Immune-Stimulants and Immune Modulators

**TNRX-257, A MULTIFUNCTIONAL LAG3 ANTAGONIST AND CONDITIONAL IL2Rγ/β PARTIAL AGONIST, IS A NOVEL IMMUNE STIMULANT WITH HIGH DOSE TOLERABILITY IN NON-HUMAN PRIMATES**

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**Background** Interleukin-2 (IL-2) is a driver of T and NK cell proliferation and activation, and has produced remarkable clinical efficacy in a few cancer patients. However, its clinical use is limited by its narrow therapeutic index, and potentially by its preferential stimulation of immune suppressing Treg cells. TNRX-257, a novel multi-specific LAG3 antagonist with unique LAG3-conditional partial agonism of the IL2Rγ/β receptors, was developed using Tentarix’s propriety Tentacles™ platform, which is based on fully human, stabilized antibody VH domains. LAG3 expression is restricted to antigen-experienced and tumor-reactive immune cells with little expression on peripheral PBMC or immune cells in normal tissues. Thus, TNRX-257 is anticipated to drive the proliferation of this tumor-antigen positive pool of cells, while minimizing the dose limiting toxicity seen in the pre-clinical models and human clinical trials, as well as the bias towards Treg proliferation seen with WT IL-2.

**Methods** TNRX-257 was assessed for the affinity for human and cynomolgus LAG3, IL2Rγ and IL2Rβ affinities by Bio-Layer Interferometry, and by cytometry for binding and pSTAT5 induction on CD3/CD28 activated human and cynomolgus monkey PBMCs. To determine the pharmacokinetics and pharmacodynamics of TNRX-257, the molecule was dosed intravenously at 2 dose levels, 2.5mg/kg or 9mg/kg, to 2 cynomolgus monkeys each, and blood was harvested at multiple timepoints over 14 days for analysis. Pharmacokinetics was determined by ELISA, cytokine release by MSD assays, and Ki67 positivity of NK and T cells by cytometry.

**Results** TNRX-257 was shown to have equivalent affinities for human and cynomolgus LAG3, IL2Rγ and IL2Rβ affinities by Bio-Layer Interferometry, and by cytometry for binding and pSTAT5 induction on CD3/CD28 activated human and cynomolgus monkey PBMCs. To determine the pharmacokinetics and pharmacodynamics of TNRX-257, the molecule was dosed intravenously at 2 dose levels, 2.5mg/kg or 9mg/kg, to 2 cynomolgus monkeys each, and blood was harvested at multiple timepoints over 14 days for analysis. Pharmacokinetics was determined by ELISA, cytokine release by MSD assays, and Ki67 positivity of NK and T cells by cytometry.

**Conclusions** These data show that TNRX-257 has pharmacokinetics, bioactivity and a unique safety profile that support its clinical development for treating multiple cancer indications.

**Ethics Approval** This study was approved by Labcorp institution’s IACUC Board; study number 8486120

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