Trabodenoson: A Highly Selective Adenosine Mimetic Targeting the A1 Subreceptor

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Forward Looking Statements

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Trabodenoson is an investigational compound and is not yet approved by the FDA for any indication.
Inotek is an Emerging Innovator in Ophthalmology

- Clinical stage pharmaceutical company working in glaucoma and neuroprotection
- Initial Public Offering in 2015
- Regulatory strategy for lead asset confirmed by FDA (EOP2 Meeting June 2015)
- Trabodenoson monotherapy program in Phase 3, FDC program in Phase 2
- For more information – www.inotekpharma.com
Inotek is Taking a Broad Approach to Treating OHT and Glaucoma

Pathophysiology: Loss of ocular pressure regulation by the Trabecular Meshwork

Pathology: Optic Neuropathy disrupts the visual signal to the brain

Front of the Eye: IOP

Back of the Eye: Neuroprotection

Present in ocular hypertension

Cause of visual loss in all types of glaucoma

Trabodenoson has the Potential to Treat Glaucoma in Two Potentially Synergistic Ways
Adenosine is a naturally occurring purine nucleoside composed of an adenine molecule (green) attached to a ribose sugar molecule (blue).

- Adenosine and its receptors are present in the eye\(^1,2\)
- Adenosine levels ↑ in ocular hypertension\(^3\)
- Four adenosine subreceptors – A\(_1\), A\(_{2a}\), A\(_{2b}\), A\(_3\)
- Receptor modulation can cause different effects\(^4,5\)
- Adenosine A\(_1\) receptor (A\(_1\)R) in key target tissues\(^1,2\)
  - trabecular meshwork
  - ciliary body
  - retina

Adenosine $A_1$R Activation Decreases IOP

Adenosine mimetics that target the $A_1$R lower IOP$^{1-6}$

Novel mechanism of action of selective $A_1$R agonists$^{6,7}$
- TM remodeling leads to improved outflow facility and IOP reduction$^{3,7}$
- Transient decrease in aqueous production acutely lowers IOP$^7$

Natural IOP Regulation and MMP-2

- Trabodenoson increases MMP-2 levels
- Increased IOP and/or stretch receptors lead to ↑ MMP-2
- ↑ MMP-2 increases turnover of the extracellular matrix
- Re-modeled ECM increases outflow facility and decreases IOP

Craig Crosson, MUSC, presented at AGS, 2016

Bradley JM IOVS 2001 Vol 42(7):1505-1513
Trabodenoson Increases Outflow Facility at the TM

- Increased outflow facility induced by trabodenoson (INO-8875) in porcine anterior segments
- Increased outflow facility is reversed by MMP inhibitor (GM6001) implicating MMP release in the outflow facility change and change in aqueous outflow

(Design: Individual outflow facilities were normalized to baseline levels (t = 0) and calculated as the percentage change from baseline. Data are presented as mean ± SE)

* In porcine anterior segment model
Trabodenoson is an adenosine mimic optimized to selectively target the $A_1$ receptor.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$A_1$ (Ki, nM)</th>
<th>$A_{2a}$ (Ki, nM)</th>
<th>$A_3$ (Ki, nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabodenoson</td>
<td>0.97</td>
<td>4,690</td>
<td>704</td>
</tr>
<tr>
<td>Adenosine</td>
<td>100</td>
<td>310</td>
<td>290</td>
</tr>
</tbody>
</table>

Developed by medicinal chemists at Inotek.
Trabecular Meshwork: The Site of Trabodenoson’s Effect to Increase Outflow Facility

The trabecular meshwork function declines with age. With OHT/POAG, outflow facility is more markedly affected, resulting in elevated IOP and higher variation in IOP.¹

Trabodenoson works to remodel the TM through MMP2 to increase outflow facility.

This augments the natural ocular biology to restore IOP regulation, resulting in lower IOP and potentially less variation.¹

Aqueous humor is produced in the ciliary epithelium, flows into the anterior chamber and drains out via trabecular meshwork (green arrows).

The trabecular meshwork is the natural, pressure-regulating drain, controlling 70% of aqueous humor outflow to maintain ideal pressure.

Increasing aqueous outflow through the trabecular meshwork helps ensure support of the TM which is an avascular structure.

