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

ABSTRACT BODY:

Purpose: Studies indicate a prominent role of inflammation in the pathogenesis of age-related macular degeneration (AMD). Both the cellular and non-cellular components of the innate immune system have been extensively studied to understand the pathophysiology of the disease. Inhibition of the complement system has recently been shown to decrease the rate of progression of geographic atrophy in randomized late 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 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, a novel sialic-acid (glyco) coated nanoparticle.-.

Methods: AVD-104 was injected intravitreally (IVT) in 40 non-human primates (NHP) to assess safety. Animals were followed for 28 days with clinical examinations, optical coherence tomography (OCT), and electroretinography (ERG). They were then euthanized for histopathology. A severe retina degeneration mouse model (bright light damage (BLD)) was used to determine in-vivo efficacy. Animals were given an IVT injection of AVD-104 one day before exposure and eyes were examined 7 days later.

Results: There were no significant structural or functional changes in NHPs following IVT injection of AVD-104 using 3 different escalating doses. There was a significant decrease in the loss of outer nuclear layer (ONL) thickness (20-25%) with p value of 0.01-.009 in treated animals compared to controls.

Conclusions: A novel sialic-acid coated nanoparticle, previously shown in in-vitro models to reduce pro-inflammatory cytokines (TNF-α, IL-1b, IL-6, IL-10) and increase complement factor H activity, is safe and very well-tolerated in NHP eyes. It also demonstrates a significant decrease in the retina and outer nuclear layers degeneration associated with the mouse BLD model. A Phase 2 Human Clinical Trial for patients with AMD planned in Q1' 2023.