | 16 (20%) |

Source: Reviewer's Analysis. Subjects who reviewed a rescue therapy were counted in the severe category.

## 3.3 Evaluation of Safety

In addition to safety data from the two Phase 3 studies and the Phase 2 study, some safety summaries provided in this section included data from a single-arm open-label study (Study oxt-14-009) involving 16 healthy subjects.

Subjects in all four studies were followed until the product was either removed (Study oxt-14-009) or could no longer be confirmed to be present in the canaliculus (Studies oxt-12-002, oxt-13-002, oxt-14-003). The applicant therefore used product visualization as a measure of exposure to Dextenza or Vehicle. Summary of product visualization/exposure in the four studies is presented in Table 12. A total of 367 subjects were administered Dextenza, of which 325 were exposed to Dextenza for the intended duration of therapy of at least 30 days. The number of subjects in whom Dextenza could be visualized decreased to 191 by the Day 60 Visit.

**Table 12: Summary of product visualization/exposure (Safety population)**

| | **OTX-14-009** | **OTX-12-002** | | **OTX-13-002** | | **OTX-14-003** | |
|---|---|---|---|---|---|---|---|
| | Dextenza (N=16) | Dextenza (N=30) | Vehicle (N=30) | Dextenza (N=162) | Vehicle (N=84) | Dextenza (N=160) | Vehicle ( N=80) |
| **Day 2** | 16 (100%) | 29 (96.7%) | 29 (96.7%) | 162 (100.0%) | 81 (96.4%) | 160 (100.0%) | 80 (100.0%) |
| **Day 4** | 16 (100%) | 29 (96.7%) | 29 (96.7%) | 162 (100.0%) | 79 (94.0%) | 159 (99.4%) | 80 (100.0%) |
| **Day 8** | 16 (100%) | 29 (96.7%) | 29 (96.7%) | 162 (100.0%) | 79 (94.0%) | 160 (100.0%) | 80 (100.0%) |
| **Day 14** | 15 (93.7%) | 29 (96.7%) | 29 (96.7%) | 161 (99.4%) | 78 (92.8%) | 159 (99.4%) | 80 (100.0%) |
| **Day 30** | 12 (85.7%) | 28 (93.3%) | 27 (93.1%) | 143 (88.3%) | 72 (85.7%) | 142 (88.7%) | 70 (87.5%) |
| **Day 60** | N/A | 20 (66.7%) | 21 (91.3%) | 100 (61.7%) | 47 (55.9%) | 71 (44.4%) | 31 (38.7%) |

Source: Adapted from Table 14.2.4.1 in CSR OTX-12-002; Table 14.3.10 in CSR OTX-13-002 and Table 14.3.10 in CSR OTX-14-003.

A total of 101 (27.5%) subjects who received Dextenza compared to 78 (40.2%) in the Vehicle arm reported at least one ocular adverse event (AE) in the study eye. The most frequently reported AEs in the study eye among subjects who received Dextenza were increased intraocular pressure (6.0%), anterior chamber inflammation (5.2%) and iritis (3.5%).

Only one reported ocular AE in the Vehicle arm was serious. At least one non-ocular AE was reported in (9.3%) and (11.3%) subjects in the Dextenza and Vehicle arms respectively. Higher proportion of subjects in the Vehicle arm (4.6%) compared to the Dextenza arm (1.6%) reported at least one serious non-ocular adverse event.

**Table 13: Summary of adverse events in the study eye**

| Adverse event (AE) | Treatment: N (%) | |
|---|---|---|
| | Dextenza N=367 | Vehicle N=194 |
| Any AE | 141 (38.4%) | 95 (49.0%) |
| Any serious AE (SAE) | 5 (1.4%) | 8 (4.1%) |
| Any ocular AE | 101 (27.5%) | 78(40.2%) |
| Intraocular Pressure Increased | 22 (6.0%) | 8 (4.1%) |
| Anterior Chamber Inflammation | 19 (5.2%) | 13 (6.7%) |
| Iritis | 13 (3.5%) | 16 (8.2%) |
| Corneal Oedema | 5 (1.4%) | 12 (6.2%) |
| Visual Acuity Reduced[1] | 7 (1.9%) | 7 (3.6%) |
| Conjunctival Hyperaemia | 4 (1.1%) | 6 (3.1%) |
| Cystoid Macular Oedema | 5 (1.4%) | 3 (1.5%) |
| Ocular Discomfort | 3 (0.8%) | 4 (2.1%) |
| Eye Pain | 5 (1.4%) | 2 (1.0%) |
| Eye Inflammation | 0 (0.0%) | 5 (2.6%) |
| Corneal Abrasion | 1 (0.3%) | 1 (0.3%) |

Source: Tables 3 and 5 of ISS.[1] visual acuity reduced from the previous visit not from baseline.

**Table 14: Summary of adverse events in the non-study eye**

| Adverse event | Treatment: N (%) | |
|---|---|---|
| | Dextenza N=367 | Vehicle N=194 |
| Anterior Chamber Inflammation | 3 (0.8%) | 2 (1.0%) |
| Iritis | 1 (0.3%) | 0 (0.0%) |
| Iridocyclitis | 1 (0.3%) | 0 (0.0%) |
| Increased intraocular Pressure | 10 (2.7%) | 3 (1.5%) |

Source: Tables 6 of ISS

### 3.3.1 Intraocular pressure

#### A. Mean change from baseline IOP by visit

One of the most frequently reported adverse events was increase in intraocular pressure. The summary results from the analysis of the change from baseline IOP at each time point using an analysis of covariance (ANCOVA) model with baseline IOP and treatment as covariates is presented in Figure 13. Both arms showed a reduction in IOP from baseline of about 1-2 mm Hg; with slightly lower reduction observed in the Dextenza arm compared to Vehicle.

#### B. IOP <=18 mm Hg and >=25% reduction in IOP from baseline

The Dextenza arm had a slightly higher proportion of subjects who attained an IOP ≤ 18 mmHg consistently at all six time points compared to Vehicle. The proportion of subjects with an IOP reduction of ≥ 25% from baseline consistently at all six time points was numerically lower in the Dextenza arm (Table 15).

**Table 15: Summary of IOP reductions (Safety Population: Observed data)**

| Response Criteria | Dextenza N=351 | Vehicle N=194 | Diff (95% CI) |
|---|---|---|---|
| IOP ≤ 18 mmHg at all six Time Points | 195 (55.6%) | 97 (50.0%) | 5.6% (-3.2%, 14.3%) |
| Percent Reduction from Baseline in Mean IOP ≥ 25% at all six Time Points | 6 (1.7%) | 8 (4.1%) | -2.4% (-5.5%, 0.7%) |

Source: Reviewer's Analysis. This analysis does not include the 16 healthy subjects from study oxt-14-009.

### 3.3.2 Visual acuity

#### A. Mean change of the number of lines read from bassline

The visual acuity measured using the Snellen chart was converted into a measure of the number of lines read using the following formula:

*VA = (logMAR value * 10) + 1; where logMAR = -log (20/SNELLD).*

For example, for a subject with a visual acuity of 20/50, the VA value will be (-log (20/50)* 10) +1 which is about 5; and similarly the VA value for a subject with a 20/25 vision will be around 2. Thus, higher values of VA imply lower vision. The two treatment arms were compared with respect to the mean change from baseline visual acuity at each time point using an ANCOVA model with baseline VA and treatment as covariates. The summary result is presented in Figure 14. In both arms, the mean change from baseline values are negative implying that on average, the number of lines read has improved in both arms.

#### B. Reduction of >=2 lines from baseline

The summary of the proportion of subjects with a visual acuity loss of more than 2 lines from baseline is presented in Figure 15. In both arms, the proportion of subjects with a reduction of more than 2 lines from baseline was relatively low (between 1-7%).

### 3.3.3 Punctum plug evaluation

In the two Phase 3 studies, the investigators rated the ease of use of the product during insertion. Over 73% and 76% of investigators in study oxt-13-002 and study oxt-14-003 respectively rated the insertion of Dextenza easy compared to more than 88% and 95% for the insertion of the Vehicle.

