Investor Q&A re: OTI-2024/Trabodenoson

Q1: *I understand that Trabodenoson had reached Phase III clinical trials in humans and then failed as it couldn't beat the placebo endpoint. I think this happens with a lot of drugs, so at least you know at a minimum they have safety in place, and all the documentation to back the primary therapeutic for human use.*

A: The prior Phase 3 clinical trial failed due to the use of an incorrect dose (4–10x higher than optimal), which stemmed from a misunderstanding of the drug's mechanisms of action. (Reference: Qiu TG. Trabodenoson on trabecular meshwork rejuvenation: a comprehensive review of clinical data. Expert Opin Investig Drugs. 2021 Mar;30(3):227-236.)

Details: Trabodenoson has a rare and unique dual action as an IOP-lowering agent (via a rapid-onset, bell-shaped dose-response curve) and as an MMP therapeutic with neural protection via IOP normalization. The prior Phase 3 trial focused solely on IOP lowering at a 3-month endpoint using doses of 3% QD, 4.5% BID, and 6% QD. However, the 6% QD dose demonstrated long-term MMP benefit, shown through a unique IOP pattern behavior of incremental IOP improvement over 12 weeks. This pattern was reproducible in Phase 2 trials at a lower 1.5% BID dose.

Q2: What does OTI plan to do differently?

For planned Phase 3 pivotal trial, OTI has defined the optimal dose of 1.5% BID, which will ensure both rapid IOP reduction and MMP mediated therapeutic benefit to achieve "synergistic" effects with maximal clinical outcomes.
With the optimal dose, we plan to have two primary endpoints to support two different indications: IOP reduction @ 3 months, and hVF readout @ 16 months. FDA has tentatively agreed OTI's Ph3 design with the hVF @ 12-18 months (ref: FDA Type D meeting minutes).

Either indication gets approval, OTI-2024 (1.5%) will be able to use for treating poor responders, refractory glaucoma, steroid induced glaucoma, uveitis glaucoma and primary angle closure glaucoma (acute onset) as well as other ECM pathologies, for which there is no effective treatment, currently.

Q3: What data do you have to ensure success this time? Or what kind of scientific data/proof do they have?

a) For the 3-month IOP lowering endpoint- evidence: Trabodenoson given at 1.5% BID led to 6-7mmHg reduction at day 28 in the Ph2 dose escalation monotherapy study (J Myers et al. J Ocul Pharmacol Ther. 2016). The primary endpoint will be a non-inferiority to timolol, highly repeatable!

b) For the 16-month HVF endpoint:

Evidence 1: 20-month Durysta Ph3 clinical trials (by J Barcharach et al) showed positive hVF results with p=0.037 at 12-month endpoint compared to Timolol. This positive hVF readout is the result of Durysta derived MMP therapeutic leading to IOP normalization (Re: R Weinreb Ph3b study). Removing the random spikes led to a better visual outcome.

Evidence -2: Trabodenoson (given at 1.5% BID) delivers MMP effectively in glaucoma patients including poor responders (prior Phase 2 study results): In prior Phase 2 monotherapy and add-on to Latanoprost poor responders, Trabodenoson (1.5% BID) demonstrated the unique IOP improvement profile leading to dosing switch (unique) at 4-8 weeks post treatment, underpinning the MMP on Tissue rejuvenation towards IOP normalization process, which was not recognized by Inotek Pharma before. The pitfall was that prior Ph2 studies ran too short (3 months), whereas MMP effect is a slow and accumulative mode. Ref: G Qiu, Expert Opin Investig Drugs. 2021 Mar;30(3):227-236.

Q4: What are the clinical benefits of MMP therapy? Or how do you measure MMP benefits in patients?

A: MMP therapy enables IOP normalization, a disease free IOP "drug holidays," reduced the number of medications (eye drops) and replace high risky invasive surgeries. These effects have been demonstrated in Durysta (Allergan) and iDose (Glaukos). Dosing switch (by Trabodenoson eye drops) is a precursor of IOP drug holiday.

FDA recognized biomarker to measure MMP benefit is HVF (Humphrey visual field) functional test, this will take 16 months (estimated) by MMP eye drops.

The FDA-recognized biomarker for MMP therapeutic benefit is the hVF (Humphrey Visual Field) test, which requires approximately 16 months to achieve statistical difference of the visual field preservation using OTI-2024 (1.5% eye drops), compared to Timolol in a superiority study.

Q5: As you reposition the compound as a new MMP agent, is there something transformational to glaucoma patient care?

OTI-2024/MMP therapy is a paradigm shift in glaucoma. It solves the pressing problems faced by glaucoma surgeons and patients: it treats poor responders and refractory glaucoma; 2) it solves poor patient compliance; 3) it has the potential to stop this unstoppable disease (vision deterioration); 4) it reduces treatment burden to one medication as maintenance. Currently glaucoma patients need 3-4 different medications (drops), multiple surgeries and lasers, none stops the disease progression. With OTI-2024, about 80-90% glaucoma patients may only need one medication to maintain their sight health.

Future: MMP platform therapy for glaucoma: Durysta and iDose deliver MMP therapy (Temporary) but at One time due to sight threatening side effects (cornea damage). SLT laser also works via MMP mechanism but limits to early stage glaucoma. OTI-2024/MMP therapy has superiority clinical safety and MMP-14 potency; it has the potential to Stop or reverse the disease progression by repairing the tissue damage that causes glaucoma blindness.

As the First curative therapy, OTI-2024 has the potential to replace prostaglandin market dominance (60%) in the past 30 years!