⁻⁷⁰% of outflow through the conventional pathway
⁻³⁰% of outflow through the uveoscleral pathway

¹Brubaker 2003
Trabodenoson and Ocular Tissue Distribution

<table>
<thead>
<tr>
<th>Ocular Structure</th>
<th>Trabodenoson (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 hrs</td>
</tr>
<tr>
<td>Aqueous Humor</td>
<td>59.6</td>
</tr>
<tr>
<td>Ciliary Body</td>
<td>101.8</td>
</tr>
<tr>
<td>Trabecular Meshwork</td>
<td>893.1</td>
</tr>
<tr>
<td>Cornea</td>
<td>438.1</td>
</tr>
<tr>
<td>Sclera</td>
<td>130.26</td>
</tr>
<tr>
<td>Iris</td>
<td>1289</td>
</tr>
<tr>
<td>Lens</td>
<td>BLQ</td>
</tr>
<tr>
<td>Retrobulbar Fat</td>
<td>215.86</td>
</tr>
<tr>
<td>Choroid</td>
<td>148.8</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>919.4</td>
</tr>
<tr>
<td>Vitreous Humor</td>
<td>BLQ</td>
</tr>
<tr>
<td>Retina</td>
<td>19.1</td>
</tr>
</tbody>
</table>

- 200 mcg of trabodenoson in cynomolgus monkeys
- CNM eye are the closest model to human eyes
- Drug is broadly distributed throughout the eye, without accumulation
- $A_1$ receptors are present in the target tissues
- Tissue concentrations exceed $K_i$ in the trabecular meshwork, ciliary body and retina
- Trabodenoson $K_i = 0.97\text{nM}$ for $A_1$ receptor
- No accumulation of drug at the lens

BLQ – Below the limit of quantification
Phase 2: IOP Reduction for 500mcg BID Dose
Statistically significant at all time points on Day 28

Myers et al., 2016, JOPT, e-pub ahead of print doi:10.1089/jop.2015.0148; IPC-01-2013:
ClinicalTrials.gov Identifier: NCT01917383

IOP similar at 8am on Days 28 and 29

* p-value < 0.05 compared to placebo group
Note: Day 28 p-values significant following Bonferroni correction
Dose-Dependent Diurnal IOP Reduction

Myers et al., 2016, JOPT, e-pub ahead of print doi:10.1089/jop.2015.0148
Phase 1: Good Safety Profile and Tolerable

Design

Results – No Dose Limiting Toxicity; no dose-related ocular or systemic side effects; limited systemic exposure at high doses

Journal of Ocular Pharmacology and Therapeutics. April 2016, ahead of print. doi: 10.1089/jop.2015.0147. Trial authors; Alan Laties¹, Cadmus C. Rich², Randall Stoltz³, Vernon Humbert⁴, Chaim Brickman², William McVicar², and Rudolf A. Baumgartner²
**TRAE Summary for Trabodenoson Program**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Ph 1 Single Drop</th>
<th>Ph 1 Safety</th>
<th>Ph2 Dose Range</th>
<th>Phase 2 Additivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Overall Active</td>
<td>Placebo</td>
<td>Overall Active</td>
</tr>
<tr>
<td></td>
<td>(n=28)</td>
<td>(n=56)</td>
<td>(n=28)</td>
<td>(n=42)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>(n=59)</td>
<td>(n=85)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>0</td>
<td>3 (5.4)</td>
<td>0</td>
<td>12 (14.1)</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye pain</td>
<td>0</td>
<td>0</td>
<td>4 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>5 (17.9)</td>
<td>4 (7.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>8 (19.0)</td>
<td>0</td>
</tr>
<tr>
<td>Vital Dye Staining</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1. Ph 1 Single drop, Ph2 Dose Range and Ph2 Additivity were performed in patients with OH or POAG. Ph1 Safety was performed in healthy adult volunteers.
2. LP = latanoprost; QAM = each morning; QPM = each evening; TVC = trabodenoson-matched placebo control

*Items with less than 2 events removed – Refractive disorder (1), Lid crusting (1), Conjunctival hemorrhage (1)

Where ≥ 2 Events were Reported in Any Given Study
Phase 2 Dose Ranging Trial: Hyperemia Incidence

Hyperemia was infrequent and unchanged by trabodenoson

Note: Percentage is representative of: (number of observed events/number of measurements), and all recorded data are reported here.