**Table 16: Summary of ease of product insertion**

| | Study | | | |
|---|---|---|---|---|
| | Oxt-13-002 | | Oxt-14-003 | |
| Ease of Insertion | Dextenza N=164 | Vehicle N=83 | Dextenza N=161 | Vehicle N=80 |
| Easy | 120 (73.6%) | 73 (88.0%) | 123 (76.4%) | 76 (95.0%) |
| Moderate | 30 (19.0%) | 10 (12.0%) | 33 (20.5%) | 4 (5.0%) |
| Difficult | 11 (7.4%) | 0 (0.0%) | 5 (3.1%) | 0 (0.0%) |

Source: Table 11-10 of the applicant's study reports

## 4 Risk-benefit analysis

This risk benefit analysis presented in this section is based on the pooled data from the two Phase 3 studies and the Phase 2 study. Compared to Vehicle, higher proportion of subjects in the Dextenza arm achieved a zero pain score (benefit) without reported increase in intraocular pressure, loss of visual acuity by more than 2 letters from prior visit, chamber cells inflammation and iritic (risks). In the Vehicle arm, nearly half of the subjects did not achieve a zero pain score at Day 8 and did not experience any of the commonly reported adverse events. Less than 3% of the subjects in the Dextenza arm reported one of the commonly reported adverse events without achieving a zero pain score at Day 8. Overall, Dextenza appears to have a favorable risk-benefit profile with respect to frequently reported adverse events (Figure 16-Figure 19).

## 5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses presented in this section are based on the pooled data from the two Phase 3 studies. The subgroup analyses results presented in this section are considered descriptive and should only be used to characterize the observed treatment differences between subgroups.

### 5.1 Age Gender Race and Region and Iris Color

Overall, the subgroup analysis results based on baseline demographics were consistent with the primary efficacy analysis results. Note that conclusive statements regarding statistical significance could not be made on the magnitude of the treatment effect for any subgroup, as the studies were not designed to test the treatment effect for any subgroup ( Figure 20 and Figure 21).

## 6 SUMMARY AND CONCLUSIONS

### 6.1 Statistical Issues

Because of the hierarchical testing procedure, conclusive inferential claim regarding the observed treatment difference for the pain outcome could only be made in one of the Phase 3 studies. Therefore, from a purely statistical point of view, the applicant had only one statistically conclusive study in support of the pain-only indication.

### 6.2 Collective evidence

A higher proportion of subjects in the Dextenza arm had zero pain scores at Day 8 compared to subjects randomized to the Vehicle arm. However, except in Study oxt-13-002, there was no statistically significant difference between Dextenza and Vehicle with respect to the proportion of subjects who had no anterior chamber cells. Consequently, because of the pre-specified fixed-sequence hierarchical testing procedure, conclusive inferential claims concerning the pain outcome could not be made in Study oxt-12-002 and Study oxt-14-003. The observed treatment differences were however numerically favorable to the Dextenza arm in both these studies.

Additionally, the proportions of subjects with absence of pain at Day 8 in the Dextenza arm in these two studies were fairly consistent with the results seen in Study oxt-13-002.

A relatively higher number of subjects in the Vehicle arm needed a rescue medication. This in itself could also be an indication that Dextenza had a pain control effect assuming subjects deservedly received rescue therapy. Additional supportive evidence for the efficacy of Dextenza was gained from the analyses of several secondary efficacy endpoints. In all studies, the proportion of subjects with absence of pain, cells and flare was consistently higher in the Dextenza arm at all of the efficacy evaluation visits.

The most frequently reported AEs in the study eye for subjects who received Dextenza were increased intraocular pressure, anterior chamber inflammation and iritis, none of which were reported as serious. Dextenza also appears to have a relatively favorable risk-benefit profile compared to Vehicle. Compared to Vehicle, a higher proportion of subjects who received Dextenza achieved a zero pain score (benefit) without reported increase in intraocular pressure, loss of visual acuity by more than 2 letters from previous visit, chamber cells inflammation and iritic (risks).

### 6.3 Conclusions and Recommendations

In conclusion, compared to Vehicle, the Dextenza arm had higher proportion of subjects with absence of pain at Day 8 in all studies and had a relatively favorable risk-benefit profile. However, conclusive inferential claim for the pain outcome could only be made in one study. Therefore, the overall-risk benefits evaluation and the subsequent determination for approval of this product is deferred to the clinical review team.

### 6.4 Labeling recommendation (if Clinical recommend approval)

The sponsor has the following text in section 14 (Clinical Trials) of the current version of the draft labeling:

*"In two randomized, multicenter, double-masked, parallel group, vehicle-controlled trials, patients received DEXTENZA* (b) (4) *or its* (b) (4) *vehicle immediately upon completion of cataract surgery. In both trials, DEXTENZA had a* (b) (4) *higher incidence of subjects who were pain free at post-operative* (b) (4)

(b) (4)

(b) (4)

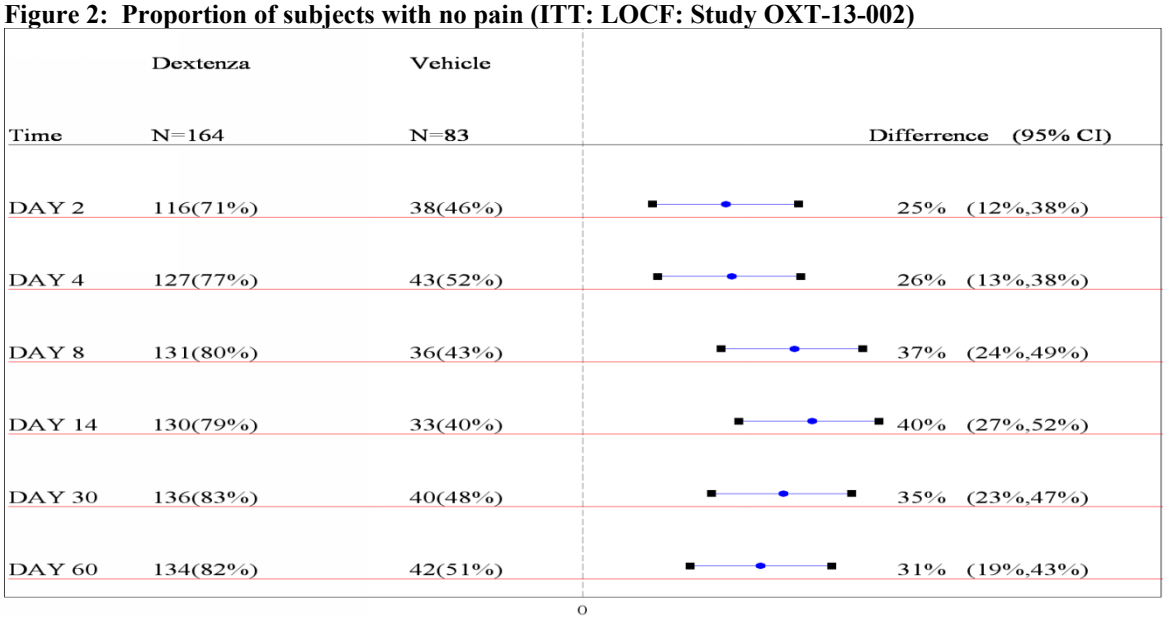
This reviewer therefore recommends the following text and table for section 14 of the drug labeling (Clinical studies)

*In two randomized, multicenter, double-masked, parallel group, vehicle-controlled trials, patients received DEXTENZA or its non-drug delivery vehicle immediately upon completion of cataract surgery. In both trials, DEXTENZA had a higher incidence of subjects who were pain free at all post-operative days. Results are shown in Table xx.*

| | Study 1 | | | Study 2 | | |
|---|---|---|---|---|---|---|
| Visit | Dextenza (N=164) n (%) | Vehicle (N=83) n (%) | Difference (95% CI) | Dextenza (N=161) n (%) | Vehicle (N=80) n (%) | Difference (95% CI) |
| Day 2 | 116 (71%) | 38 (46%) | 25% (12%, 38%) | 105 (65%) | 32 (40%) | 25% (12%, 38%) |
| Day 4 | 127 (77%) | 43 (52%) | 26% (13%, 38%) | 117 (73%) | 39 (49%) | 24% (11, 37%) |
| Day 8 | 131 (80%) | 36 (43%) | 37% (24%, 49%) | 124 (77%) | 47 (59%) | 18% (6%, 31%) |
| Day 14 | 130 (79%) | 33 (40%) | 40% (27%, 52%) | 123 (76%) | 46 (58%) | 19% (6%, 32%) |
| Day 30 | 136 (83%) | 40 (48%) | 35% (23%, 47%) | 128 (80%) | 50 (63%) | 17% (5%, 29%) |
| Day 60 | 134 (82%) | 42 (51%) | 31% (19%, 43%) | 129 (80%) | 50 (63%) | 18% (5%, 30%) |

