INTERIM RESULTS OF A DOSE ESCALATION STUDY OF NT-503 ENCAPSULATED CELL THERAPY FOR THE TREATMENT OF CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION

A Loewenstein1, H Quiróz Mercado2, JL Guerrero Narango3, S Rojas4, A Santos5, JS Altamirano5, Y Morales6, C Johnson7
1. Tel Aviv Medical Center, Tel Aviv, Israel; 2. Denver Health Medical Center, Denver, CO, United States; 3. Asociación para evitar la ceguera en Mexico, Coyocan, Mexico; 4. Hospital de la Luz, IAP Mexico City, Cuernavaca, Mexico; 5. Centro de Retina Medica y Quirurgica, Zapopan, Mexico; 6. Instituto de Ojos Videuri, Monterrey, Mexico; 7. Neurotech Pharmaceuticals Inc., Cumberland, RI

PURPOSE
Intravitreal therapies targeting VEGF led to a paradigm shift in the treatment of neovascular AMD.1 However, the risk of rare but serious adverse events resulting from the procedure, coupled with the significant logistical and financial burden of monthly visits to a retinal specialist, have limited efforts to decrease injection frequency.2 Overall, decreasing treatment frequency to quarterly or “as needed” regimens has not shown to be as effective as maintaining vision in some patients. Moreover, recent studies of the “real world” frequency of anti-VEGF injections have demonstrated that some patients are being dosed much less frequently and therefore, may not experience the visual benefits seen in pivotal studies.3 Even with recent labeling changes to be dosed much less frequently and therefore, may not experience the frequency of anti-VEGF injections have demonstrated that some patients are maintaining vision in some patients. Moreover, recent studies of the “real world” setting of neovascular AMD.1 However, the risk of rare but serious adverse events during a brief procedure and is easily reversible, if necessary.

The ECT utilized in this dose-escalation study contains NT-503, a soluble VEGF receptor (sVEGFR) fusion protein, which has an in vitro binding affinity similar to aflibercept and is 100-fold more potent than ranibizumab in VEGF neutralization. Preclinical studies have shown a 95% reduction in CNV lesion size in a rodent model after a single injection of NT-503, as well as efficacious release rates and continuous steady state delivery of NT-503 over 18 months.

This is an ongoing Phase 2, open-label, dose-ranging, prospective, non-randomized, multicenter, pilot study conducted at 5 sites in Mexico and 4 sites in South Africa. The purpose of this study is to evaluate the safety and efficacy of NT-503 ECT in the treatment of CNV associated with AMD.

METHODS
Subjects with active subfoveal CNV associated with AMD were enrolled in two arms. Subjects in the first arm received a single NT-503 ECT implant (releasing 2.0-2.5 µg/d of sVEGFR), while subjects in the second arm received either (1) a single implant with a pre-implant loading injection of ranibizumab (and a second implant if response was adequate after 2 months) or (2) two initial NT-503 ECT implants (releasing 4.0-5.0 µg/d of sVEGFR) without a pre-implant ranibizumab loading injection. Follow up visits occurred for 12 months after which, subjects were followed every 4 months up to 2 years.

Rescue therapy with ranibizumab was permitted if it was at least 4 weeks after implantation, a subject experienced a 10-letter drop in best-corrected visual acuity (BCVA) and a 100-µ increase in central retinal thickness (CRT) on spectral domain OCT or, if in the opinion of the investigator, rescue therapy was warranted. The mean number of rescue injections and the number of subjects requiring rescue therapy were assessed.

The main outcome measures include ETDRS BCVA and CRT measurements from registered sd-OCT images read by masked graders at the Duke Reading Center. Safety was evaluated through an examination of adverse events, clinical laboratory findings, symptoms of immune disorders or allergy, and stroke, cardiac arrest, or thrombosis.

RESULTS
A total of 47 subjects have been enrolled. In the per protocol population, 26 treatment-naive subjects received a single ECT implant (~2.0-2.5 µg/d of sVEGFR) and 21 subjects received two implants (4.0-5.0 µg/d of sVEGFR). 7 of whom were previously treated with anti-VEGF injections. The mean age was 74.6 years and 29 subjects were female.

The baseline CRT in the single implant group was 465 µm (range 282-800 µm). The baseline CRT in the double implant group was 462 µm (range 218-897 µm). NT-503 ECT demonstrated a clinically significant improvement in central retinal thickness at 20 months (Figure 3).

In the single implant group, baseline BCVA was 52.8 letters (SD 7.9 letters). In the double implant group, baseline BCVA was 50.0 letters (SD 10.7). Subjects with double ECT 503 implants (~4.0-5.0 µg/d of sVEGFR) demonstrated a clinically significant improvement in visual acuity at 20 months (Figure 4).

CONCLUSION
NT-503 ECT appears to be safe and well tolerated. A clear dose response was observed for all efficacy parameters. Evidence of a clinically meaningful reduction in macular thickening and improvement in vision were observed in patients who had double the exposure to NT-503 with two ECT implants. This study provides preliminary evidence for the long-term therapeutic potential of NT-503 ECT.

A next generation ECT implant, with approximately twice the output of sVEGFR (~8.0-12 µg/d), is currently being studied in a Phase 1 clinical trial. The safety and tolerability of the optimized NT-503 ECT, as well as its efficacy compared to intravitreal aflibercept during every 8 weeks, will be evaluated in patients with recurrent CNV secondary to AMD.

Figure 4. Median Change (+/- SEM) in ETDRS Visual Acuity Data censored for missed visit and all subsequent visits for patients receiving rescue