Results of A Randomized, Double-Masked, Parallel-Arm Phase 2b Study Evaluating the Safety and Efficacy of OTX-TP (travoprost insert) Compared to Timolol Drops for the Treatment of Patients with Open-Angle Glaucoma or Ocular Hypertension

Wilson C, Sall K, Bafna S, Gira JP, McLaurin E, Protzko E, Sampson R, Tekwani N, Tepedino M, Vold S, Walters TR, Metzinger JL, Mulani D, Talamo JH

BACKGROUND

There are limitations associated with the application of topical glaucoma drops: difficulty with handling the bottle, limited instillation accuracy, potential washout of drops, and poor patient compliance

As blindness can result from poorly managed glaucoma, patient adherence is a critical issue. Studies have shown less than 50% of glaucoma patients continue therapy and refill prescriptions as required

A resorbable hydrogel intracanalicular insert has been developed as a platform for ophthalmic drug delivery. The OTX-TP Intracanalicular Insert drug product may have advantages over available eye drop treatments since it is designed to remain in place for a 90 day duration of therapy, obviating subject non-compliance while continuously delivering therapeutic levels of travoprost to the ocular surface.

Initial Phase 2 studies evaluating OTX-TP sustained release travoprost drug product in two different formulations, has been completed. A subsequent Phase 2 study with a similar study design, evaluating the safety and IOP-lowering efficacy of OTX-TP placed in the canaliculus of the eyelid compared to an active comparator in subjects with open angle glaucoma (OAG) or ocular hypertension (OHT) is reported herein. The study was designed to assess clinically meaningful response to treatment and was not powered to measure any efficacy endpoints with statistical significance

STUDY OBJECTIVES

To evaluate the safety and IOP-lowering efficacy of OTX-TP, a sustained release travoprost insert, compared to Timolol Maleate Ophthalmic Solution, 0.5%, in patients with OAG or OHT over a period of 90 days

METHODS

Patient Population

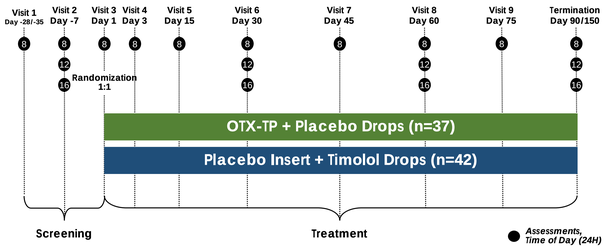
Key inclusion/exclusion criteria are presented in Table 1

Table 1: Study Population

Major Inclusion Criteria	Major Exclusion Criteria
≥ 18 years of age	Mean baseline IOP > 34 in either eye during the Baseline Visits
Documented diagnosis of ocular hypertension, open angle glaucoma	A history of an inadequate response or no response to topical prostaglandin or beta-blocker eye drops for OAG/OHT
IOP controlled with a topical prostaglandin or a topical prostaglandin in conjunction with one other topical ocular hypotensive drug (not including any fixed-combination formulations)	Best-corrected visual acuity of worse than 0.6 logMAR (20/80 Snellen) in either eye as measured using an ETDRS chart
	Narrow or potentially occludable anterior chamber angle, defined as less than grade 2 (Schaffer classification)
	Cup to disc ratio > 0.80 (horizontal or vertical measurement) in either eye
Untreated IOP ≤ 34 mmHg at Baseline	Subject requiring the use of any ocular topical medication(s), over-the counter drops, ointments or gels other than the study ocular hypotensive medications in either eye; Use of certain topical or systemic medications
Mean baseline IOP following washout in at least one eye of ≥ 24 mmHg at 8:00 AM at Baseline V1 and V2 and ≥ 22 mmHg at 12:00 PM and 4:00 PM at Baseline V1	Advanced diabetic retinopathy, or significant retinal pathology; Macular edema
	Punctum size smaller than 0.4 mm or greater than or 0.9 mm in either eye; unsuccessful dilation of either punctum, or punctum is too small to allow transient dilation to 0.8 mm for insertion of OTX-TP or PV

Study Design & Primary Endpoints

Figure 1: Study Design



- Study assessments are presented in Figure 1
- Patients were randomized 1:1 to receive OTX-TP bilaterally and placebo drops dosed twice a day in each eye, or PV bilaterally and Timolol Maleate Ophthalmic Solution, 0.5% dosed twice a day in each eye
- Primary endpoints were:
  - Difference in mean change from baseline average diurnal IOP between treatment groups at Day 60 and Day 90 Visits
  - Difference in mean change from baseline IOP between treatment groups to each individual time point at Day 60 and 90 Visits
  - Difference in mean IOP between treatment groups for average diurnal IOP and to each individual time point at Day 60 and 90 Visits
  - Difference in the mean percent change from baseline IOP between treatment groups for average diurnal IOP and to each individual time point at Day 60 and 90 Visits
- Other data collected: insertion results and ease of insertion, ocular complaints, visualization of insert by the Investigator and subject, number of inserts required in each eye over 90 day study period
- Safety evaluations included best corrected visual acuity, slit lamp biomicroscopy, assessment and grade of ocular hyperemia, subjective ocular comfort assessment, dilated fundus exam and adverse events (AEs)

