SU1784

Rosnilimab, a Novel PD-1 Agonist Monoclonal Antibody, Reduced T Cell Proliferation, Inflammatory Cytokine Secretion, and PD-1+ Expressing CD4 and CD8 T Cells: Results From a Phase 1 Healthy Volunteer Clinical Trial

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ABSTRACT

Background: Programmed cell death protein 1 (PD-1) is expressed on activated T cells and is a key co-inhibitory node in immune regulation. By targeting regulatory mechanisms to modulate immune cells driving disease, there is an opportunity to restore immune balance. Rosnilimab is a PD-1 agonist antibody designed to reduce T cell proliferation and inflammatory cytokine secretion and deplete PD-1high T follicular helper, T peripheral helper, and T effector cells. It is being studied for ulcerative colitis (UC), where PD-1+ T cells are prevalent in inflamed lamina propria (>40%) and the periphery. The primary objective of this healthy volunteer Phase 1 study was to assess the safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of rosnilimab. Findings from pharmacokinetic (PK) and pharmacodynamic (PD) assessments are summarized. **Methods:** This single-center study included 14 cohorts in SAD and 3 cohorts in MAD. Each cohort had 8 participants (6 active, 2 placebo [PBO]). Cohorts were enrolled sequentially in each phase. Intravenous (IV) and subcutaneous (SC) administration were assessed in SAD; SC route was assessed in MAD. **Results:** A total of 144 participants were enrolled; 90 to active SAD cohorts, 18 to active MAD cohorts, and 30 and 6 to SAD and MAD PBO cohorts, respectively. Rosnilimab was well tolerated with no dose-limiting toxicities or deaths. Two serious adverse events were reported in SAD (deemed unrelated to treatment) and 0 in MAD. PD-1 expressing cells were reduced by ~50% in both CD4+ and CD8+ subsets, in a dose-dependent manner and in correlation with full receptor occupancy (RO) through Day 30 in SAD. PD activity was rapid with sustained reduction in PD-1+ T cells, and ex-vivo stimulation resulted in reduced T cell functional activity. This reduction was maximized on PD-1high expressing T cells: ~90% reduction vs baseline. There was no significant impact on the overall total T cell or regulatory T (Treg) cell numbers, resulting in restoration of T cell composition to a less activated state and a positive shift in the Treg:Teff ratio. An antigen-specific functional T cell assay measuring ex vivo interferon-gamma release in response to antigen challenge was inhibited up to ~90% vs baseline and the response lasted for more than 30 days following a single dose. Rosnilimab had a favorable PK profile consistent with full RO, a 2-week half-life, and dose-proportional exposure in IV and SC dosing. **Conclusion:** Rosnilimab demonstrated favorable safety, PK, and PD activity. The role of PD-1 in UC pathophysiology coupled with these results and translational data, demonstrate proof of mechanism and support progression into a phase 2 study of rosnilimab in UC. (NCT06127043)

INTRODUCTION

Programmed cell death protein 1 (PD-1)

- Co-inhibitory checkpoint receptor that functions to downregulate activated T cells when engaged with its ligand PD-L1[1,2]
- PD-1 pathway mutations increase human susceptibility to multiple autoimmune diseases; insufficient PD-1 signaling can lead to dysregulated T cell responses (**Figure 1**)
- PD-1 agonism has achieved proof-of-concept in rheumatoid arthritis, which has a prominent role for PD-1+ T cells in the pathophysiology of disease

PD-1 expressed preferentially on activated Teff and Tfh/Tph cells mediating autoimmune pathology

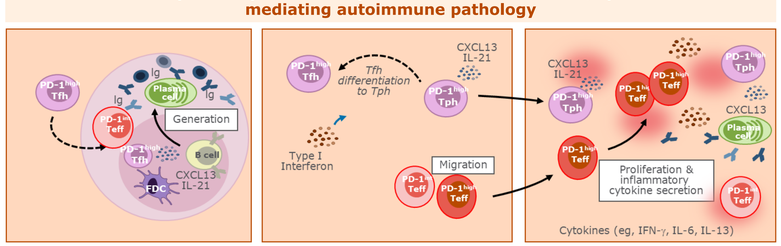

Figure 1. Adapted from Akiyama et al, Ann Rheum Dis, 2023.

