Transforming Ophthalmic Care with Sustained Therapies

Investor Day
Palace Hotel, New York City
April 6, 2016
12:00-12:05p Welcome and Introduction
Brad Smith, CFO

12:05-12:20p Vision and Strategy
Amar Sawhney, Ph.D., CEO

12:20-1:10p DEXTENZA Clinical Data & MD Panel
Jonathan H. Talamo, M.D., CMO

1:10-1:20p DEXTENZA Commercialization
Scott Corning, V.P., Sales & Marketing

1:20-2:05p OTX-TP Glaucoma Program & MD Panel
Richard Lindstrom, M.D.

2:05-2:30p Back of the Eye Programs
Jeffrey S. Heier, M.D.

2:30p Wrap-up
Amar Sawhney, Ph.D., CEO
This presentation contains forward-looking statements about future expectations, plans and prospects for the Company, including statements about the development and regulatory status of the Company’s product candidates, such as the Company’s expectations and plans regarding regulatory submissions for and the timing and conduct of clinical trials of DEXTENZA for post-surgical inflammation and pain, DEXTENZA for allergic conjunctivitis, DEXTENZA for dry eye disease and OTX T-P for glaucoma and ocular hypertension, the ongoing development of the Company’s sustained released hydrogel depot technology, pre-commercial activities, the potential commercialization of DEXTENZA, the potential utility of any of the Company’s product candidates, the advancement of the Company’s other product candidates and earlier stage pipeline, future sales of ReSure® Sealant, the sufficiency of the Company’s cash resources and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend", "goal," "may," "might," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors. Such forward-looking statements involve substantial risks and uncertainties that could cause Ocular Therapeutix’s clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, those related to the timing and costs involved in commercializing ReSure® Sealant and DEXTENZA, the initiation and conduct of clinical trials, availability of data from clinical trials and expectations for regulatory submissions and approvals, the Company’s scientific approach and general development progress, the availability or commercial potential of the Company’s product candidates, the sufficiency of cash resources and need for additional financing or other actions and other factors discussed in the “Risk Factors” section of the Company’s filings with the Securities and Exchange Commission, including the Company’s most recent Annual Report on Form 10-K. In addition, the forward-looking statements included in this presentation represent the Company’s views as of the date of this presentation. The Company anticipates that subsequent events and developments will cause the Company’s views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company’s views as of any date subsequent to the date of this presentation.
Vision and Strategy

Amar Sawhney, Ph.D., CEO
Drug-eluting intracanalicular depots and intravitreal injections are investigational new drugs and not commercially available in the United States or other geographies.

Transforming Ophthalmic Care with Sustained Therapies

Anterior Segment Sustained Release Therapies

Posterior Segment Sustained Release Injections

Hydrogel Sealant
Challenges:

• Peaks and valleys of drug concentration lead to highly variable therapeutic effect

• Low concentrations before the next dose are well below the desired therapeutic level

• Peak concentrations above desired therapeutic level can cause side effects
Compliance is Key

Real World Outcomes Are Not Optimal

Burden of Daily Eye Drops

In an observational study, 92.6% of post-cataract patients showed improper administration technique with steroid drops:

• Missing eye
• Instilling incorrect amount
• Contaminating bottle tip
• Failing to wash hands

Advantages of Sustained Release Therapy

• Vastly improved compliance could lead to more assurance of efficacy and reduced disease progression
  – >50% of patients discontinue therapy within 6 months for glaucoma

• No reliance on patient administration or frequent dosing
  – Control with the physician
  – Entire course of therapy assured without errors
  – Significantly more convenient

• Slow-eluting therapeutic concentrations minimize “peak and trough”-related issues

• Preservative-free medications preserve the ocular surface\(^1\)

Targeting Markets in the U.S. Currently Totaling $11Bn\textsuperscript{1,2}

US Sales ($Bn)

- **OTX-IVT**
  - Anti-VEGF
  - $4.2

- **OTX-TP**
  - Glaucoma
  - $2.7

- **Inflammatory Conditions**
  - $4.1

- **Dry eye**
  - $1.6

- **Allergy**
  - $1.0

- **Pain & Inflammation (Anti-Inflammatories)**
  - $1.5

\textsuperscript{1} IMS data, March 2016
Posterior Segment Programs

**Protein Therapeutics**
- Demonstrated:
  - Protein stability
  - Tolerability
  - Release profile
- Seek partnership for anti-VEGF drug

