One Sentence Objective: Inhibition of the innate immune system with an engineered glycan (sialic-acid) nanoparticle is effective in reducing retinal degeneration in two animal models of age-related macular degeneration (AMD) without significant safety signals and a phase 2 clinical trial in geographic atrophy is planned.

Title: Modulation of Macrophages and Complement Dysfunction in Nonexudative AMD utilizing Novel Sialic-acid Coated Nanoparticles.

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Purpose: Both the cellular and non-cellular components of the innate immune system have been implicated in the pathophysiology of AMD. Inhibition of the complement system has been shown to decrease the rate of progression of geographic atrophy (GA) in randomized Phase 3 clinical trials. However, the therapeutic effect has been modest, and a significant number of patients have converted to the neovascular form of AMD. A novel therapeutic strategy to address chronic inflammation via the body's own self recognition system on immune cells was explored using an engineered glycan (sialic-acid) nanoparticle (Aviceda Therapeutics, Cambridge, MA) with dual therapeutic functions. It directly modulates the self-pattern recognition receptors on overly activated retina immune cells (macrophages & microglia) called Siglecs (**s**ialic-acid binding **i**mmuno**g**lobulin-like **lec**tins) thereby dampening the inflammatory activity of these immune cells and repolarizing them to the resolution state. It also enhances the activity of complement factor H, a key regulator for complement cascade, to downregulate the alternative complement cascade.

Methods: AVD-104 was injected intravitreally (IVT) in two doses 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 bright light exposure and the outer nuclear layer (ONL) architecture 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* < 0.0001*)* in the BLD animals treated with AVD-104 compared to controls. In the laser CNV mice, there was a dose dependent reduction in the size of the CNV lesion and reduction of C5b-9 deposition (terminal membrane attack complex) with AVD-104 treatment compared to controls. The drug was well-tolerated in both studies and the safety profile was excellent at the two tested doses without any significant safety signals seen.

Conclusions: AVD-104, a novel sialic-acid coated nanoparticle, has shown a statistically significant beneficial effect in reducing inflammatory retinal damage in two

different well-established ocular animal models of AMD and has previously been shown to be safe in 3 animal species, including non-human primates. A phase 2 human clinical trial for patients with AMD-related GA is planned to begin in Q1’ 2023.