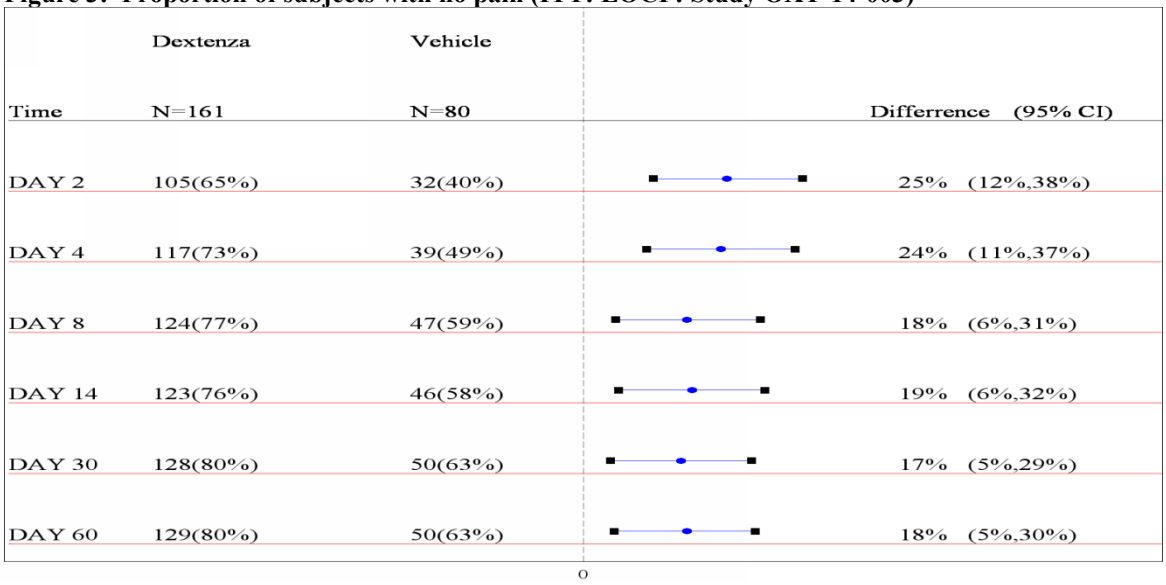
# 7 Appendix

**Figure 2: Proportion of subjects with no pain (ITT: LOCF: Study OXT-13-002)**



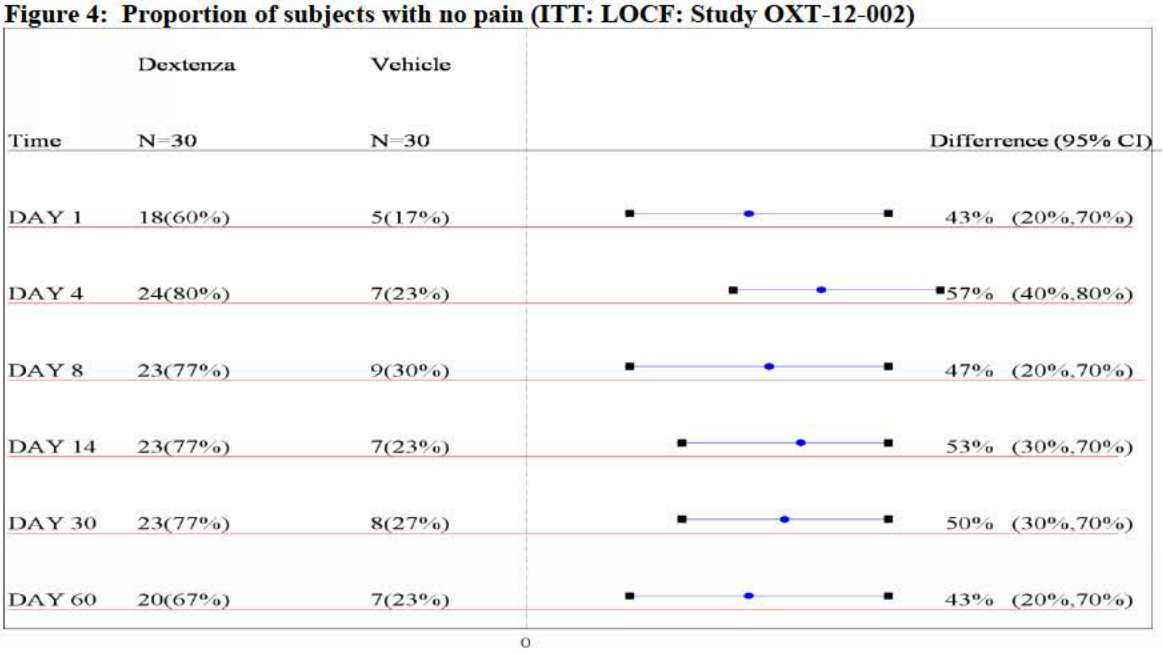

Source: Reviewer's analysis. Adapted from Table 11-3 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 3: Proportion of subjects with no pain (ITT: LOCF: Study OXT-14-003)**



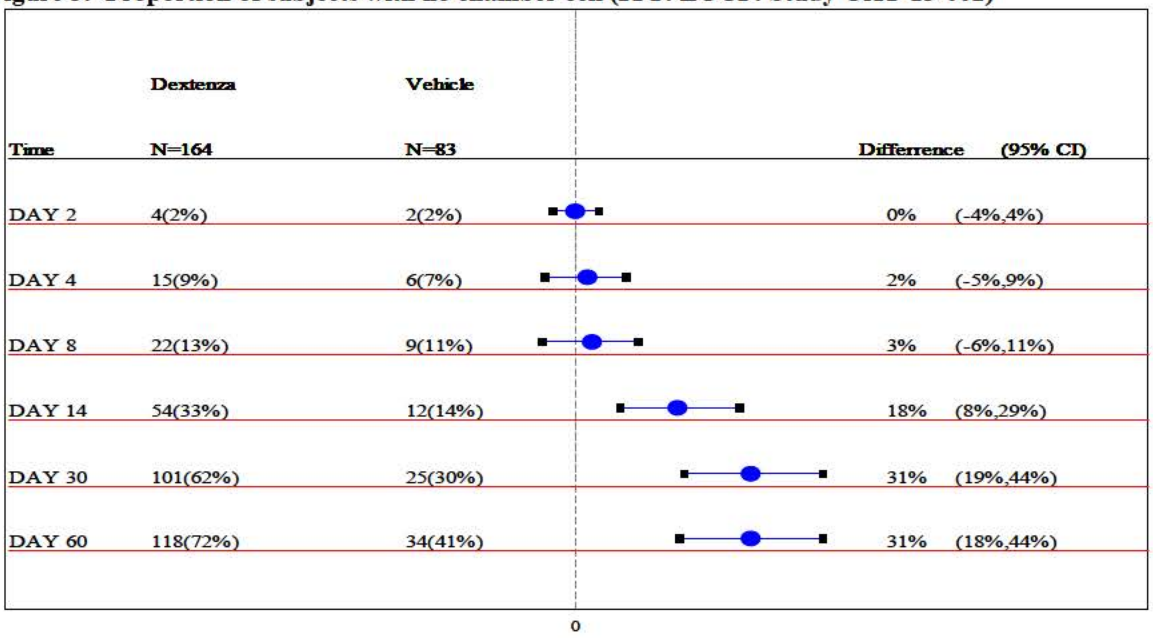

Source: Reviewer's analysis. Adapted from Table 11-3 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 4: Proportion of subjects with no pain (ITT: LOCF: Study OXT-12-002)**