**Small Molecule Drugs**
- Tyrosine Kinase Inhibitors (TKIs)
- Pursuing internal development
- Initial PK/PD and tolerability demonstrated
Multi-layer protection – 23 issued US patents, 7 US patent applications
Protection out through 2033

- **Composition** of matter for hydrogels
- **Method** of visualization for depots (fluorescent depots)
- **Method** of *in situ* forming hydrogel sealants and depots
- **Methods** of using hydrogels for drug delivery
  - Intracanalicular plugs for ocular drug delivery
  - Composite hydrogel drug delivery systems
  - Tissue tract/lumen occlusion with rod shaped hydrogel
  - Implants
- **Composition and methods** for protein drug encapsulation and delivery
  - Organogel encapsulation technology
  - Fiber formation technology
  - In situ envelope technology
- **Trade secrets** and manufacturing methods
# Product Pipeline

<table>
<thead>
<tr>
<th>Product/Program</th>
<th>Indication</th>
<th>Description (API)</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Regulatory Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved Product</strong></td>
<td></td>
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<tr>
<td>ReSure Sealant</td>
<td>Cataract incision closure</td>
<td>Ocular sealant</td>
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</table>

| **Late Stage Product Candidates** |                             |                                    |             |         |         |         |                     |
| Dextenza           | Post-surgical ocular pain and inflammation | Intracanalicular depot (dexamethasone) |             |         |         |         |                     |
| Dextenza           | Allergic conjunctivitis     | Intracanalicular depot (dexamethasone) |             |         |         |         |                     |
| OTX-TP (travoprost)| Glaucoma                    | Intracanalicular depot (travoprost)  |             |         |         |         |                     |

| **Earlier Stage Product Candidates** |                             |                                    |             |         |         |         |                     |
| Dextenza           | Inflammatory Dry Eye        | Intracanalicular depot (dexamethasone) |             |         |         |         |                     |
| OTX-IVT            | Wet AMD                     | Hydrogel depot (Anti-VEGF compounds) |             |         |         |         |                     |
## Program and Pipeline Progress

### Near-term Milestones Announced Beginning of 2015

<table>
<thead>
<tr>
<th>Program</th>
<th>Milestones</th>
<th>Progress Made in 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glaucoma</strong></td>
<td>• Initiate enrollment for Phase 2b trial for OTX-TP to treat glaucoma</td>
<td>• Trial complete – topline results reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• End-of-Phase 2 meeting scheduled</td>
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<tr>
<td></td>
<td></td>
<td>• 1st Phase 3 expected to be initiated Q3 2016</td>
</tr>
<tr>
<td><strong>Allergy</strong></td>
<td>• Phase 2 results for OTX-DP in allergic conjunctivitis</td>
<td>• Results reported for Phase 2</td>
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<tr>
<td></td>
<td></td>
<td>• Completed first Phase 3 and reported topline results</td>
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<tr>
<td></td>
<td></td>
<td>• Second Phase 3 enrollment complete</td>
</tr>
<tr>
<td><strong>Post-op</strong></td>
<td>• Complete Phase 3 clinical trials for OTX-DP post-surgical inflammation and pain</td>
<td>• Two Phase 3 trials completed</td>
</tr>
<tr>
<td></td>
<td>• Plan for submission of NDA Q2 2015</td>
<td>• Third Phase 3 currently enrolling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PDUFA date for pain indication July 24, 2016</td>
</tr>
<tr>
<td><strong>Anti-VEGF</strong></td>
<td>• Demonstrate feasibility for Anti-VEGF hydrogel depot</td>
<td>• Feasibility demonstrated for protein (Stability, release, tolerability shown)</td>
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<tr>
<td></td>
<td></td>
<td>• Initial PK/PD and tolerability demonstrated for TKI</td>
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</table>
Ocular Therapeuixx sustained delivery

Platform Building Blocks

- COMPLIANCE
- SURGEON CONTROL
- PRESERVATIVE-FREE
• **TRANSFORMING TREATMENT** from pulsed, frequently administered therapies to sustained delivery

• **MULTIPLE LATE-STAGE** product candidates with proven platform

• **LARGE MARKET OPPORTUNITIES** with addressable market of $11Bn in the U.S.