Statistical Analysis

- Primary efficacy variables (mean changes in IOP) were summarized using continuous summary statistics at Days 30, 60, and 90 Visits for each treatment group; differences in mean changes in IOP was calculated and the resultant difference tested using two- sided 90% and 95% two-sample t-distribution confidence intervals
- An additional analyses of the change from baseline endpoints was to include an analysis of variance (ANOVA) model
- The study was designed to assess clinically meaningful response to treatment and was not powered to measure any efficacy endpoints with statistical significance
- A post-hoc analysis was completed to control for the effects of multiple medications and washout on the results of the trial. Patients who underwent less than a 5 week washout were excluded from the analysis

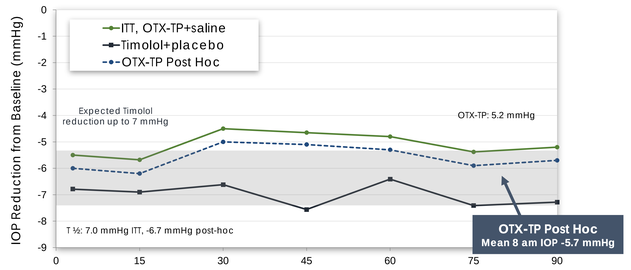
RESULTS

Patient Disposition

- A total of 79 (OTX-TP, n=37; Timolol, n=42) were randomized into the study at 10 sites in the United States
  - The majority of subjects were female (63.9%), ≥ 65 years of age (63.9%), White (75%), not of Hispanic of Latino ethnicity (86.1%), and had brown irides (61.1%)
  - Demographic characteristics were similar in the OTX-TP and Timolol treatment groups
  - 15 subjects withdrew prior to completion (OTX-TP: 2 due to an AE; 3 consent withdrawal; 1 investigator decision; 4 due to inability to insert the OTX-TP; Timolol: 2 due to an AE; 1 consent withdrawal; 2 due to inability to insert the PV)

Primary Endpoint Analysis

Figure 2: OTX-TP Comparison to Timolol and Placebo Insert; Mean 8:00 AM Change



- Both OTX-TP (+ placebo drops) and Timolol (+ placebo insert) produced clinically relevant reductions from baseline in average diurnal IOP at the Day 30, 60 and 90 Visits; IOP reductions ranged from 3.27 to 3.54 mmHg for OTX-TP and from 5.84 to 6.29 mmHg for Timolol, from an average diurnal baseline IOP of 25 to 26 mmHg (Figure 2)
- Clinically relevant reductions from baseline were observed in both treatment groups at all three time points (8:00 AM, 12:00 PM and 4:00 PM) at the Day 30, 60 and 90 Visits (Table 2); mean reductions in IOP in the Timolol group were numerically greater than those observed in the OTX-TP group at all visits/time points with the smallest difference at 8:00 AM (12 hours after Timolol dosing) and greatest at 12:00 PM (4 hours after Timolol dosing)
- Mean IOP reduction from baseline in the OTX-TP group was clinically relevant at all 13 time points, with reductions ranging from 2.30 to 5.68 mmHg

Table 2: OTX-TP Mean Change from Baseline in the Study Eye, mmHg

Time Point	Baseline IOP	Day 30	Day 60	Day 90
8:00 AM	26.03	-4.50	-4.71	-5.11
12:00 PM	24.58	-3.00	-2.30	-2.48
4:00 PM	24.21	-3.18	-2.79	-3.03

Other Assessments

- OTX-TP and Placebo insert were rated as easy or moderately easy to insert in the majority of eyes, and could be visualized in ≥ 87% and in ≥ 91% of OTX and placebo eyes, respectively, through Day 60
- A replacement OTX-TP or PV was required by 12 of 72 subjects during the study, five of whom required replacements in both eyes. Furthermore, four eyes of three subjects in the OTX-TP group required replacement twice during the study

Safety Analysis

- A similar percentage of subjects in the OTX-TP and Timolol groups reported at least one ocular or non-ocular AE
- Ocular AEs were reported for 39.4% and 37.5% of subjects in the OTX-TP and Timolol groups, respectively (Table 3), and non-ocular AEs were reported for 9.1% and 7.5% of subjects in the OTX-TP and Timolol groups, respectively
- Additionally, similar percentages of subjects in the OTX-TP and Timolol groups reported at least one treatment-related AE (33.3% and 32.5%, respectively) and similar percentages of subjects in the two groups reported at least one expected AE (33.3% and 32.5%, respectively)
- There were no deaths or other serious adverse events reported for the study. Two subjects in the OTX-TP group and two in the Timolol group discontinued study participation due to an ocular AE

Table 3: Most Common Ocular Adverse Events in the Study Eye (Safety Population)

Ocular Event, n (%)	OTX-TP + Placebo n=33	Timolol + PV n=40
Dacryocanaliculitis	4 (12.1)	4 (10.0)
Acquired Dacryostenosis	2 (6.1)	2 (5.0)
Eyelid Edema	2 (6.1)	0
Scar	2 (6.1)	0

CONCLUSIONS

OTX-TP drug product produced clinically relevant IOP reductions from baseline at Day 60 and 90. OTX-TP could be readily visualized by the subject and investigator allowing for replacement. OTX-TP was well tolerated in adult subjects with OAG or OHT based on an analysis of adverse events and other observations related to safety. This information has aided in the design of the Phase 3 clinical development program for OTX-TP

Ocular Therapeutix™ | MEDICAL AFFAIRS

PO A0172; Abstract #2111 | Presented at the Association for Research in Vision and Ophthalmology 2017 Annual Meeting; Baltimore, MD, May 7-11, 2017 | Author Contact: cwilson@ocutx.com