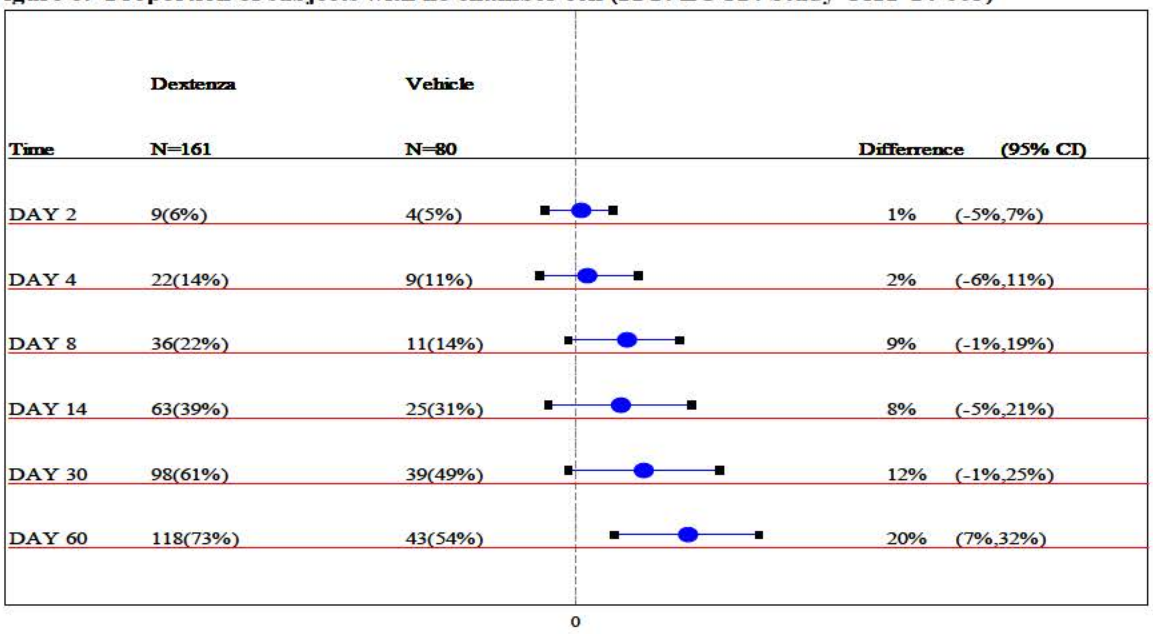

Source: Reviewer's analysis. Adapted from Table 11-3 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 5: Proportion of subjects with no chamber cell (ITT: LOCF: Study OXT-13-002)**



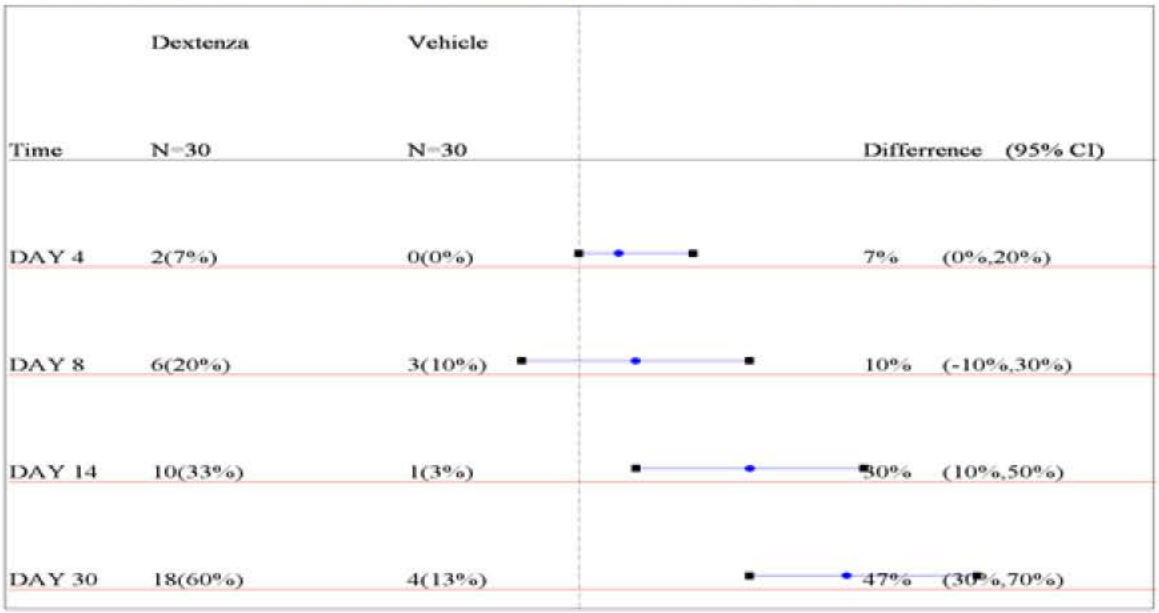

Source: Reviewer's analysis. Adapted from Table 11-3 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 6: Proportion of subjects with no chamber cell (ITT: LOCF: Study OXT-14-003)**



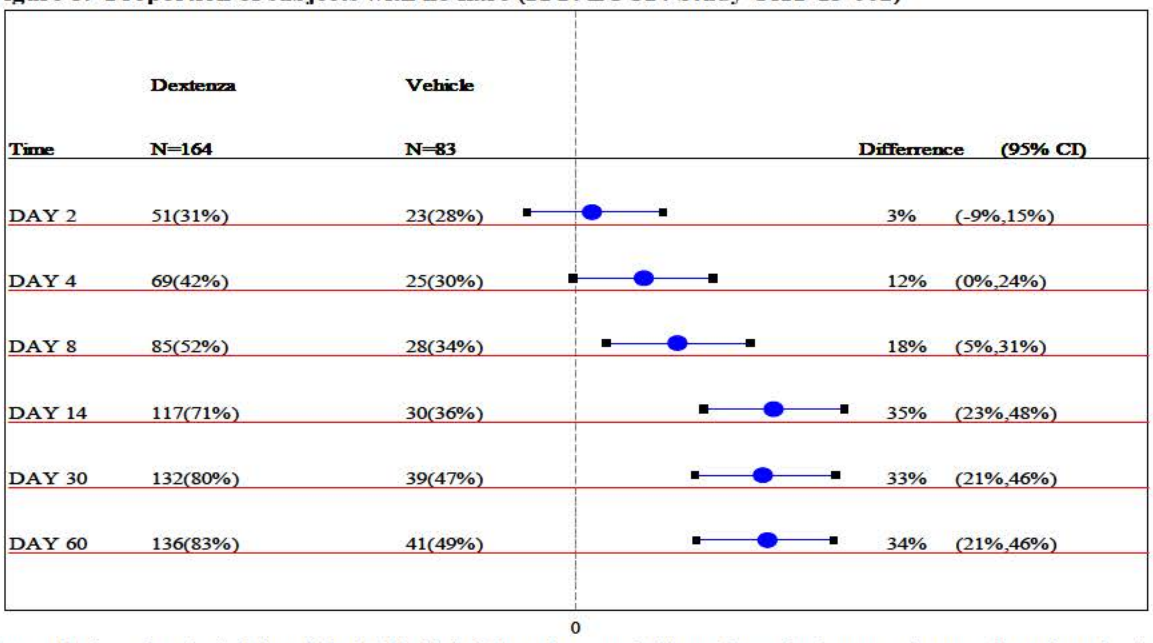

Source: Reviewer's analysis. Adapted from Table 11-3 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 7: Proportion of subjects with no chamber cell (ITT: LOCF: Study OXT-12-002)**



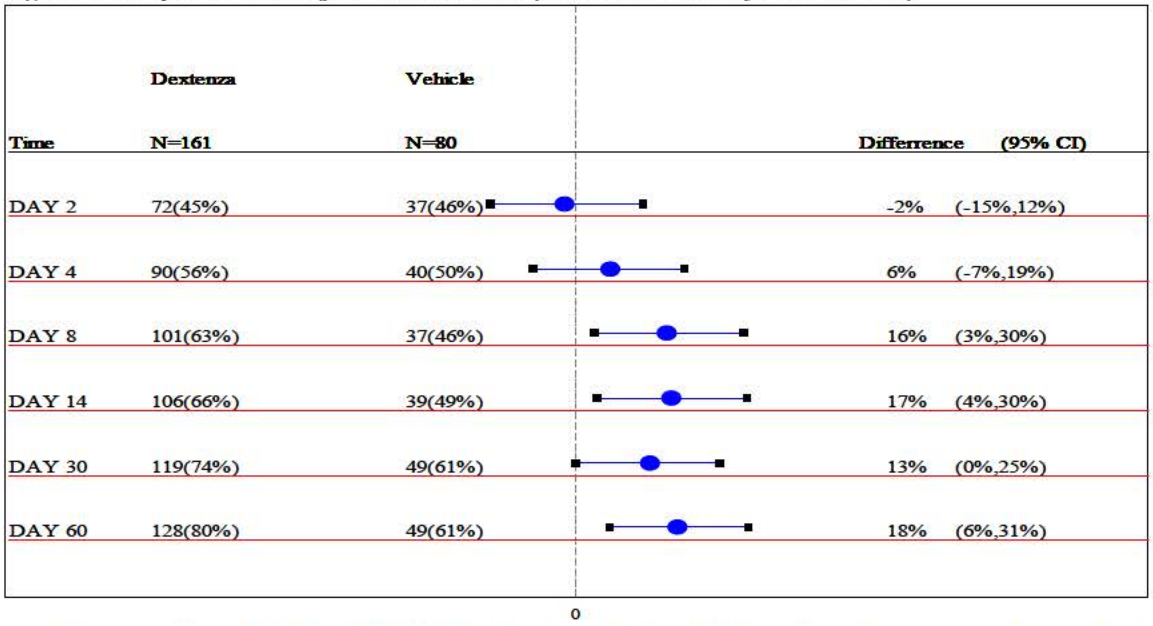

Source: Reviewer's analysis. Adapted from Table 11-3 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 8: Proportion of subjects with no flare (ITT: LOCF: Study OXT-13-002)**