• **DEVELOPING PROPRIETARY DRUG PRODUCTS** using FDA-approved APIs combined with Ocular proprietary technology

• **SOLID IP PORTFOLIO** with worldwide exclusive rights for all ophthalmic indications

• **COHESIVE MANAGEMENT TEAM** with track record of success
Panel Participants

Richard Lindstrom, M.D.*, Founder & Attending Surgeon of Minnesota Eye Consultants; Adjunct Professor Emeritus at the University of Minnesota Department of Ophthalmology

Eric D. Donnenfeld, M.D., Clinical Professor of Ophthalmology, NYU; Trustee, Dartmouth Medical School

John Hovanesian, M.D., Clinical Faculty, UCLA Jules Stein Eye Institute; Harvard Eye Associates, Laguna Hills, CA

John Berdahl, M.D., Vance Thompson Vision, Cataract, Cornea and Glaucoma Surgeon

Robert J. Noecker, M.D., M.B.A., Ophthalmic Consultants of Connecticut; Yale University School of Medicine Clinical Faculty; Quinnipiac University Frank Netter School of Medicine Professor of Surgery

Jeffrey S. Heier, M.D.*, Co-President, Ophthalmic Consultants of Boston; Co-Director, Vitreoretinal Fellowship, Tufts Medical School

*Member of Ocular Board of Directors
Jonathan H. Talamo, M.D., Chief Medical Officer
Corticosteroid Mechanism of Action

Phospholipid

Arachidonic Acid

Corticosteroid inhibits this step

Cyclooxygenase Pathway

Prostaglandins

NSAIDs inhibit this step

Other Pathways (Like Lipooxygenase)

Inflammatory Mediators (i.e. proteins, leukotriens)

Diagram re-created from www.eophtha.com
### DEXTENZA Market Opportunity

<table>
<thead>
<tr>
<th>Clinical Need</th>
<th>Prescriptions</th>
<th>Opportunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op (steroid)</td>
<td>8.9 Million</td>
<td>$0.8 Billion</td>
</tr>
<tr>
<td>Allergic Conjunctivitis</td>
<td>7.1 Million</td>
<td>$1.0 Billion</td>
</tr>
<tr>
<td>Dry eye</td>
<td>3.3 Million</td>
<td>$1.6 Billion</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>19.3 Million</strong></td>
<td><strong>$3.4 Billion</strong></td>
</tr>
</tbody>
</table>
1st Phase 3 complete October 2015
2nd Phase 3 enrollment completion expected 2Q 2016
sNDA expected 2H 2016

Post-Surgical Pain

PDUFA date: July 24, 2016

Post-Surgical Inflammation

Phase 3 trial currently enrolling
sNDA expected 1Q 2017
Description:
• One-time sustained release depot
• Designed to replace complex topical dosing regimen
• Preservative-free

Potential Indication:
• Treatment of ocular pain associated with ophthalmic surgery

Delivery Method:
• Non-invasive
• Physician-administered: inserted into canaliculus following ophthalmic surgery
• Provides sustained and tapered delivery for 30 days
Ease of insertion and visualization
### Post-Surgical Ocular Inflammation and Pain Phase 2 and Phase 3 Results

<table>
<thead>
<tr>
<th></th>
<th>Phase 2</th>
<th>1st Phase 3</th>
<th>2nd Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dextenza</td>
<td>Placebo</td>
<td>Dextenza</td>
</tr>
<tr>
<td>Absence of AC Cells at Day 14</td>
<td>34.5%</td>
<td>3.4%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Absence of Pain at Day 8</td>
<td>79.3%</td>
<td>31.0%</td>
<td>80.4%</td>
</tr>
</tbody>
</table>

- Statistically significant difference vs. placebo

- Statistically significant difference between treatment and placebo arms in absence of pain at day 8 in both Phase 3 trials and the Phase 2 trial
- Statistically significant difference between treatment and placebo in absence of inflammatory cells at day 14 in first Phase 3 trial and the Phase 2 trial
- Strong safety profile observed in both studies
  - Favorable safety data can be used to support additional indications
Comparative Pain Data from FDA Clinical Trials

Absence of Pain at Day 8

Data from fda.gov, Summary Basis for Approval, DUREZOL and LOTEMAX, https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

*LOTEMAX is a registered trademark of Valeant. **DUREZOL is a registered trademark of Novartis.
Comparative IOP Data from FDA Clinical Trials

% of Patients with IOP Increase ≥10mmHg from Baseline*

Note: trials were not head-to-head comparisons

Data from fda.gov, Summary Bases for Approval, DUREZOL,
https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist and

