**Key Takeaways**
- Results from in vitro assays demonstrate VRDN-001 and VRDN-003 provide indistinguishable and near-complete inhibition of IGF-1 binding and IGF-1R signaling.
- Prior studies with VRDN-001 have shown robust increases in IGF-1 levels in healthy volunteers and patients with TED as well as rapid, marked improvements in TED symptoms in a small cohort of TED patients (ARVO oral #5432).
- Given that VRDN-001 and VRDN-003 antagonist properties are the same, VRDN-003 should achieve similar in vivo pharmacodynamics and efficacy.

**Introduction**
Clinical and preclinical studies have confirmed IGF-1R antagonism can reduce the inflammation and proptosis that occur in TED. VRDN-001, a full antagonist antibody to IGF-1R with subnanomolar affinity, is under development for the treatment of TED. VRDN-003 is a next-generation, half-life extended version of VRDN-001 designed to optimize subcutaneous administration via a self-administered pen. Given that VRDN-003 is identical to VRDN-001 except for the half-life extension modification, we assessed whether they have the same in vitro antagonist characteristics.

**Methods**
- Antibody binding to IGF-1R: Antibody binding to endogenously expressed cell surface IGF-1R was characterized in human ocular choroid fibroblasts (HOCFs).
- Inhibition of ligand binding: Dose responses of inhibition of biotinylated IGF-1 binding to IGF-1R-expressing FreeStyle™ 293-F cells were assessed by flow cytometry.
- Antagonist properties: Dose responses of inhibition of IGF-1R and AKT phosphorylation (endpoints of IGF-1-mediated signaling) were assessed in HOCFs.
- Representative experiments are shown for each endpoint.

**Antibody Binding to IGF-1R**

**Antibody Antagonism of IGF-1R Signaling**

**Antibody Inhibition of Ligand Binding to IGF-1R**

**Therapeutic Implications**
- The similar antagonist characteristics for VRDN-003 vs VRDN-001 shown here suggest VRDN-003 should show similar clinical effect to that observed in the VRDN-001 phase 2 proof-of-concept study in patients with active TED (ARVO oral #5432).
- VRDN-003 pharmacodynamic parameters observed in cynomolgus monkeys demonstrated VRDN-003 half-life was twice as long as VRDN-001 half-life (ARVO poster #4043), reinforcing its potential for subcutaneous self-administration.

References:

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**Figure Images**
- Binding to IGF-1R-expressing HOCF cells
- Inhibition of IGF-1R phosphorylation (proximal signaling)
- Inhibition of AKT phosphorylation (distal signaling)