Myers et al., 2016, JOPT, e-pub ahead of print doi:10.1089/jop.2015.0148
Phase 2 Dose Ranging Trial: Hyperemia Score Graded (0-3)

Hyperemia scores were low and unchanged by trabodenoson

0 = none/trace
1 = mild
2 = moderate
3 = severe

Myers et al., 2016, JOPT, e-pub ahead of print doi:10.1089/jop.2015.0148
# Phase 2 Study Program Conclusions

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dependent IOP-lowering observed up to 500 mcg BID</td>
<td></td>
</tr>
<tr>
<td>IOP drop from diurnal baseline of 3.5 - 5 mmHg (median 4.1 mmHg)</td>
<td></td>
</tr>
<tr>
<td>IOP-lowering efficacy improved with increasing time on therapy (to day 28)</td>
<td></td>
</tr>
<tr>
<td>IOP reduction persisted 24 hours post last dose</td>
<td></td>
</tr>
<tr>
<td>QD dosing potential should be investigated in Phase III clinical trials</td>
<td></td>
</tr>
<tr>
<td>Well-tolerated with no dose limiting tolerability</td>
<td></td>
</tr>
<tr>
<td>MOA is not associated with hyperemia (results through Phase 2 support this)</td>
<td></td>
</tr>
<tr>
<td>No treatment-related drop outs in any completed study to date</td>
<td></td>
</tr>
</tbody>
</table>
Identical population to Phase 2

- IOP >24 mmHg
- ~ 360 patients treated for 12 weeks

Three trabodenoson doses:
- 3.0% OU QD* (1000 mcg)
- 4.5% OU BID (1500 mcg)
- 6.0% OU QD* (2000 mcg)

Placebo controlled
- Statistical comparator

Timolol 0.5% OU BID
- Internal control
- Not part of statistical comparison

* Drops are administered BID, one active trabodenoson QAM and placebo QPM to maintain masking
## Phase 3 Monotherapy Development Program

<table>
<thead>
<tr>
<th>Studies</th>
<th>MATrX-1</th>
<th>MATrX-2</th>
<th>MATrX-3 - LTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Adult with OHT or POAG; off all meds; baseline IOP ≥ 24mm Hg</td>
<td>Same as MATrX-1</td>
<td>Same as MATrX-1, without IOP lower limit</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>1000mcg (3.0%); 2000mcg (6.0%) QD; 1500mcg (4.5%) BID delivered to both eyes</td>
<td>Selected from MATrX-1</td>
<td>Selected from MATrX-1</td>
</tr>
<tr>
<td><strong>Treatment Duration</strong></td>
<td>12 weeks</td>
<td>Same as MATrX-1</td>
<td>Up to 12 months</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Superiority vs. placebo 4 time points during day Weeks 4, 6, 12</td>
<td>Same as MATrX-1</td>
<td>Safety</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 300 subjects at 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 100 subjects at 12 months</td>
</tr>
<tr>
<td><strong>Internal Control</strong></td>
<td>Timolol</td>
<td>Same as MATrX-1</td>
<td>Same as MATrX-1</td>
</tr>
</tbody>
</table>
Adenosine, A₁R and Cytoprotection

- Adenosine A₁ receptor activation is neuroprotective in the retina and brain.¹-³
  - Decreased excitotoxicity – glutamate release and regulation of intracellular calcium²-⁴
  - Ischemic preconditioning (ischemia reperfusion) and increased survival with oxidative stress⁵-⁹
  - Modulation of cellular metabolism may reduce energy needs¹⁴, ⁹-¹⁰
  - Adenosine acts in an autocrine and paracrine manner via the A₁R so effects are transferable surrounding cells¹¹

- Trabodenoson, as a highly selective A₁R agonist, may reduce excitotoxicity, induce ischemic preconditioning and modulate metabolism and contribute to increased neuronal survival

## Inotek/Trabodenoson Summary

### MOA/Target
- New target and new sites in the eye (TM, Ciliary Body and Retina)
- Highly selective adenosine mimetic targeting the $A_1$ receptor
- Improved outflow facility lowers and stabilizes IOP

### Pre-Clinical and Clinical Data
- Efficacy – increasing with dose/time (higher doses in Phase 3)
- Safety – Good ocular tolerability, no systemic effects in Phase 1 + 2
- Cytoprotective potential – preclinical data and adenosine biology

### Ongoing Development
- Monotherapy, adjunctive therapy and fixed dose combination
- Trabodenoson may give doctors another option in OHT and POAG
- Neuroprotection in preclinical development
- Monotherapy NDA planned 2018
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