*LOTEMAX is a registered trademark of Valeant. **DUREZOL is a registered trademark of Novartis.
Market Research

**Qualitative**

- Objective was to explore receptivity/potential adoption of new modality to treat post-op pain and future indications including inflammation, allergic conjunctivitis and dry eye
- **Blinded mix** of academically- and community-based ophthalmologists and KOLs (n=42)
  - 1-on-1 in-depth telephone interviews
  - Geographically dispersed sample
  - Double-blinded
  - 60 minute duration

**Quantitative**

- Objective was to develop, refine, validate most compelling positioning strategy/associated messaging
- 50 ophthalmologists
  - US only
  - Board certified
  - ≤65 years old
  - ≥2 years in practice ≤30
  - >50 ocular surgeries in past 6 months

States represented in the study: 28 States
79% of Ophthalmologists stated that DEXTENZA could become new standard of care.
Compliance Is a Concern

3 main reasons for patient non-compliance according to surgeons:

- **Forget**: 81%
- **Unwilling**: 63%
- **Unable (Manual dexterity, dementia, etc.)**: 79%

Drops can be difficult to impossible for some patients...

- Elderly/Mentally Challenged
- Coordination/Dexterity
- Uncontrollable Blink Reflex
- Trauma to eye, wasted medication, contamination of tip common even if does get into eye...

Video courtesy of Alan Robin, MD
“Preservative free agents are highly desirable and exceedingly welcome.”

“It would address each [challenge] very effectively. The compliance would obviously be significantly improved, and they’re preservative free… I think that’s one of the biggest obstacles that we face – the preservative load that we prescribe.”

“If you have something that lasts for 30 days that doesn’t cause problems and doesn’t leave [preservative] behind, that is amazing.”
DEXTENZA delivers on improving patient compliance with a product with limited toxicity concerns...

...93% believe core value proposition of DEXTENZA is potential to improve patient compliance and ultimately outcomes

Rank Order of Key Benefits
N=42 Ophthalmologists

- Improved compliance: 39
- Preservative free/ less toxic: 25
- Ease-of-use: 17
- No IOP spikes: 15
- Self-tapering: 15
- Consistent dex delivery: 13
- HCP control: 11

“88% of clinicians believe that a ‘pain only’ indication with inflammation data in the literature is acceptable to support the broad use of DEXTENZA”\(^{(1)}\)

Statistical significance of “differences in mean cell score” secondary endpoint was achieved in both phase 3 trials

\*Statistically Significant

Statistical significance of “absence of flare” secondary endpoint was achieved in both phase 3 trials.

1\textsuperscript{st} Phase 3 Absence of Flare

- Day 8: *Statistically Significant, p = 0.004
- Day 14: *Statistically Significant, p < 0.0001

2\textsuperscript{nd} Phase 3 Absence of Flare

- Day 8: *Statistically Significant, p = 0.013
- Day 14: *Statistically Significant, p = 0.009

*Statistically Significant
Phase 3 Allergic Conjunctivitis Results

Mean Ocular Itching Scores at 7 days post-insertion
(p<0.0001) at all post-CAC time points

Per FDA guidance, **Treatment Success:**
- ≥ 0.5 units for all 3 post-CAC time points AND
- ≥ 1 unit for majority of post-CAC time points

Treatment Success for Itching Achieved
Steroids for Allergic Conjunctivitis

- 1/3 of patients don’t respond well to anti-histamines
- Steroids can block both early and late phase response
- BUT concern over side effects if patient usage can’t be controlled

• How could DEXTENZA change the treatment paradigm for AC?
Corneal staining can cause irritation and decreased visual acuity

**DEXTENZA significantly reduced total staining at 15 and 30 days after placement**

*Includes all patients (n=43). Error bars represent standard error. Fluorescein (Total) is the average for five regions.*
Dry eye causes discomfort but can also reduce vision

- Multifactorial disease
- Treating inflammation is a key component of therapy

**Discussion**

- Steroids as induction therapy\(^{(1)}\)
- More rapid improvement in ocular surface health/symptoms?
- Importance of preservative-free regimens
- Added benefit of punctal occlusion

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\(^{(1)}\) Sheppard, Donnenfeld, Holland, et al. Effect of loteprednol etabonate 0.5% on initiation of dry eye treatment with topical cyclosporine 0.05%. Eye Contact Lens. 2014 Sep;40(5):289-96.
DEXTENZA™ Commercialization

