VRDN-002, a Next-Generation Half-life Extended Antagonist Antibody to IGF-1 Receptor for Thyroid Eye Disease (TED): Safety and Pharmacokinetic/Pharmacodynamic (PK/PD) Results in Healthy Volunteers

KEY TAKEAWAYS
In healthy volunteers (HVs) treated with a single infusion of VRDN-002 at 3, 10, or 20 mg/kg:
- All doses were generally well tolerated.
- VRDN-002 elicited rapid and sustained increases in IGF-1 serum levels, a biomarker for target engagement and IGF-1R inhibition.
- VRDN-002 displayed a half-life of up to 43 days and elicited maximal target engagement as early as 15 days after dosing, with serum IGF-1 levels reaching 2-3-fold above baseline.

INTRODUCTION
- VRDN-002 is a next-generation, half-life extended antagonist antibody to IGF-1R under development for the treatment of TED.
- TED is a debilitating autoimmune disorder associated with orbital inflammation, proptosis, diplopia, and soft tissue changes.
- Clinical and preclinical evidence indicates a central role for IGF-1R inhibition in reducing inflammation and proptosis in TED.
- We present safety, PK/PD, and modeling results from our phase 1 clinical trial evaluating VRDN-002 dosed at 3, 10, or 20 mg/kg.

STUDY DESIGN AND PARTICIPANTS
- 12 adult HVs were randomized to receive a single IV infusion of placebo or VRDN-002; mean age was 55 years (range: 29 to 72); 7 were male and 5 female.
- One HV (20 mg/kg) was withdrawn because of their protocol noncompliance and was followed for safety through Day 29.
- Adverse events (AEs) and PK and PD parameters (IGF-1 serum levels) were assessed at regular intervals through 85 days.

SAFETY RESULTS
- 4 HVs had 4 AEs, all transient and mild in severity.
- There were no withdrawals due to AEs.
- There were no serious AEs or cases of hyperglycemia, muscle spasms, infusion reactions, or hearing impairment.

PHARMACOKINETIC RESULTS
- VRDN-002 has extended half-life up to 43 days in HVs:
  - 3 mg/kg
  - 10 mg/kg
  - 20 mg/kg

- Compared with standard Igg antibodies including VRDN-001 (10-11 days), VRDN-002 half-life is extended ~4x.
- Clearance was displayed at 3 mg/kg, consistent with saturable elimination kinetics associated with target-mediated drug disposition.

PHARMACODYNAMIC RESULTS
- VRDN-002 increased IGF-1 serum levels in HVs:
  - Placebo
  - 3 mg/kg
  - 10 mg/kg
  - 20 mg/kg

- Mean IGF-1 serum levels across the VRDN-002 groups increased from 137–148 ng/mL at baseline to 350–429 ng/mL after 15 days following 1 infusion.
- IGF-1 serum levels started to increase within a day and reached 2–3-fold above baseline by Day 15 for all VRDN-002 doses; they remained elevated through Day 85 for the 10 mg/kg and 20 mg/kg groups.

PK MODELING FOR POTENTIAL SC ADMINISTRATION
- A 2-compartment model with linear and Michaelis-Menten clearance was employed to estimate Cmax and exposure for a range of dosing regimens.
- VRDN-002 yields exposures enabling SC administration when dosed at 300 mg following a 600-mg loading dose at Q2W or Q4W intervals.

THERAPEUTIC IMPLICATIONS
- The robust PD response with a favorable safety profile suggests VRDN-002 could be an effective anti-IGF-1 antibody for the treatment of TED.
- VRDN-002’s half-life extension (up to 43 days) could enable therapeutic concentrations to be achieved with low-volume SC injection via self-administered pen, potentially decreasing the treatment burden for patients with TED.

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