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

Rosnilimab (rosnilimab) is an agonist PD-1 monoclonal antibody designed to bind with high affinity to PD-1 and, through this engagement, induce T cell activation and proliferation. Rosnilimab was studied in previously healthy volunteers to assess its safety, tolerability, PK, and immunogenicity. Rosnilimab was well tolerated, with no serious adverse events (SAEs), no increased risk of infections or carcinogenic events, and no increased incidence of localized or any other adverse events compared to placebo. Pharmacokinetic (PK) analysis showed mean reduction up to 90% in the production of cytokines IL-2, IFN-γ, IL-10 and IL-17 as well as dampening of the inflammatory cycle and restoration of immune balance. Safety, tolerability, and PK

BACKGROUND/PURPOSE

Programmed cell death protein 1 (PD-1), a T cell checkpoint receptor, functions to dampen inappropriate T-cell responses by inducing a negative signaling pathway when engaged with its ligand PD-L1. PD-1 is expressed preferentially on activated T cells, >80% of T cells in the periphery (Figure 1A), and a clinically validated target in the treatment of hematologic malignancies (5).

Rosnilimab, a PD-1 agonist, IgG1 isotype monoclonal antibody, binds to a membrane-proximal epitope of PD-1 to prevent ITIM-mediated T cell costimulation, to enable tight immune synapse formation (Figure 1B): – Depletes PD-1+ T effector cells (Teff) and T follicular/peripheral helper cells (Tfh/Tip) – Agonizes PD-1+ T effector cells

RESULTS

TPD for SAD Cohorts: PD-1+ T cells

TPD for MAD Cohorts: PD-1+ T cells

Figure 3A. FACS Plot of PD-1+ T Cells

Figure 3B. ISNE Plot Showing Reduction of PD-1+ T Cells

Figure 4. Tetanus Toxoid Recall

CONCLUSIONS

In this Phase 1 healthy volunteer study, rosnilimab was well-tolerated with no clinically significant safety signals and a favorable PK profile.

Receptor occupancy increased in a dose-dependent manner consistent with PK and sustained for at least 30 days.

Pharmacodynamic activity resulted in rapid and sustained reduction in the frequency and functional activity of PD-1+ T cells for >30 days.

Rosnilimab targets PD-1+ T cells, prevalent in inflamed tissue and in the periphery, and may have the potential to deliver differentiated efficacy and safety by broadly impacting pathogenic drivers in systemic autoimmune and inflammatory indications, such as RA.

ACKNOWLEDGEMENTS

1. This work was supported by AnaptysBio, Inc.
2. Author disclosures: All authors are employees of AnaptysBio, Inc.

REFERENCES