Scott Corning, Vice President, Sales & Marketing
Objective: Maximize product uptake and revenue at launch, expected 1H 2017

Key Factors for Success in 2016

- Establishing reimbursement pathway
- Pricing effectively
- Preparing and opening channel with MSLs and reimbursement personnel
- Branding and promoting with various field personnel and within industry
Takeaways from Research for Launch Strategy

1. Position DEXTENZA as a therapy that addresses patient compliance
   - **Why?** Compliance identified as unmet need and main product advantage
   - **OTX:** Develop value messages, and test with select physician and payer contacts

2. Price at rate to satisfy pass-through and to maximize revenue in near term
   - **Why?** Respondents would prescribe >70% up to $500 per dose if reimbursed
   - **OTX:** Develop reimbursement materials to garner payer coverage and support providers

3. Accelerate uptake during pass-through period
   - **Why?** Secure more favorable payment rate adjustment and utilization after pass-through
   - **OTX:** Invest in sales force efforts (consider co-promotion to supplement internal force)

Source: Simon-Kucher pricing research
Deploy key field resources prior to launch to **educate**, and to create **access** and **awareness**.

**MSLs**
- **EDUCATION**
  - Disease State
  - KOL interaction

**NAM/RAM**
- **ACCESS**
  - Payer and Provider Reimbursement
  - Positioning HUB Services
  - Payer Clinical Data

**Sales**
- **AWARENESS**
  - Clinical Data
  - Procedure Training
Key Takeaways: Message Platform Validation Research

Majority of ophthalmologists indicated DEXTENZA could become new post-operative standard of care (assuming reimbursement)

Asked which statements MOST STRONGLY support the main idea of the product:

- **Allows control** of patient experience from start to finish
- Increases **compliance** by avoiding complex dosing regimens
- Ensures consistent steroid coverage throughout post-op recovery
- Provides the care patients need without any additional burden

Positioning and Messaging Validation Qualitative Research; n=50 US Board certified cataract surgeons, OptiBrand Rx LLC, 2015.
One-time seasonal prophylaxis
Reduced risk of overmedication

Dezinza Value Proposition

Post-Surgical
Strong pain relief
Early onset (Day 2)

Allergic Conjunctivitis

Dry eye
Dual mechanism:
- Build up tear level
- Treat inflammation

Compliance, physician control, preservative-free
OTX-TP: Sustained Release Travoprost for the Treatment of Glaucoma

Clinical Program Summary, Jonathan H. Talamo, M.D.
Sustained Release Travoprost (OTX-TP) Addresses Compliance Issues

Description:
• Sustained release depot
• Designed to replace daily therapy
• Preservative-free
• Product can be monitored by patient

Potential Indication:
• Intraocular pressure reduction for glaucoma and ocular hypertension

Delivery Method:
• Non-invasive
• Physician-administered: inserted into canaliculus
• Provides sustained delivery for up to 90 days
Pilot Phase 2 Study

• Single-arm, 60-day OTX-TP, no drops

Phase 2a

• Three-arm, “double dummy” design, 60- and 75-day OTX-TP, timolol comparator arm

Phase 2b

• Two-arm, “double dummy” design, 90-day OTX-TP and placebo drops BID vs. placebo depot and timolol 0.5% BID
2-Month Pilot Phase 2 Study
Mean IOP Reduction at 8AM

Baseline = 28.7 mm Hg
n=22 eyes

No placebo eye drops used

Error bars = SEM
Phase 2a Trial Results

OTX-TP Comparison to Timolol and Placebo Plug
Mean 8:00 AM Reduction from Baseline

IOP Change (mmHg)

Days

OTX-TP
Timolol

Error Bar = SEM
Phase 2b IOP Reduction

Mean 8 am Reduction from Baseline

Expected Timolol reduction up to 7 mmHg
Phase 2b IOP Reduction

Mean 8 am Reduction from Baseline

**ITT, OTX-TP+saline**

OTX-TP: 5.2 mmHg

Expected Timolol reduction up to 7 mmHg
IOP Reduction from Baseline

**Mean 8 am Reduction from Baseline**

- **ITT, OTX-TP+saline**
  - OTX-TP: 5.2 mmHg
- **Timolol+placebo**

**Expected Timolol reduction up to 7 mmHg**

**T ½: 7.0 mmHg ITT, -6.7 mmHg post-hoc**

Days

0 15 30 45 60 75 90
Phase 2b IOP Reduction

Mean 8 am Reduction from Baseline

- **ITT, OTX-TP+saline**
- **Timolol+placebo**
- **OTX-TP Post Hoc**

- **T ½: 7.0 mmHg ITT, -6.7 mmHg post-hoc**
- **OTX-TP: 5.2 mmHg**
- **Expected Timolol reduction up to 7 mmHg**
- **Mean 8 am IOP -5.7 mmHg**
### Phase 2a and 2b Clinical Trials

