active, will be administered in either arm. We expect that the FDA will require that OTX-TP show both a statistically
superior reduction of intraocular pressure, when compared to the placebo, as a primary efficacy endpoint, and a clinically
meaningful reduction of intraocular pressure in the absolute. We expect to hold an end of Phase 2 meeting with the FDA
in the second quarter of 2016 and finalize the Phase 3 clinical trial protocol at that time.

Clinical Trials for Glaucoma and Ocular Hypertension

Completed Singapore Pilot Study

In 2012, we completed a prospective, single arm, open label pilot study evaluating the initial safety and efficacy of
the one-month version of OTX-TP for the treatment of glaucoma and ocular hypertension. We conducted this trial in 17
patients, and in 26 eyes, at two sites in Singapore.

We enrolled patients in this trial who were at least 21 years of age with a documented diagnosis of ocular
hypertension or open-angle glaucoma, baseline intraocular pressure within a specified range and a specified minimum
level of visual acuity in each eye. The trial protocol provided that if the participant’s intraocular pressure was high despite
treatment with OTX-TP, rescue medication would be made available to the patient. For patients who were currently under
treatment for ocular hypertension or glaucoma, we required a drug washout period for these medications between
screening and first visit.

We evaluated patients at days 3, 10, 20 and 30 following insertion of the depot and made the following assessments:
• mean intraocular pressure at 8:00 a.m. at each evaluation date as measured in millimeters of mercury, or mmHg;
• mean intraocular pressure at 10:00 a.m. and 4:00 p.m. at days 10, 20 and 30;
• change in mean intraocular pressure from baseline at each time point measured; and
• retention of the depot in the canaliculus at days 10, 20 and 30.

We assessed intraocular pressure at multiple time points on each evaluation date because intraocular pressure
naturally varies over the course of the day.

For patients who are affected bilaterally, if both eyes met all eligibility criteria, both eyes were treated, but only the
eye with the higher mean intraocular pressure at baseline was included in the efficacy analysis.

Efficacy: On day 10, 100% of the depots were retained, on day 20, 88% of the depots were retained, and on day 30,
79% of the depots were retained.
We observed a clinically meaningful reduction in mean intraocular pressure over the 30 day trial period. For eyes that retained the depot, from a mean baseline intraocular pressure of 27.2 mmHg, the mean intraocular pressure during treatment was maintained at or below 22 mmHg at each evaluation date and time point. The mean reduction in intraocular pressure from baseline ranged from 5.3 mmHg (20%) to 8.2 mmHg (30%) across all evaluation dates and time points. In studies conducted by third parties, a sustained 5.0 mmHg reduction in intraocular pressure reduced risk of disease progression by approximately 50%. The results for change in mean intraocular pressure from baseline at 8:00 a.m. on each evaluation date are set forth in the graph below.

Safety: In this trial, there were no serious adverse events or unanticipated adverse events. There was only one adverse event, bilateral epiphora, or excess tearing of both eyes, which was transient in nature and completely resolved after depot removal. There were no significant changes in hyperemia scores from baseline through day 30. There were no notable observations of clinical relevance among the slit lamp biomicroscopy assessments.

*Completed South Africa Pilot Study*

In 2012, we completed a prospective, single arm, open label pilot study evaluating the initial safety and efficacy of the two-month version of OTX-TP for the treatment of glaucoma and ocular hypertension. We conducted this trial in 20 patients, and in 36 eyes, at two sites in South Africa.

Enrollment criteria were comparable to our Phase I Singapore trial described above, except that the minimum patient age was 18.

We evaluated patients at days 3, 15, 30, 45 and 60 following insertion of the depot and made the same assessments with respect to mean intraocular pressure, change in mean intraocular pressure from baseline and retention of the depot in the canaliculus at each evaluation date following day 3 as in our Phase 1 Singapore trial described above.

**Efficacy:** On day 15, 97% of the depots were retained, on day 30, 92% of the depots were retained, on day 45, 78% of the depots were retained, and on day 60, 59% of the depots were retained. Because of the limitations of the visualization of the violet color through pigmented eyelids, it is possible that intracanicular depots identified as not being retained were in fact retained but not visible, particularly given the sustained reduction in intraocular pressure through day 60 described below. We have since eliminated the violet colorant in favor of a fluorescent PEG hydrogel, resulting in greatly improved visualization.