Ulcerative Colitis & PD-1

- Checkpoint antagonists have transformed the treatment of many cancers. Frequent immune related adverse events include diarrhea and colitis suggesting these symptoms are regulated by dysfunctional checkpoint receptor signaling[3]
- PD-1+ T cells are highly inflammatory and activate multiple downstream pathways, which are clinically validated targets for the treatment of UC
- PD-1+ T cells are prevalent in inflamed lamina propria (>40%) and the periphery[4] and PD-1 pathway gene expression is dysregulated in UC tissues[5]
- Mayo clinical score, erythrocyte sedimentation rate, C-reactive protein all positively correlated with frequency of circulating Tfh cells in UC[6]
- Reduction of elevated PD-1^{high} Tph cells in both UC colon and periphery correlates with remission[7,8]

Rosnilimab (PD-1 agonist, IgG1 isotype antibody)

- Binds to a membrane-proximal epitope of PD-1 together with Fc receptor-mediated crosslinking, to enable tight immune synapse formation (**Figure 2**)
- Rosnilimab depletes PD-1^{high} T effector cells (Teff) and T follicular/peripheral helper cells (Tfh/Tph) and agonizes PD-1+ Teff

Objective

- To assess safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of rosnilimab in a Phase 1 healthy volunteer study

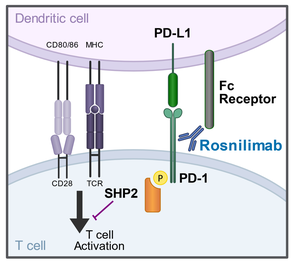

Figure 2. Proposed mechanism of action for rosnilimab

METHODS

Single-Center Study (N=144)

- SAD: IV and SC administration assessed in 14 cohorts of 8 participants each (6 active, 2 PBO)
- MAD: SC administration assessed in 3 cohorts of 8 participants each (6 active, 2 PBO)
- Cohorts enrolled sequentially in each phase

Translational Pharmacodynamics

- Non-competing labeled anti-PD1 antibody and rosnilimab were used to evaluate receptor occupancy
- T cell subsets were analyzed for PD-1 expression by flow cytometry and tSNE

  Flow cytometry gating strategy:

  Treg = lymphocytes → CD3+ → CD4+ → CD127 → CD25+

  Tcells = lymphocytes → CD3+ → CD4+ (Tcon CD127+/-, CD25-) & CD8+

  PD-1^{high} = lymphocytes → CD3+ → PD-1^{high} gate

  PD-1+ = lymphocytes → CD3+ → PD-1+ gate
- T cell function was evaluated by tetanus toxoid recall assay to evaluate IFN-γ secretion

RESULTS

Safety, Tolerability, and PK

- 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

Translational Pharmacodynamics: 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 3**)