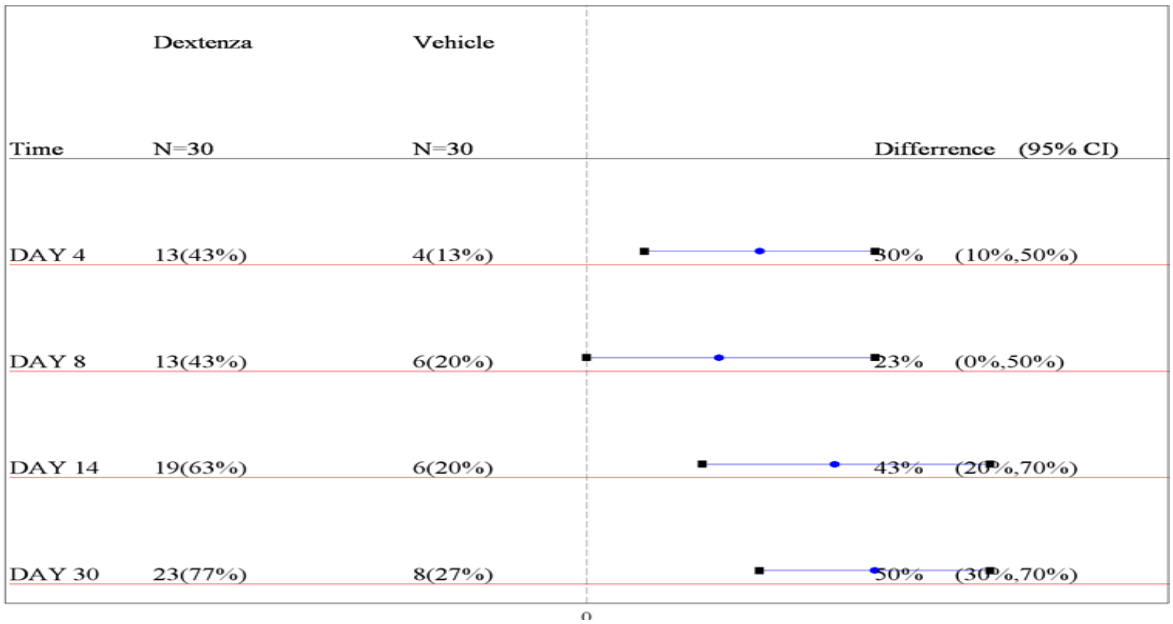

Source: Reviewer's analysis. Adapted from Table 11-4 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 9: Proportion of subjects with no flare (ITT: LOCF: Study OXT-14-003)**



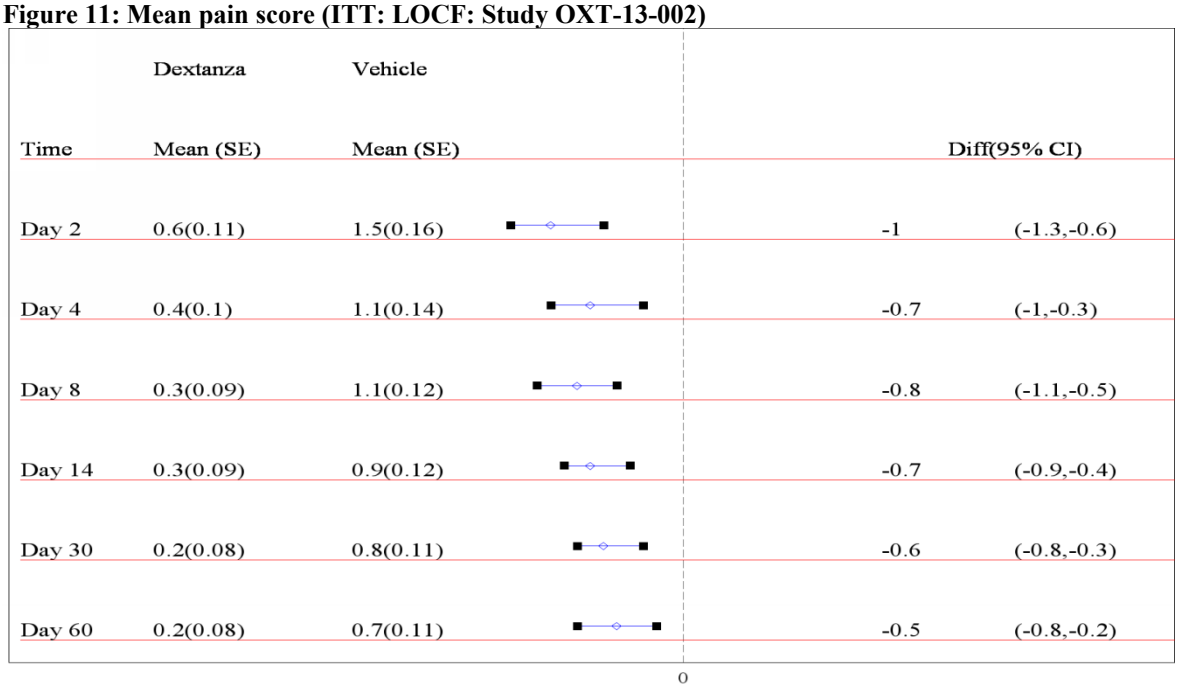

Source: Reviewer's analysis. Adapted from Table 11-4 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 10: Proportion of subjects with no flare (ITT: LOCF: Study OXT-12-002)**



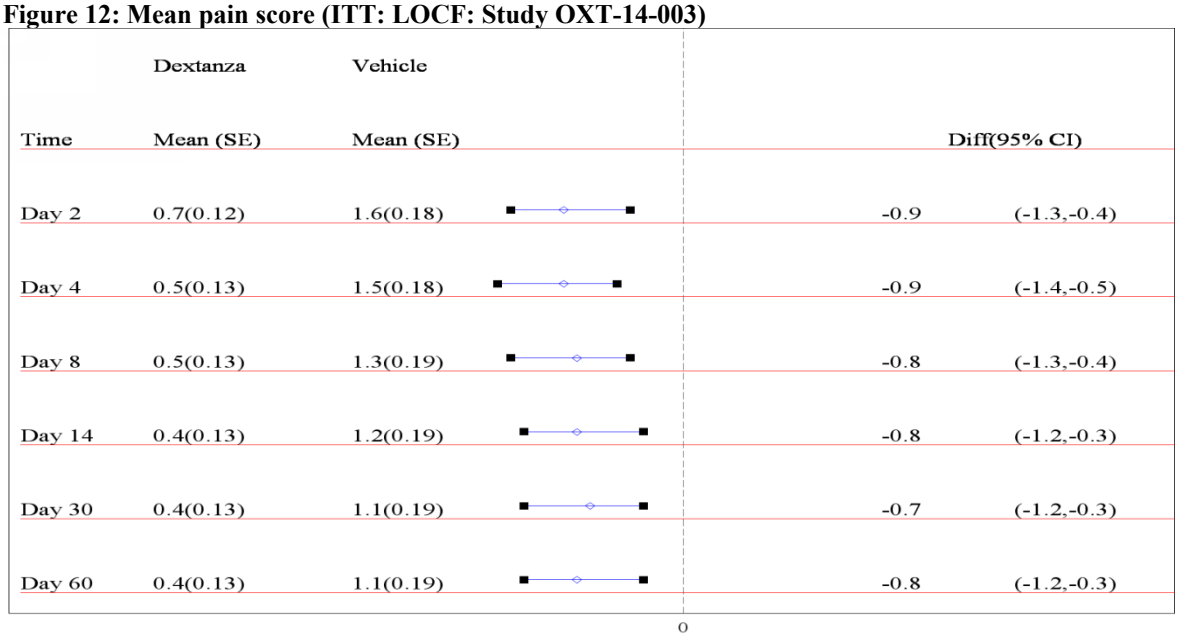

Source: Reviewer's analysis. Adapted from Table 11-4 of the study reports Subjects who received a rescue therapy prior to time of evaluation were set as treatment failures