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We observed a clinically meaningful reduction in mean intraocular pressure over the 60 day trial period. For eyes that retained the depot, from a mean baseline intraocular pressure of 28.7 mmHg, the mean intraocular pressure during treatment was maintained at or below 22.0 mmHg beginning on day 15 and at all subsequent evaluation dates. The mean reduction in intraocular pressure from baseline ranged from 5.0 mmHg (18%) to 7.1 mmHg (25%) across all evaluation dates and time points. The results for change in mean intraocular pressure from baseline at 8:00 a.m. on each evaluation date are set forth in the graph below for patients who retained the depot on such date.

There were only two cases in which intraocular pressure remained high even though the depot was confirmed to be present. In each of these cases, the investigator prescribed rescue medication at the end of the visit. It is possible that this elevated intraocular pressure was the result of the participants not responding to travoprost.

Safety: In this trial, there were no serious adverse events or unanticipated adverse events. The most common adverse event was inflammatory reaction, which was noted in three patients. All adverse events were transient in nature and completely resolved by the end of the trial. There were no significant changes in hyperemia scores from baseline through day 60. There were no notable observations of clinical relevance among the slit lamp biomicroscopy assessments.

Completed South Africa Phase 2a Clinical Trial

In May 2014, we completed a prospective, randomized, multi-arm, active-controlled, multicenter, double masked Phase 2 clinical trial evaluating the safety and efficacy of two versions of OTX-TP for the treatment of glaucoma and ocular hypertension. The OTX-TPa version was intended to release travoprost over a two-month period, and the OTX-TPb version was intended to release travoprost at a slower rate over a three-month period. Based on in vitro testing, the OTX-TPa version had an average daily drug delivery rate of 3.5 micrograms per day and the OTX-TPb version had an average daily drug delivery rate of 2.8 micrograms per day. We conducted this trial in 41 patients at four sites in South Africa. In this trial, we randomized 11 patients for treatment with OTX-TPa and placebo eye drops, 17 patients for treatment with OTX-TPb and placebo eye drops and 13 patients for treatment with a placebo vehicle control intracanalicular depot without active drug and timolol eye drops. One patient randomized into the timolol group was excluded from the trial because the investigator was unable to insert the depot. We randomized more patients in the OTX-TPb group than in the OTX-TPa group because we ceased enrolling patients in the OTX-TPa group during the trial based on an amendment to our trial protocol intended to facilitate the completion of the trial and to allow us to evaluate a larger number of patients being treated with a three-month version of the depot. Timolol is the most commonly prescribed non-PGA drug for the treatment of glaucoma and has been used as a comparator drug in pivotal clinical trials for other approval glaucoma products.
The primary efficacy endpoints in this trial are differences between treatment groups in:

- mean change in intraocular pressure from baseline on each evaluation date and at each time point;
- mean percent change in intraocular pressure from baseline on each evaluation date and at each time point; and
- mean intraocular pressure on each evaluation date and at each time point.

We designed our Phase 2a clinical trial to assess clinically meaningful response to treatment, and did not power the trial to measure any efficacy endpoints with statistical significance. We also evaluated retention of the depot as a secondary endpoint.

We enrolled patients in this trial who were at least 18 years of age with a documented diagnosis of ocular hypertension or open-angle glaucoma, baseline intraocular pressure within a specified range and a specified minimum level of visual acuity in each eye. We excluded patients from this trial if, among other reasons, they had a history of inadequate response to treatment with prostaglandins or beta-blockers. For patients who were currently under treatment for ocular hypertension or glaucoma, we required a drug washout period for these medications between screening and first visit.

We evaluated patients at days 3, 15, 30, 45, 60, 75 and 90 following insertion of the depot and made the following assessments:

- mean intraocular pressure at 8:00 a.m. at each evaluation date;
- mean intraocular pressure at 12:00 p.m. and 4:00 p.m. at days 30, 60 and 90;
- change in mean intraocular pressure from baseline at each time point measured; and
- retention of the depot in the canaliculus at each evaluation date.

For patients who are affected bilaterally, if both eyes met all eligibility criteria, both eyes were treated, but only the eye with the higher mean intraocular pressure at baseline was included in the primary efficacy analysis.

We evaluated safety in all patients at each study visit with an assessment of general eye conditions, including visual acuity, along with any adverse events.