RO Increased in Dose-Dependent Manner and Consistent with PK

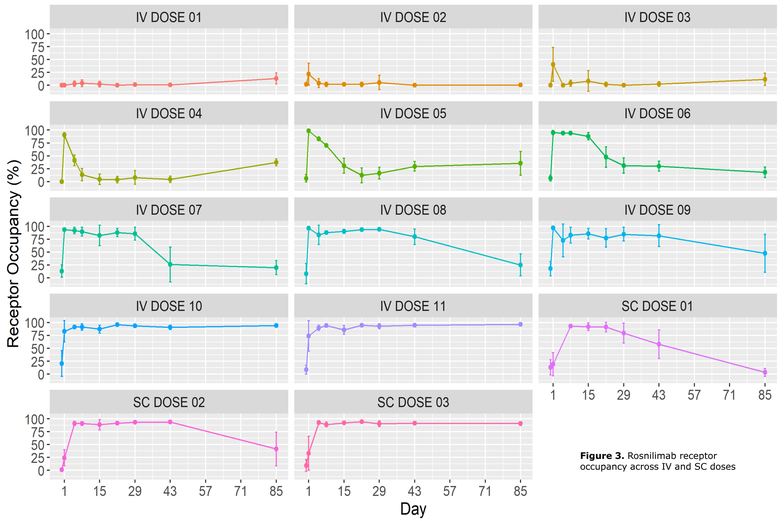

Figure 3. Rosnilimab receptor occupancy across IV and SC doses

RESULTS

Rosnilimab Depleted PD-1^{high} Pathogenic T cells without Modulating the Distribution of Other Lymphocyte Subsets

- PD-1^{high} expressing T cells were reduced by >90% at day 15 post-dose **(Figure 4A)**
- PD-1^{high} cells from the CD4 and CD8 T cells were reduced (red circle) at day 15 post-dose compared to pre-dose, while not modulating the distribution of the other lymphocyte subsets **(Figure 4B)**

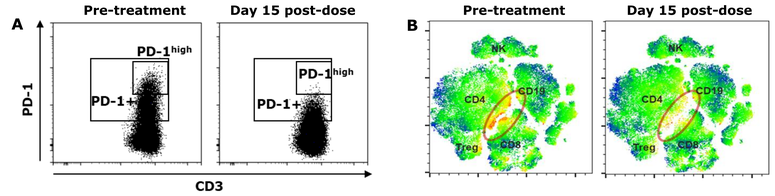

Figure 4. Reduction in PD-1^{high} expressing T cells 15 days following administration of rosnilimab evaluated by flow cytometry (A) and tSNE of merged data of all dosed subjects from SC Dose 02 (B)

Reduction in PD-1+ T cells and IFN-γ Production by T cells was Rapid and Durable, Lasting >30 days Following Rosnilimab Administration

- 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 total PD-1+ T cells at day 5 from SC Dose 03 (400 mg) (**Figure 5A**)
- Mean reduction up to -92% of IFN-γ in an ex-vivo antigen-specific T cell assay consistent with reduction of PD-1+ T cells; response lasted for more than 30 days (**Figure 5B**)

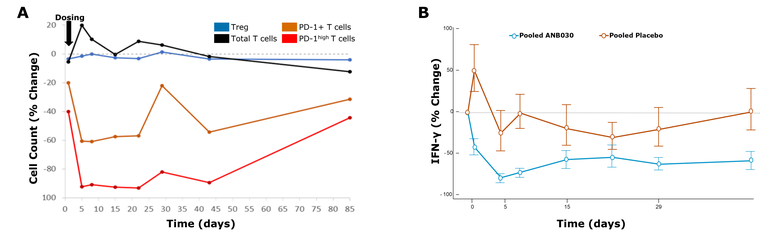

Figure 5. Reduction of PD-1 expressing T cells and IFN-γ over time following a single rosnilimab dose measured by FACS (A) and tetanus toxoid recall (B)

CONCLUSIONS

- Checkpoint agonism is a novel approach to UC treatment and rosnilimab is the first such therapy to be studied in UC
- In this Phase 1 healthy volunteer study, rosnilimab was well tolerated with no clinically significant safety signals and a favorable PK profile
- RO 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
- These data, combined with preclinical data demonstrating a prominent role for PD-1 in the pathogenesis of UC, support the rationale for evaluating rosnilimab in UC in an ongoing Phase 2 study (NCT06127043)
- Information on mechanistic data for rosnilimab (abstract 695) will be presented on Monday, May 20 at 11:15 am

ACKNOWLEDGEMENTS

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2. All authors are employees and shareholders of Anaptys
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