**Figure 11: Mean pain score (ITT: LOCF: Study OXT-13-002)**



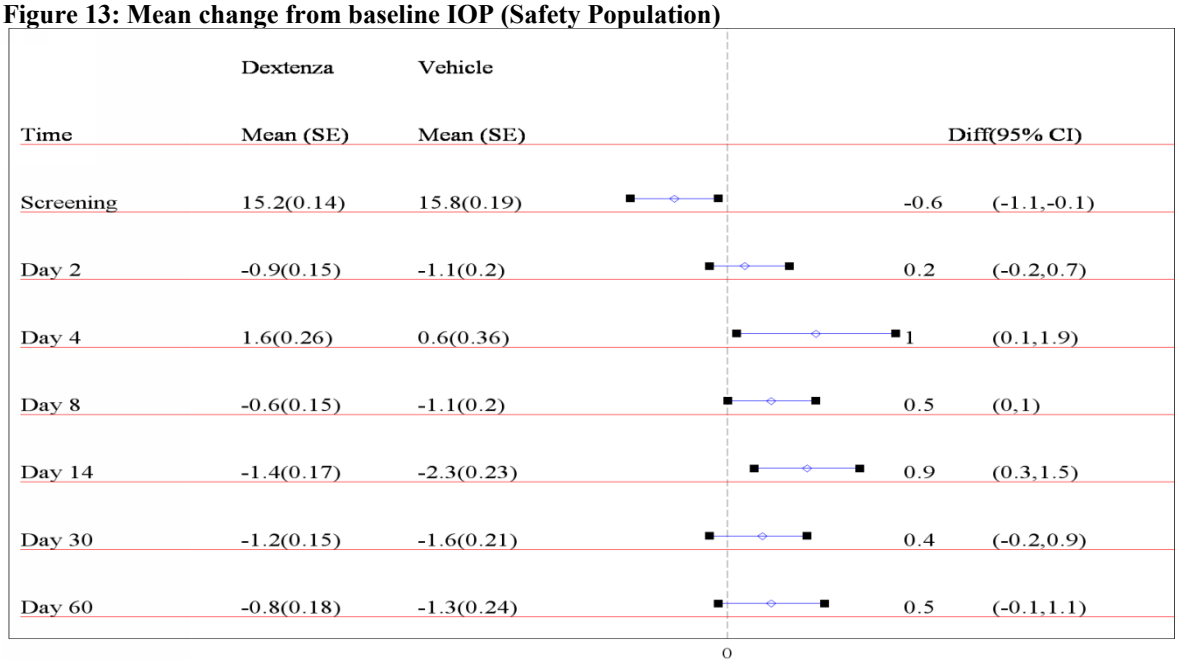

Source: Reviewer's analysis. Adapted from Table 11-7 of the study reports

**Figure 12: Mean pain score (ITT: LOCF: Study OXT-14-003)**



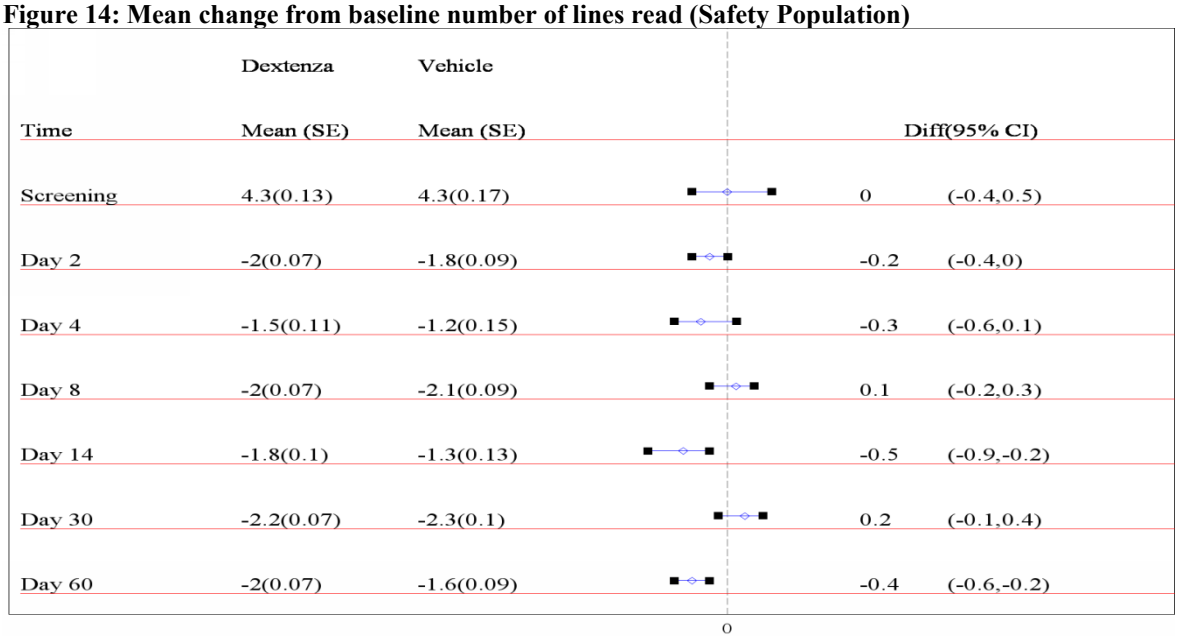

Source: Reviewer's analysis. Adapted from Table 11-7 of the study reports

**Figure 13: Mean change from baseline IOP (Safety Population)**



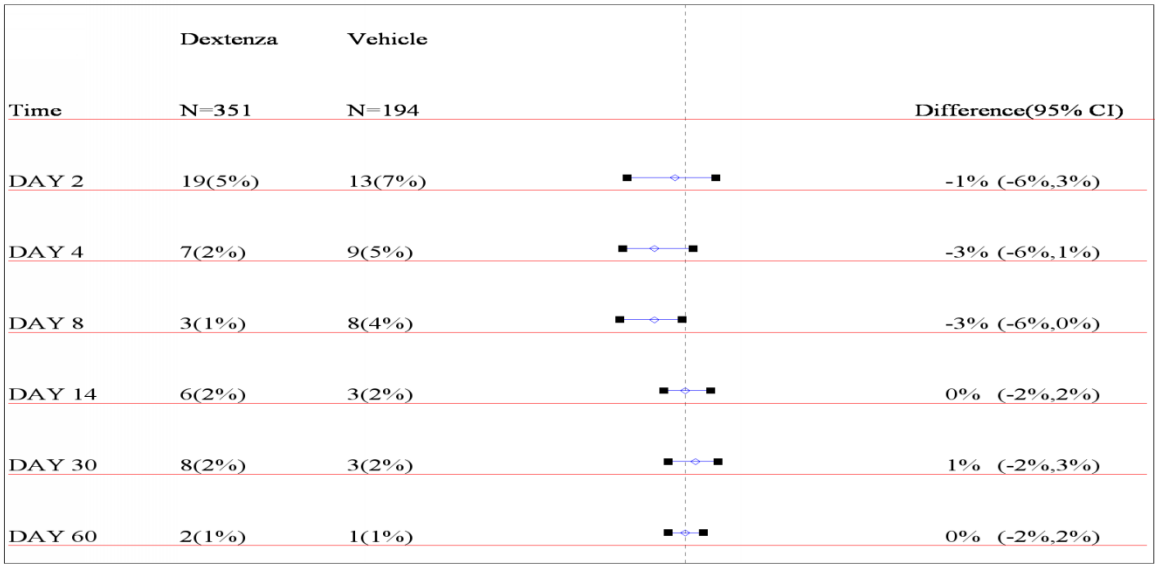

Source: Reviewer's Analysis. This analysis does not include the 16 healthy subjects from study 0xt-14-009.