**Efficacy:** In the timolol group, for eyes that retained the depot, from a mean baseline intraocular pressure of 26.1 mmHg, the mean intraocular pressure during treatment was maintained at or below 21.4 mmHg beginning on day 15 and at all subsequent evaluation dates and time points. The mean reduction in intraocular pressure from baseline ranged from 3.2 mmHg (13%) to 6.4 mmHg (25%) across all evaluation dates and time points through day 75.

In the OTX-TPa group, for eyes that retained the depot, from a mean baseline intraocular pressure of 25.8 mmHg, the mean intraocular pressure during treatment was maintained at or below 21.0 mmHg beginning on day 15 and at all subsequent evaluation dates and time points through day 75. The OTX-TPa formulation, originally intended to deliver drug over a two-month period, exceeded our expectations, delivering drug for 75 days. The mean reduction in intraocular pressure from baseline ranged from 3.2 mmHg (14%) to 6.0 mmHg (24%) across all evaluation dates and time points through day 75.

In OTX-TPb group, for eyes that retained the depot, from a mean baseline intraocular pressure of 26.4 mmHg, the mean intraocular pressure during treatment was maintained at or below 22.2 mmHg beginning on day 15 and at all subsequent evaluation dates and time points. The mean reduction in intraocular pressure from baseline ranged from 2.0 mmHg (9%) to 5.4 mmHg (20%) across all evaluation dates and time points.

The results for change in mean intraocular pressure for patients in the OTX-TPa group, for patients in the OTX-TPb group and for patients in the timolol group from baseline at 8:00 a.m. on each applicable evaluation date are set forth in the graph below, in each case for patients who retained the depot on such date. We believe...
that the lower average daily drug delivery rate in the OTX-TPb group resulted in less reduction of mean intraocular pressure in this group as compared to the OTX-TPa group. As discussed below, we evaluated an improved three-month version of OTX-TP in our Phase 2b clinical trial.

**Safety:** In this trial, there were no serious adverse events. The most common adverse event was inflammatory reaction, which was noted in five patients. All adverse events were transient in nature and resolved by the end of the trial. There were no significant changes in hyperemia scores from baseline through day 90. There were no notable observations of clinical relevance among the slit lamp biomicroscopy assessments.

**Completed U.S. Phase 2b Clinical Trial**

In November 2014, we initiated a prospective, randomized, parallel-arm, active-controlled, multicenter, double-masked Phase 2b clinical trial to evaluate the safety and efficacy of OTX-TP for the treatment of glaucoma and ocular hypertension after submitting an IND to the FDA for this indication. We treated 73 patients at 11 sites in the United States pursuant to our effective IND. We randomized patients in a 1:1 ratio to receive either OTX-TP and placebo eye drops or a placebo vehicle control intracanalicular depot without active drug and eye drops containing timolol. Patients were instructed to use the placebo drops or timolol drops twice daily for the duration of the trial. Based on the results of our completed Phase 2a clinical trial, we designed the OTX-TP depot for use in our Phase 2b clinical trial to deliver drug over a 90 day period at the same daily rate as the OTX-TPa depot used in the Phase 2a clinical trial. To achieve this, we modified the design of the OTX-TP depot to enlarge it in order to enable the depot to carry a greater amount of drug. We previously evaluated in our Phase 1 clinical trial of OTX-MP in patients following cataract surgery a depot of similar length to the depot we are using in our Phase 2b clinical trial. These structural changes were previously evaluated in NSR studies that we describe below.

The primary efficacy endpoint in this trial was the difference between treatment groups in the mean change in intraocular pressure from baseline at day 60 following insertion of the intracanalicular depot, calculated by averaging the change from baseline across the three time points at the assessment date, which is known as diurnal intraocular pressure. The secondary efficacy endpoints in this trial were the difference between treatment groups in the mean change from baseline in average diurnal intraocular pressure at day 90, the difference between treatment groups in the mean change from baseline in intraocular pressure at each individual time point at day 60 and day 90, the difference between treatment groups in the mean change in average diurnal intraocular pressure and intraocular pressure at each individual time point at day 60 and day 90, and the difference between treatment groups in the mean percent change from baseline in average diurnal intraocular pressure and intraocular pressure.
We designed our Phase 2b clinical trial to assess clinically meaningful response to treatment, and did not power the trial to measure any efficacy endpoints with statistical significance.

