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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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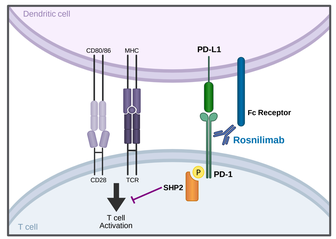
ABSTRACT

Background/Purpose: PD-1 pathway mutations increase human susceptibility to multiple autoimmune diseases, and insufficient PD-1 signaling can lead to dysregulated T cell responses. By targeting natural immune regulatory mechanisms to modulate immune cells driving disease, there is an opportunity to dampen the inflammatory cycle and restore immune balance. Rosnilimab is a PD-1 agonist antibody designed to inhibit activated T cells for the treatment of inflammatory diseases, including rheumatoid arthritis (RA). The primary objective of this first-in-human (FIH), healthy volunteer (HV) Phase 1 study was to assess the safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of rosnilimab. Other objectives included the assessment of pharmacokinetic (PK) profile, immunogenicity, and translational pharmacodynamic (TPD) endpoints (e.g. PD-1 receptor occupancy (RO), reduction in various T cell populations and associated cytokine signaling). **Methods**: This study was conducted at a single study center in the United States with 14 cohorts in SAD and 3 cohorts in MAD. Each cohort had 8 participants (6 active, 2 placebo (PBO)). Treatment cohorts were enrolled sequentially in each SAD/MAD phase. Intravenous (IV) and subcutaneous (SC) routes of administration were assessed in the SAD; SC route was assessed in the MAD. **Results:** A total of 144 participants were enrolled; 90 randomized to the active SAD cohorts, 18 to the active MAD cohorts, and 30 and 6 randomized to the SAD and MAD PBO cohorts, respectively. All participants were assessed for safety and PD. Rosnilimab was well tolerated, with no dose-limiting toxicities or deaths. Two serious adverse events (SAEs) were reported in the SAD (obstructive pancreatitis in a PBO-dosed participant; COVID-19 infection in a rosnilimab-dosed participant leading to discontinuation; unrelated to treatment). No SAEs were reported in the MAD. TPD activity was rapid with sustained reduction in quantity and functional activity of PD-1+ T cells. Conventional T (Tcon) cells in the periphery expressing PD-1 were reduced, on average through Day 30 in the SAD where full RO was sustained following rosnilimab dosing, by ~50% in both CD4+ and CD8+ subsets, in a dose-dependent manner and in correlation with RO. This reduction was maximized on PD-1 high expressing T cells, ~90% reduction relative to baseline. There was no significant impact on the overall total T cell, Tcon or regulatory T (Treg) cell numbers, thereby resulting in an observed bias in favor of Treg:Tcon cell ratio post-dosing. An antigen-specific functional T cell assay measuring ex vivo interferon-gamma release in response to antigen challenge was inhibited up to ~90% relative to baseline within 30 days following a single dose. Rosnilimab has a favorable PK profile consistent with full RO, a two-week half-life, and exposure nearly dose-proportional in both IV and SC dosing. **Conclusion**: Rosnilimab demonstrated favorable safety, PK, and TPD activity. These results demonstrate proof of mechanism in humans and support advancing rosnilimab into a phase 2b study in RA. AnaptysBio was the study sponsor.

BACKGROUND/PURPOSE

- Programmed cell death protein 1 (PD-1), a T cell checkpoint receptor, functions to down regulate activated T cells by inducing a negative signaling pathway when engaged with its ligand PD-L1[1,2]
- PD-1 is expressed preferentially on activated T cells, > 80% of T cells in the synovium and elevated in the periphery.[3,4] PD-1 is a clinically validated target in the treatment of rheumatoid arthritis (RA)[5]
- Rosnilimab, a PD-1 agonist, IgG1 isotype monoclonal antibody, binds to a membrane-proximal epitope of PD-1 together with Fc receptor-mediated crosslinking, to enable tight immune synapse formation **(Figure 1)**:
  - Depletes PD-1^{high} T effector cells (Teff) and T follicular/peripheral helper cells (Tfh/Tph)
  - Agonizes PD-1+ Teff
- Results are reported here from a first-in-human, healthy volunteer Phase 1 study of rosnilimab

Figure 1. Rosnilimab Proposed Mechanism of Action



Rosnilimab

- Depletes and agonizes PD-1+ T cells in inflamed tissue and in the periphery
- Does not block PD-L1 engagement
- Effector function is enabled via IgG1 isotype
- Potential to restore immune balance in numerous autoimmune and inflammatory indications

OBJECTIVES & ASSESSMENTS

Primary Objective:

- Safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of rosnilimab or placebo (PBO); rosnilimab/PBO were administered IV or SC in SAD and SC is MAD

Other Assessments:

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

RESULTS

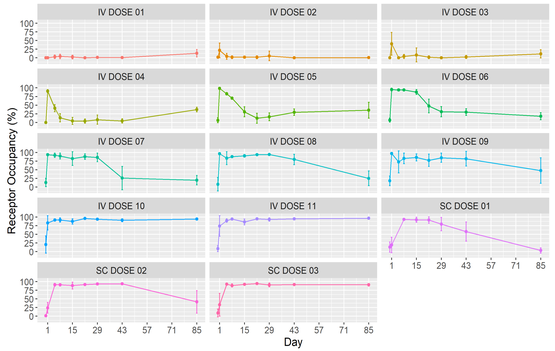
Safety, Tolerability, and PK

- 144 subjects were enrolled
  - SAD cohorts: 90 rosnilimab, 30 PBO
  - MAD cohorts: 18 rosnilimab, 6 PBO
- Rosnilimab was well tolerated and there were no dose-limiting toxicities or deaths
  - SAD cohorts: 2 unrelated SAEs (1 rosnilimab COVID-19 with study discontinuation; 1 PBO obstructive pancreatitis)
  - MAD cohorts: No SAEs
- No carcinogenic events observed; no increased risk of infections
- Favorable PK profile with a 2-week half-life, and nearly dose-proportional exposure in both IV and SC dosing
- SAD and MAD cohorts had similar results; only SAD cohort data are shown

TPD for SAD Cohorts: Receptor Occupancy (RO)

- RO increased in a dose-dependent manner; consistent with PK. Transient full RO at doses starting in low to medium SC and IV doses
- Onset of full RO as early as Day 1 for IV and Day 5 for SC; sustained for at least 30 days for most dose levels tested **(Figure 2)**

Figure 2. Rosnilimab Receptor Occupancy (RO)



TPD for SAD Cohorts: PD-1^{high} or PD-1+ Reduction

- PD-1^{high} expressing T cells were reduced by >90% at Day 15 following rosnilimab administration in SC Dose 02 **(Figure 3A)**
- Data from all dosed subjects from SC Dose 02 merged into one tSNE plot showing PD-1^{high} cells from the CD4 and CD8 T cells reduced (red circle) at day 15 postdose compared to predose, while not modulating the distribution of the other lymphocyte subsets **(Figure 3B)**
- Near complete reduction of PD-1^{high} expressing T cells following rosnilimab administration persisted for >30 days, with >90% reduction of PD-1^{high} T cells at day 5, and >50% reduction of PD-1+ T cells at day 5 from SC Dose 03 (400 mg) **(Figure 3C)**

Figure 3A. FACS Plot of PD-1^{high} & PD-1+ T Cells

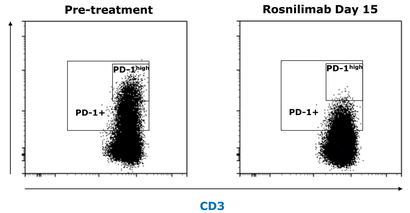


Figure 3B. tSNE Plot Showing Reduction of PD-1^{high} T Cells

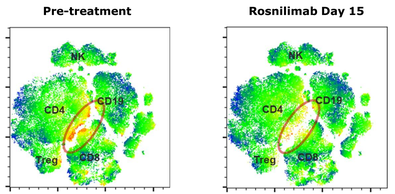
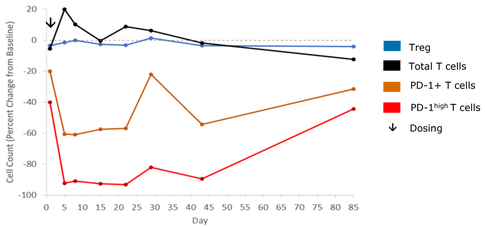


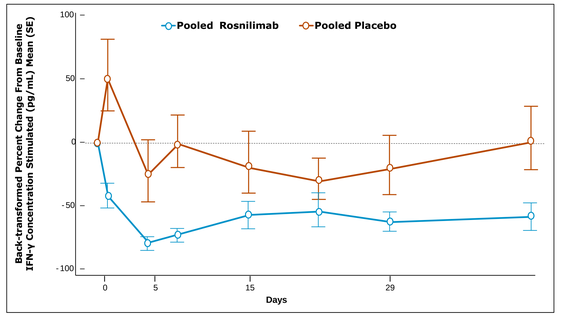
Figure 3C. Reduction of PD-1^{high} and PD-1+ T Cells After Single Dose of Rosnilimab



TPD for SAD Cohorts: PD-1^{high} or PD-1^{int} Reduction

- Mean reduction up to -92% of IFNγ in an *ex vivo* antigen-specific, subject-derived whole blood T cell assay consistent with reduction of PD-1+ T cells; response lasted for more than 30 days **(Figure 4)**

Figure 4. Tetanus Toxoid Recall



CONCLUSIONS

- In this first-in-human 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 stained reduction in the quantity 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 diseases, such as RA[3,4]
- Mechanistic data (see Parmley, et al. ACR2023 Poster 0086), these robust Phase 1 data and clinical validation of PD-1 agonism in RA[5] provide rationale for an ongoing global Phase 2 study of rosnilimab in RA patients (NCT06041269)

ACKNOWLEDGEMENTS

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