Title: Modulation of Macrophages and Complement Dysfunction in Geographic Atrophy utilizing Sialic-acid Coated Nanoparticles.

Purpose: Both the cellular and non-cellular components of the innate immune system have been implicated in the pathophysiology of age-related macular degeneration (AMD). Inhibition of the complement system has been shown to decrease the rate of progression of geographic atrophy in randomized clinical trials. However, the therapeutic effect has been modest, and some patients have converted to the neovascular form of AMD. We utilize a novel therapeutic strategy to address chronic inflammation via the body's own self recognition system on immune cells. Our therapeutic molecule (AVD-104) is a glycan (sialic-acid) engineered nanoparticle exhibiting dual functions. It directly modulates the self-pattern recognition receptors on immune cells called Siglecs (**s**ialic-acid binding **i**mmuno**g**lobulin-like **lec**tins) thus dampening the inflammatory activity of these immune cells (Macrophages & Microglia). It also enhances the activity of complement factor H to down-regulate the alternative complement cascade. We have previously shown in-vitro data confirming the anti-inflammatory effect of AVD-104.

Methods: AVD-104 was injected intravitreally (IVT) in humanized Siglec 11 transgenic mice to assess efficacy in both the bright light damage (BLD) model (n=15 eyes) and the laser induced choroidal neovascularization (CNV) model (n=21 eyes). In the BLD model, animals were given an IVT injection of AVD-104 one day before exposure and the outer nuclear layer (ONL) and tumor necrosis factor-**α** (TNF-**α**) levels in the retinal pigment epithelium (RPE)/choroid were examined 7 days later. In the laser CNV model animals were given an IVT injection of AVD-104, lasered on the same day, and examined 8 days later.

Results: There was a dose dependent preservation of the ONL (p value < 0.01) and reduction in TNF-**α** levels ($p < .0001$) in the BLD animals treated with AVD-104. In the laser CNV mice, there was a dose dependent reduction in the size of the CNV lesion and reduced C5b-9 complement deposition with AVD-104 treatment.

Conclusions: AVD-104, a novel sialic-acid coated nanoparticle has shown a statistically significant beneficial effect in reducing inflammatory retinal damage in two different animal models and has previously been shown to be safe in 3 species including non-human primates. A Phase 2 Human Clinical Trial for patients with AMD will begin in Q2' 2023.