We enrolled patients in this trial who are at least 18 years of age with a documented diagnosis of ocular hypertension or open-angle glaucoma, baseline intraocular pressure within a specified range and a specified minimum level of visual acuity in each eye. We excluded patients from this trial if, among other reasons, they had a history of inadequate response to treatment with prostaglandins or beta-blockers. For patients under treatment for ocular hypertension or glaucoma, we required a drug washout period for these medications between screening and first visit. We also evaluated the effect of a four week and five week washout duration on the change in 8:00 a.m. intraocular pressure in both groups.

We enrolled patients in this trial who are at least 18 years of age with a documented diagnosis of ocular hypertension or open-angle glaucoma, baseline intraocular pressure within a specified range and a specified minimum level of visual acuity in each eye. We excluded patients from this trial if, among other reasons, they had a history of inadequate response to treatment with prostaglandins or beta-blockers. For patients under treatment for ocular hypertension or glaucoma, we required a drug washout period for these medications between screening and first visit. We also evaluated the effect of a four week and five week washout duration on the change in 8:00 a.m. intraocular pressure in both groups.

We evaluated patients at days 3, 15, 30, 45, 60, 75 and 90 (with insertion of the depot on day 1) and made the following assessments:

- mean intraocular pressure and change in mean intraocular pressure from baseline at 8:00 a.m. at days 3, 15, 45 and 75; and
- mean intraocular pressure and change in mean intraocular pressure from baseline at 8:00 a.m., 12:00 p.m. and 4:00 p.m. at days 30, 60 and 90.

We also collected data on intracanalicular depot presence along with visualization of the depot by both the study patient and the investigator. The patients were instructed to assess depot presence on a daily basis and report the absence of a depot immediately. This data has provided a method for us to assess the accuracy of patient self-examination for depot presence, and we expect that this will maximize the consistency of dosing.

We evaluated safety in all patients at each study visit with an assessment of general eye conditions, including visual acuity, along with any adverse events.

**Efficacy:**

In this trial, the mean change from baseline intraocular pressure at 8:00 a.m. on day 30, 60, and 90 in the OTX-TP group was a decrease of 4.5, 4.7, and 5.1 mm Hg, respectively.

In this trial, on day 60, the OTX-TP group experienced a mean diurnal intraocular pressure lowering effect of 3.3 mmHg compared to baseline, versus mean diurnal intraocular pressure lowering of 5.9 mmHg compared to baseline for the timolol group. On day 90, the OTX-TP group experienced a mean diurnal IOP lowering effect of 3.6 mmHg compared to baseline, versus mean diurnal intraocular pressure lowering of 6.3 mmHg compared to baseline for the timolol group.

On day 60, the OTX-TP group experienced a mean intraocular pressure lowering effect compared to baseline of 4.7 mmHg at 8:00 a.m., 2.3 mmHg at 12:00 p.m. and 2.8 mmHg at 4:00 p.m., versus mean intraocular pressure lowering compared to baseline of 6.4 mmHg at 8:00 a.m., 6.1 mmHg at 12:00 p.m. and 5.6 mmHg at 4:00 p.m. for the timolol group. On day 90, the OTX-TP group experienced a mean intraocular pressure lowering effect compared to baseline of 5.1 mmHg at 8:00 a.m., 2.5 mmHg at 12:00 p.m. and 3.0 mmHg at 4:00 p.m., versus a mean intraocular pressure lowering effect compared to baseline of 7.2 mmHg at 8:00 a.m., 6.1 mmHg at 12:00 p.m. and 5.5 mmHg at 4:00 p.m. for the timolol group.

The mean intraocular pressure in the OTX-TP treatment group on day 60 was 21.73 mmHg at 8:00 a.m., 22.27 mmHg at 12:00 p.m. and 21.42 mmHg at 4:00 p.m. In the timolol group, the mean intraocular pressure on day 60 was 20.74 mmHg at 8:00 a.m., 19.05 mmHg at 12:00 p.m. and 18.85 mmHg at 4:00 p.m. The mean intraocular pressure in the OTX-TP treatment group on day 90 was 21.33 mmHg at 8:00 a.m., 22.09 mmHg at 12:00 p.m. and 21.18 mmHg at 4:00 p.m. In the timolol group, the mean intraocular pressure on day 90 was 19.87 mmHg at 8:00 a.m., 19.08 mmHg at 12:00 p.m. and 18.95 mmHg at 4:00 p.m.
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The mean diurnal intraocular pressure in the OTX-TP treatment group on day 60 was 21.81 mmHg. The mean diurnal intraocular pressure in the timolol treatment group on day 60 was 19.54 mmHg.