**Figure 14: Mean change from baseline number of lines read (Safety Population)**



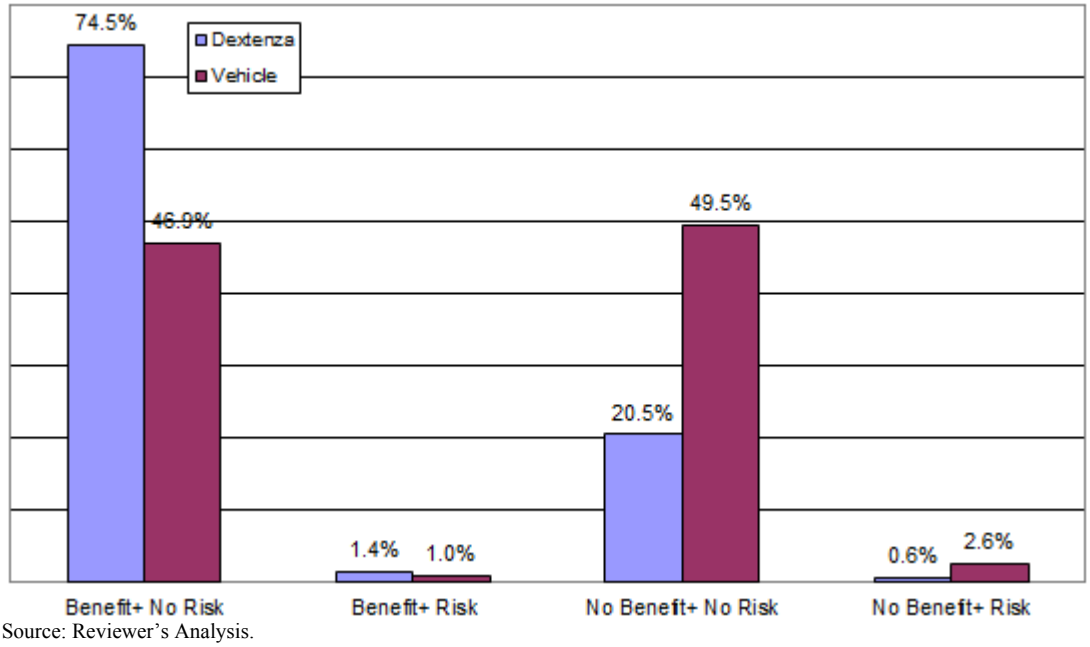

Source: Reviewer's Analysis. This analysis does not include the 16 healthy subjects from study oxt-14-009.

**Figure 15: Proportion of subjects with a >=2 lines loss from baseline (Safety Population)**



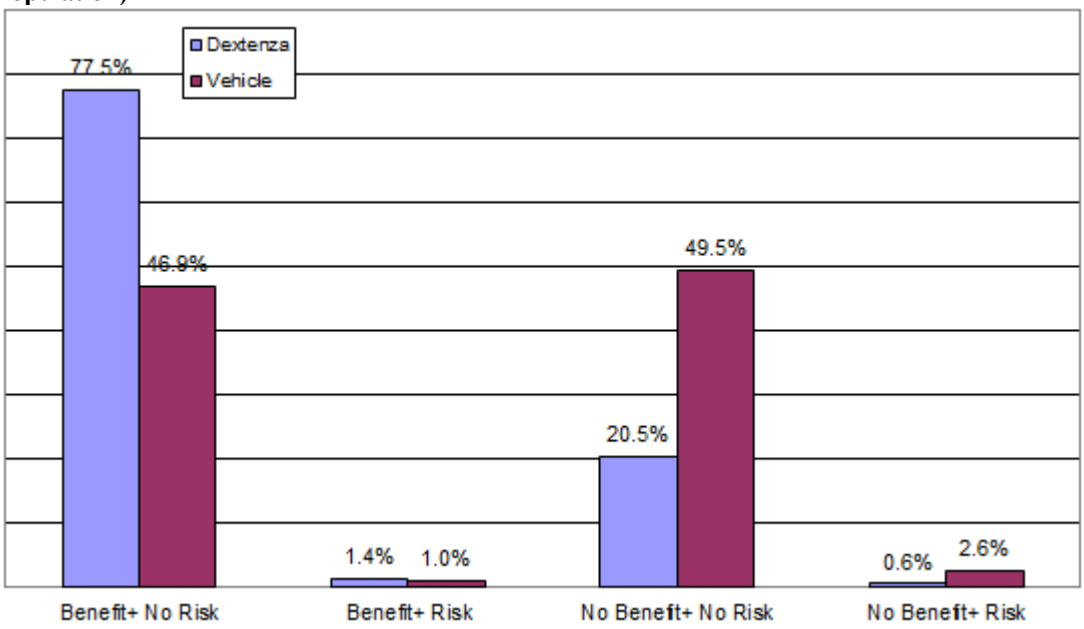

Source: Reviewer's Analysis. This analysis does not include the 16 healthy subjects from study 0xt-14-009.

**Figure 16: Risk benefit: IOP increase from bassline versus and pain score of zero at day 8 (Safety Population)**



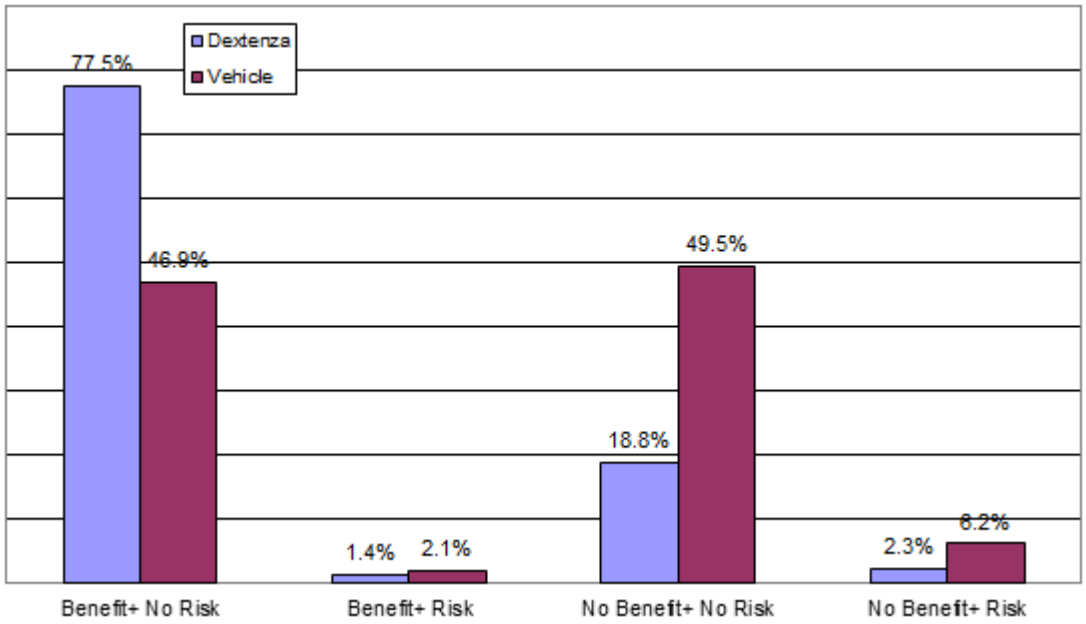

Source: Reviewer's Analysis.

**Figure 17: Risk benefit: BCVA loss >=2 lines from prior visit versus and pain score of zero at day 8 (Safety Population)**



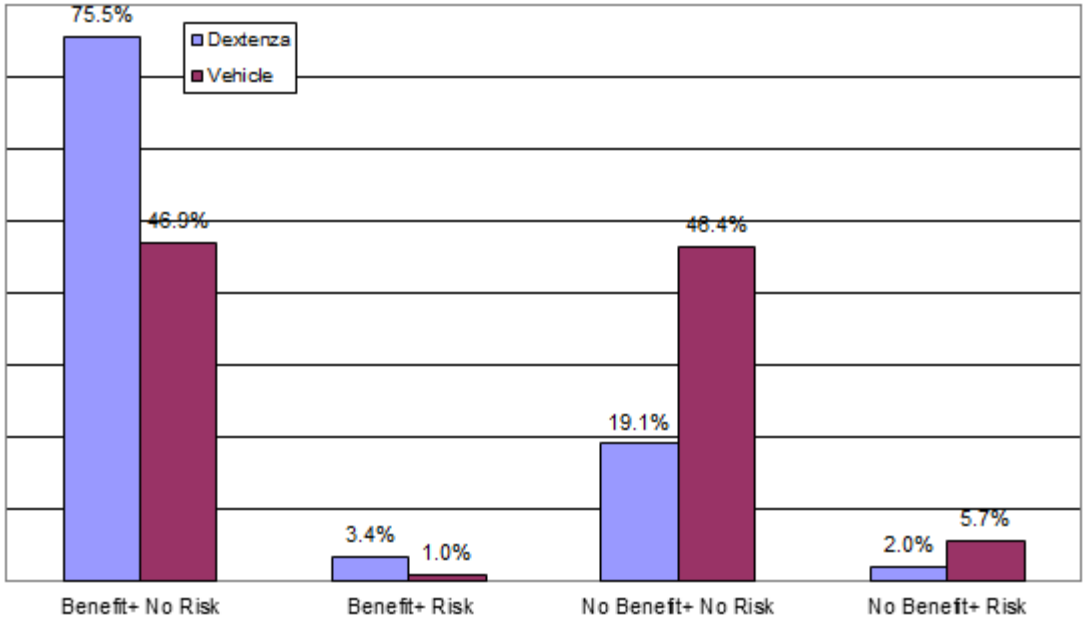

Source: Reviewer's Analysis.