<table>
<thead>
<tr>
<th>Safety</th>
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<tbody>
<tr>
<td>• No SAEs</td>
</tr>
<tr>
<td>• No hyperemia change from baseline</td>
</tr>
<tr>
<td>• Punctum-related AEs mainly related to insertion</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Depot visualization by patient possible</th>
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<tbody>
<tr>
<td>Accurate correlation between physician and patient observations</td>
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</table>

<table>
<thead>
<tr>
<th>Retention of Depot</th>
<th>Phase 2b 8 am IOP (ITT)</th>
<th>Phase 2b 8 am IOP (post-hoc*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 60</td>
<td>91%</td>
<td>-4.8</td>
</tr>
<tr>
<td>Day 75</td>
<td>88%</td>
<td>-5.4</td>
</tr>
<tr>
<td>Day 90</td>
<td>48%</td>
<td>-5.2</td>
</tr>
</tbody>
</table>

*Post hoc: 5 week washout IOP, single medication subjects only*
Influence of Visualization of Depot on IOP

- Mild effect on Mean IOP
- Depot material may still be present in partially resorbed state

**OTX-13-004: Depot visualized at Day 75, but not at Day 90 - Observed data**

<table>
<thead>
<tr>
<th>OTX-TP, n = 13</th>
<th>IOP*</th>
<th>Mean</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>26.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 75</td>
<td>21.08</td>
<td>-5.15</td>
<td></td>
</tr>
<tr>
<td>Day 90</td>
<td>22.00</td>
<td>-4.23</td>
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* 8 am IOP values
OTX-TP
Phase 3 Program
OTX-TP Phase 3 Development Strategy

• Two planned trials: OTX-TP treatment arm vs. placebo comparator arm (intracanalicular depot without drug)
  – ~550 subjects/study; 100+ to be followed in one trial to 1 year for safety

• Based on FDA input, no timolol comparator or validation arm planned
  – Eye drops, placebo or active, not expected to be administered in either arm

• Expect FDA to require OTX-TP show a statistically superior and clinically meaningful IOP reduction vs. placebo as a primary efficacy endpoint

• Subject to outcome of FDA End-of-Phase 2 meeting, anticipate initiation of first Phase 3 trial Q3 2016
Open-angle glaucoma or ocular hypertension
IOP ≥ 24 and ≤ 34mmHg (~550 patients per study in ITT population)

Washout at 6 weeks

Patients randomized 3:2

OTX-TP  Placebo Vehicle

Mean IOP at 60 and 90 days
Follow-up continued to Day 150 and beyond based on depot replacements
OTX-TP Glaucoma Panel Discussion

Richard L. Lindstrom, M.D.
Placebo Arm Phase 3 Studies

• Patient and protocol considerations
  – Rescue strategy
  – Disease state severity

• What are the pros and cons of a placebo vehicle comparator arm study?

• What enrollment challenges might you anticipate?
• High risk (fast-progressing) patients excluded (PXE, PDS, VF loss)

• Subject with IOP > 34 mm/Hg excluded

• “Rescue plan” allows broad latitude if IOP deemed unsafe

• Based on the patient population specified, the literature (EMGT 1, OHTS 2) predicts low-risk visual field progression over the course of the study.
What do you think is the biggest problem with medical therapy for glaucoma

- Cost
- Compliance
- Side effects
- Lack of efficacy

U.S. Glaucoma Prescription Market

First-line Agents: Prostaglandin Analogs (PGAs)

- Travoprost
- Bimatoprost
- Latanoprost

53% Prescription Market Share

PGAs
18 mill. Rxs

Second-line Agents: Non-PGAs

- Beta-blockers
- Beta-blocker combos
- Alpha agonists
- TCAIs

47% Prescription Market Share

Non-PGAs
16 mill. Rxs

34 million U.S. glaucoma prescriptions

Source: IMS data, March 2016
• >50% of patients discontinue therapy within 6 months\(^{(1)}\)

• Difficulty in administration
  - Limited accuracy administering drops
  - Elderly patients suffer from arthritis, dementia

• Preservatives can cause side effects
  - Antimicrobial preservatives such as BAK can damage tear film and cause irritation\(^{(2)}\)

• Result is disease progression

What is your first-line glaucoma eye drop?