The mean diurnal intraocular pressure in the OTX-TP treatment group on day 90 was 21.53 mmHg. The mean diurnal intraocular pressure in the timolol treatment group on day 90 was 19.3 mmHg.

This Phase 2b glaucoma clinical trial was designed to evaluate the non-inferiority of OTX-TP compared to timolol and to inform the further clinical development for OTX-TP. This trial was not powered to show statistical significance between treatment groups. The OTX-TP treatment group included placebo eye drops that may have reduced the efficacy measures for OTX-TP, by washing out drug eluted from the depot on the ocular surface, whereas the timolol group included a placebo depot that may have improved the efficacy of timolol. Through occlusion of the punctum thereby prolonging its retention on the ocular surface. Several peer-reviewed medical journals have reported studies in which an additional intraocular pressure lowering effect of 1.32 to 1.80 mmHg was observed in patients taking timolol eye drops in combination with a non-drug eluting punctum plug compared to those patients only taking timolol eye drops. These include studies reported in September 2011 in Clinical and Experimental Optometry, February 1989 in the American Journal of Ophthalmology and August 1996 in Acta Ophthalmologica Scandinavica. The expected design for our Phase 3 clinical trials of OTX-TP for the treatment of glaucoma and ocular hypertension is addressed below under “—Regulatory Pathway”.

In the timolol group, the mean intraocular pressure at day 30, 60 and 90 at all time points ranged from 18.9 mmHg to 20.7 mmHg. The mean reduction in intraocular pressure from baseline at day 30, 60 and 90 at all time points ranged from 5.3 mmHg to 7.3 mmHg.

In the OTX-TP group, the mean intraocular pressure at day 30, 60 and 90 at all time points ranged from 21.0 mmHg to 22.3 mmHg. The mean reduction in intraocular pressure from baseline at day 30, 60 and 90 at all time points ranged from 2.3 mmHg to 5.2 mmHg.

In our completed South Africa Phase 2a clinical trial in which OTX-TP intracanalaric depot were inserted in 36 eyes in 20 patients with no placebo eye drops used, on day 30 we observed a reduction in intraocular pressure of 6.1 mmHg at 8:00 a.m., 5.1 mmHg at 12:00 p.m. and 5.6 mmHg at 4:00 p.m. following insertion of the intracanalaric depot. In this trial, on day 60 we observed a reduction in intraocular pressure of 6.7 mmHg at 8:00 a.m., 5.1 mmHg at 12:00 p.m. and 4.3 mmHg at 4:00 p.m. following insertion of the intracanalaric depot. The diurnal averages of the reduction in the intraocular pressure were 5.6 mmHg at day 30 and 5.4 mmHg at day 60 in this trial. We believe that the higher intraocular pressure reduction observed in this trial may be due to the lack of placebo eye drops.

We performed additional post-hoc analyses that were not pre-specified in the trial protocol for the Phase 2b glaucoma clinical trial to provide further insight on the performance of OTX-TP. Although post-hoc analyses performed using an unlocked clinical trial database can result in the introduction of bias, we believe that these analyses provide important information regarding our OTX-TP product candidate and are helpful in determining the study population and inclusion and exclusion criteria for future clinical trials. When we excluded patients on more than one glaucoma medication and used the baseline of five weeks of washout for comparisons of the OTX-TP group and the timolol group, the differences in mean reduction in intraocular pressure between the OTX-TP treatment group and the timolol group at the 8:00 a.m. time point on day 30, 60 and 90 narrowed to an average of 1.1 mmHg from an average of 2.2 mmHg based on the pre-specified criteria. These results are shown in the table below:

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<th>8:00 am Results for Intraocular Pressure (mmHg)</th>
<th>Intent to Treat Population</th>
<th>Post-hoc analysis Baseline of 5 weeks, single drug only</th>
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<td>OTX-TP Timolol</td>
<td>OTX-TP Timolol</td>
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<tr>
<td>Day 30</td>
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<td>Difference</td>
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http://cfdocs.btogo.com:27638//drv15/pub/edgar/2016/03/10/0001193125-16-499184/d466... 7/31/2017