**Figure 18: Risk benefit: Irtritis versus and pain score of zero at day 8 (Safety Population)**



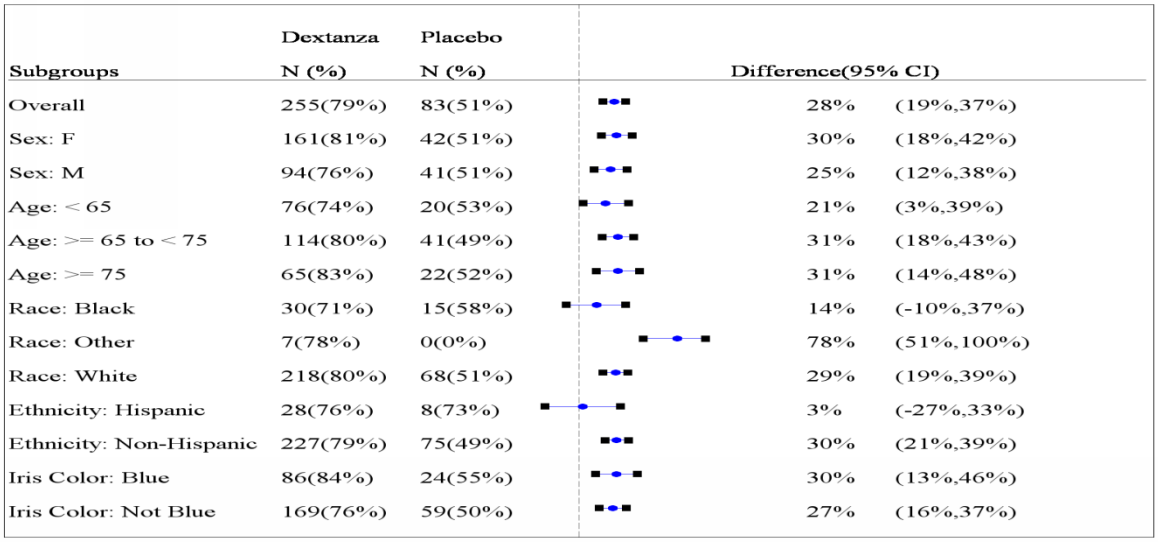

Source: Reviewer's Analysis.

**Figure 19: Risk benefit: Inflammation versus and pain score of zero at day 8 (Safety Population)**




Source: Reviewer's Analysis.

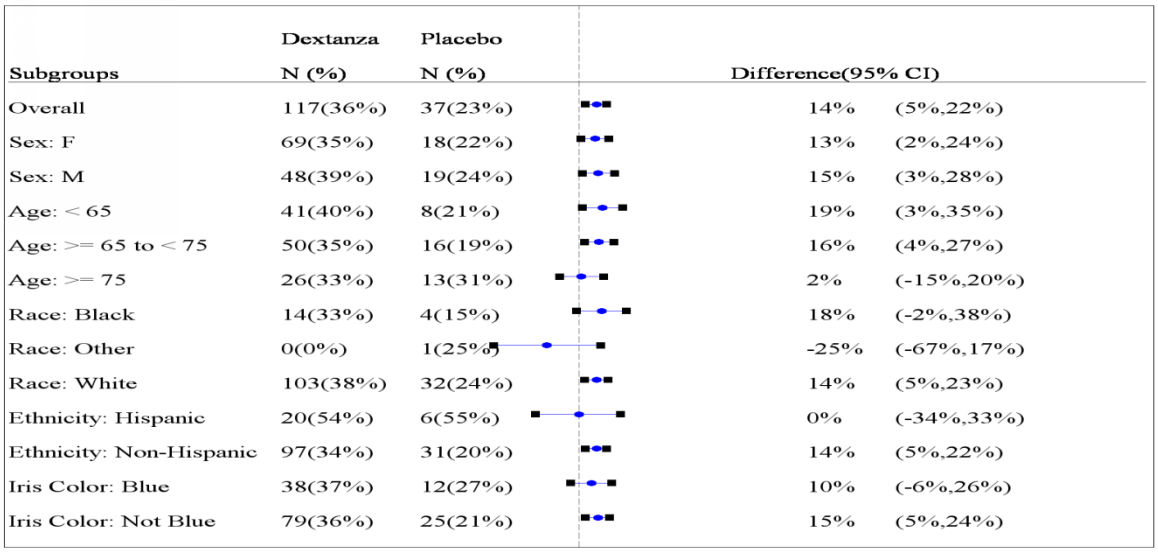
**Figure 20: Subgroup Analysis: Proportion of subjects with no pain at day 8 (ITT: LOCF)**



| Subgroups | Dextanza N (%) | Placebo N (%) | Difference(95% CI) | |
|---|---|---|---|---|
| Overall | 255(79%) | 83(51%) | 28% | (19%,37%) |
| Sex: F | 161(81%) | 42(51%) | 30% | (18%,42%) |
| Sex: M | 94(76%) | 41(51%) | 25% | (12%,38%) |
| Age: < 65 | 76(74%) | 20(53%) | 21% | (3%,39%) |
| Age: >= 65 to < 75 | 114(80%) | 41(49%) | 31% | (18%,43%) |
| Age: >= 75 | 65(83%) | 22(52%) | 31% | (14%,48%) |
| Race: Black | 30(71%) | 15(58%) | 14% | (-10%,37%) |
| Race: Other | 7(78%) | 0(0%) | 78% | (51%,100%) |
| Race: White | 218(80%) | 68(51%) | 29% | (19%,39%) |
| Ethnicity: Hispanic | 28(76%) | 8(73%) | 3% | (-27%,33%) |
| Ethnicity: Non-Hispanic | 227(79%) | 75(49%) | 30% | (21%,39%) |
| Iris Color: Blue | 86(84%) | 24(55%) | 30% | (13%,46%) |
| Iris Color: Not Blue | 169(76%) | 59(50%) | 27% | (16%,37%) |

Source: Reviewer's Analysis. Subjects who received rescue therapy are treated as treatment failures

**Figure 21: Subgroup Analysis: Proportion of subjects with no anterior chamber cell at day 14 (ITT: LOCF)**



| Subgroups | Dextanza N (%) | Placebo N (%) | Difference(95% CI) | |
|---|---|---|---|---|
| Overall | 117(36%) | 37(23%) | 14% | (5%,22%) |
| Sex: F | 69(35%) | 18(22%) | 13% | (2%,24%) |
| Sex: M | 48(39%) | 19(24%) | 15% | (3%,28%) |
| Age: < 65 | 41(40%) | 8(21%) | 19% | (3%,35%) |
| Age: >= 65 to < 75 | 50(35%) | 16(19%) | 16% | (4%,27%) |
| Age: >= 75 | 26(33%) | 13(31%) | 2% | (-15%,20%) |
| Race: Black | 14(33%) | 4(15%) | 18% | (-2%,38%) |
| Race: Other | 0(0%) | 1(25%) | -25% | (-67%,17%) |
| Race: White | 103(38%) | 32(24%) | 14% | (5%,23%) |
| Ethnicity: Hispanic | 20(54%) | 6(55%) | 0% | (-34%,33%) |
| Ethnicity: Non-Hispanic | 97(34%) | 31(20%) | 14% | (5%,22%) |
| Iris Color: Blue | 38(37%) | 12(27%) | 10% | (-6%,26%) |
| Iris Color: Not Blue | 79(36%) | 25(21%) | 15% | (5%,24%) |

Source: Reviewer's Analysis. Subjects who received rescue therapy are treated as treatment failures

## Summary of Study oxt-14-009

This study was an open-label study designed to evaluate the plasma pharmacokinetics of Dextenza in healthy volunteers. This study was conducted at a single center as an adjunctive evaluation in support of the Phase 3 clinical program for treatment of post-operative inflammation and pain. A total of 16 healthy volunteers ranging in age from 19 to 55 years (mean: 31.7 years) were entered into the study. Based on the summary of the PK (AUC, Cmax and Tmax) and adverse event summary, the applicant concluded that Dextenza results in negligible systemic exposure to dexamethasone with the vast majority of samples being below the LLOQ. The safety profile of Dextenza is consistent with that reported previously with the ocular administration of dexamethasone.

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

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/s/

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ABEL T ESHETE
06/14/2016

YAN WANG
06/14/2016
I concur with overall conclusion of efficacy/safety.