- **Prostaglandin**: 80%
- **Beta blocker**: 20%
- **Alpha-agonist**: 10%
- **Carbonic anhydrase inhibitor**: 0%

Assuming that the following medical glaucoma treatments have the same efficacy, which would you pick for yourself?

- An eye drop taken once per day
- An insert placed under the eye lids or in the punctum that needs to be changed monthly
- An injection into the anterior chamber that lasts 3 months
- An injection into the vitreous that lasts 6 months

If OTX-TP has a profile of 75 or 90-day retention and average IOP reduction of 5mm Hg, what % of glaucoma patients would be candidates?

1. <20%
2. 20-40%
3. 40-60%
4. 60-80%
5. >80%

~90% predict >20% of patient base would be candidates whether 75- or 90-day plug
~50% predict >40% of patient base would be candidates whether 75- or 90-day plug

Panel: How would you incorporate OTX-TP into your practice?
OTX-IVT Depot

Jeffrey S. Heier, M.D.
Age Related Macular Degeneration (AMD)

AMD is the leading cause of irreversible visual impairment among people in the developed world and ranked third worldwide after cataracts and glaucoma. While this disease often begins with little to no impact on vision, progression to geographic atrophy (GA) or to the exudative (wet) form can lead to severe vision loss.
Similar Efficacy in the Majority of Patients

Current Anti-VEGF Agents

IVAN Trial
- Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial

GEFAL Trial
- Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial

MANTRA TRIAL
- A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration

VIEW Trials

CATT Trial

HARBOR TRIAL
“With less frequent follow-up leading to less treatment, there was an incremental decline of the visual acuity (VA) gains achieved with monthly treatment.”

Ophthalmology 2012;119:1175–1183
• Assessed long-term outcomes 7-8 years after initiation of ranibizumab therapy

• Those with more injections had significantly better mean gain in visual acuity

Ophthalmology 2013;120:2292-2299
The Neovascular Age-Related Macular Degeneration Database: Multicenter Study of 92,976 Ranibizumab Injections

Report 1: Visual Acuity

Wet AMD: 11,135 Patients Treated with Ranibizumab

Ophthalmology. 2014 Jan 23. pii: S0161-6420(13)01153-6
Ocular Therapeutix technology provides a sustained release vehicle designed to work well with common intravitreal injection practice – and with known anti-angiogenesis drugs.
Posterior Segment Programs

Protein Therapeutics
- Demonstrated:
  - Protein stability
  - Tolerability
  - Release profile
- Seek partnership for anti-VEGF drug

Small Molecule Drugs
- Pursuing internal development
- Initial PK/PD and tolerability demonstrated
Product Profile: Potential first-in-class, 6-month sustained release anti-VEGF hydrogel for retinal diseases

- OTX potential sustained delivery benefits:
  - 6 months sustained release
  - Fine needle injection (25-27g)
  - No interference with vision
  - Biocompatible
  - Absorbable
• **Target antibodies currently in use**
  – Combine with Ocular Therapeutix technology for sustained delivery
  – **Bevacizumab** (Avastin) (anti-VEGF)
  – **Aflibercept** (Eylea) (anti-VEGF, anti-PIGF)
  – **Ranibizumab** (Lucentis) (anti-VEGF)

• **Gain access to antibody through partnership**
  – Feasibility collaborations

• **Jointly develop the technology**
  – Hydrogel is tailored to the antibody
Implant resides within the vitreous – does not penetrate the sclera

Other intravitreal implants have employed rigid plastics, such as PLA, or non-degradable materials.

The depot is composed of the drug powder embedded in a soft, lubricious biodegradable hydrogel (~90% H2O).

