Rosnilimab, a Novel PD-1 Agonist Monoclonal Antibody, Inhibits Peripheral T Cell Proliferation and Cytokine Secretion and Reduces Circulating PD-1 High Expressing CD4 and CD8 T Cells: Results from a Phase 1 Healthy Volunteer Clinical Trial

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ABSTRACT

Background/Purpose: PD-1 agonists have shown promise in multiple autoimmune diseases, and modified Fc signaling can lead to decreased T cell dependence by targeting natural killer (NK) cell-mediated killing. Rosnilimab is a PG1 monoclonal antibody (mAb) that is a modified CD28 agonist, which engages the PD-1 signaling pathway to enable tight immune synapse formation and modulate immune cell function. The primary objective of this single ascending dose (SAD) and multiple ascending dose (MAD) study was to evaluate the safety, tolerability, and pharmacodynamic (PD) effects of single (SAD) and multiple (MAD) doses of rosnilimab administered IV or SC in healthy volunteers.

Safety, Tolerability, and PK: 144 subjects were enrolled (90 rosnilimab, 30 placebo (PBO)). Treatment cohorts were enrolled sequentially in each SAD/MAD phase. Rosnilimab was well tolerated with no dose-limiting toxicities or deaths. Two serious adverse events (SAEs) were reported in the SAD (malignant mesothelioma and axillary lymphadenopathy) and MAD phases (pancreatitis in a PBO cohort). Transient full receptor occupancy (RO) at doses starting in low to medium SC and IV doses was demonstrated favorable safety, PK, and exposure nearly dose proportional; consistent with PK. Transient full RO at doses starting in low to medium SC and IV doses was demonstrated. Transient full RO is significantly associated with a reduction in PD1-expressing T cells and associated cytokine signaling. Safety, Tolerability, and PK: Rosnilimab was well tolerated with no dose-limiting toxicities or deaths. Two serious adverse events (SAEs) were reported in the SAD (malignant mesothelioma and axillary lymphadenopathy) and MAD phases (pancreatitis in a PBO cohort). Transient full receptor occupancy (RO) at doses starting in low to medium SC and IV doses was demonstrated. Transient full RO is significantly associated with a reduction in PD1-expressing T cells and associated cytokine signaling.

RESULTS

Safety, Tolerability, and PK: 144 subjects were enrolled (90 rosnilimab, 30 placebo (PBO)). Treatment cohorts were enrolled sequentially in each SAD/MAD phase. Rosnilimab was well tolerated with no dose-limiting toxicities or deaths. Two serious adverse events (SAEs) were reported in the SAD (malignant mesothelioma and axillary lymphadenopathy) and MAD phases (pancreatitis in a PBO cohort). Transient full receptor occupancy (RO) at doses starting in low to medium SC and IV doses was demonstrated. Transient full RO is significantly associated with a reduction in PD1-expressing T cells and associated cytokine signaling.

Primary Objectives: Safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of rosnilimab as an injectable (PBO), rosnilimab/PBO were administered IV or SC in SAD and SC is MAD

Other Assessments: Pharmacodynamic (PK) Translational pharmacodynamics (TPD), including PD-1 receptor occupancy (RO), reduction in various T cell populations and associated cytokine signaling.

TPD for SAD Cohorts: PD-1<sup>+</sup> or PD-1<sup>+</sup> Reduction

- PD-1<sup>+</sup> expressing T cells were reduced by >100% at Day 15 following full RO administration in SC Dose 02 (Figure 3A)
- Data from all dosed subjects from SC Dose 2 merged into one USNE plot showing PD-1<sup>+</sup> mAb cells from the CD8+ T cells released (red circle) at Day 15 following administration in SC Dose 2 (400 mg) (Figure 3C)

REFERENCES