Depot presents a smooth, hydrophilic, biocompatible surface to tissues

Coiling action forms compact depot in situ

Fiber hydrates and coils as it exits needle
Anti-VEGF Release *in vitro* (PBS, pH7.2)
Minimal Aggregation Through 5 Months

- Monomer
- High MW species

Target is 100% in 4-6 Months

Highly stable in hydrogel

Meets 4-6 Month Target
FA images are scored for blood vessel morphology and fluorescein leakage

Inject Depot, Placebo or Avastin → Wait X Weeks → Inject 1μg VEGF → Wait 2 Days → Inject Fluorescein → Score FA

Bevacizumab loaded fiber showed continued inhibition up to 12 weeks compared to less than 6 weeks from single human Avastin dose (1.25mg)

Representative FA Images

Empty Depot Control
Fluorescein leaking from vessels

No Inhibition- Leakage:
score = 4

Avastin Pre-treatment

Inhibition- Leakage
score = 0
• Blank coils implanted in rabbits
• Currently at 4 weeks
• Time points
  – 4, 12, 26 weeks
• Measurements (all normal at 4 weeks)
  – IOP
  – Preclinical observations
  – OCT
  – OCT-FA
  – ERG
  – IR Imaging
• IR Images of blank hydrogel coil in rabbit eyes at 4 weeks
  – Shows compact coiling
  – No fouling or inflammation
Histologist remarks: The injected material (black arrows) is present free-floating in the vitreous chamber with no inflammation around it. The top panel is a low magnification image, and the inset box is shown in the bottom panel at higher magnification.
• In vitro release for 4-6 months achieved with multiple antibodies

• Sustained PD (bevacizumab) achieved in rabbit screening model through 3 months

• Development activities
  – Process scale and efficiency
  – Injector design and prototyping
  – Aseptic process
• Antibody drugs bind angiogenic growth factors before they reach their receptors
• TKIs prevent downstream activity by inhibiting kinases associated with the receptors
• **TKI must be selective for angiogenesis targets**
  - Potent inhibitor of VEGFR2, PDGFRβ
  - No off-target effects

• **Must be compatible with hydrogel technology**
  - Sustained drug release for 6 months

• **Depot must be biocompatible**
  - Small enough to fit through a fine needle
  - Small enough to avoid visual axis
  - Non-inflammatory
  - Hydrogel disappears soon after drug release
Problems with TKIs:

- Low solubility
- Liquid formulations must be suspensions
- Low bioavailability from drops, injections problematic
- Low ocular concentrations from oral, side effects if drug not highly specific
- Short half-life of dissolved drug in eye (hours – not days) – quickly cleared

Solution: Local sustained delivery

Trademarks are the property of their respective owners.
Initial testing done with straight fiber – followed later by coiled fiber version

Pharmacodynamic (PD) study shows sustained activity against VEGF challenge at 6 mo.

IR Image: Presence of white drug evident in fiber after 16 weeks in vivo

Pharmacokinetic (PK) data shows high tissue concentrations through 4 months

<table>
<thead>
<tr>
<th>Retina Drug Concentration</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Time (months)</td>
<td>IC₅₀</td>
<td>IC₅₀</td>
<td>IC₅₀</td>
<td>IC₅₀</td>
</tr>
<tr>
<td>Multiple of IC₅₀</td>
<td>1699</td>
<td>1879</td>
<td>2192</td>
<td>3228</td>
</tr>
</tbody>
</table>
Advantages of TKI properties for OCUL technology

• High potency small molecules
  – need only about 1/10 the drug load compared to antibody drugs
• Low solubility – enables slow release from hydrogel
• Short half-life in solution – good for local delivery

Drug selection criteria

• Existing, approved drug (cancer)
• Drug availability – cGMP compliant
• Target selectivity and high potency
  – High potency for target kinases: VEGFR2 and PDGFRβ
  – Low potency for off-target kinases
• Low solubility – controls drug release rate
• Drug patents expire before potential product commercialization
• TKI coils implanted in rabbits
• Time points: 4, 12, 26 weeks
• Measurements all normal at 4 weeks:
  - IOP
  - Preclinical observations
  - OCT
  - OCT-FA
  - ERG
  - IR imaging

IR images of TKI coils in rabbit eyes at 4 weeks
• Form and maintain compact coiled shapes
• White drug clearly visible
Histologist remarks: The injected material (black arrows) is present free-floating in the vitreous chamber with no inflammation around it. The top panel is a low magnification image, and the inset box is shown in the bottom panel at higher magnification.
TKI Summary

- Effective in repeated VEGF challenge Dutch-belted rabbit model through 6 months
  - Screening model
  - Monkey laser CNV model planned
- PK data shows high sustained retinal concentration
- Tolerability in rabbit eyes good through 4 weeks
- Development activities
  - Process scale and efficiency
  - Injector design and prototyping
Transforming Ophthalmic Care with Sustained Therapies

Investor Day
Palace Hotel, New York City
April 6, 2016