Rosnilimab, a Novel PD-1 Agonist Monoclonal Antibody, Demonstrated Modulation of Peripheral T cell Activity and Reduction of Circulating PD-1 high Expressing CD4 and CD8 T cells in a Phase 1 Healthy Volunteer Clinical Trial

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Abstract
Genetic studies have demonstrated that PD-1 pathway mutations increase human susceptibility to multiple autoimmune diseases and insufficient PD-1 signaling can lead to dysregulated T cell responses. Rosnilimab is a PD-1 agonist antibody designed to modulate activated T cells for the treatment of inflammatory diseases. Rosnilimab’s pharmacodynamic activity resulted in rapid and sustained reduction in the quantity and functional activity of PD-1+ T cells, which are known to be pathogenic drivers of inflammatory diseases. Conventional T (Tcon) cells expressing PD-1 were reduced, on average through Day 30 in single ascending dose cohorts where full receptor occupancy was sustained following Rosnilimab treatment, by approximately 50%, including in both CD4+ and CD8+ subsets, in a dose-dependent manner and in correlation with receptor occupancy. This reduction was maximized on high PD-1+ expressing Tcon cells, with approximately 85% reduction relative to baseline. Rosnilimab did not modulate total T cells, total Tcon cells, or total regulatory T (Treg) cells, resulting in a favorable shift in the ratio of PD-1+ Tcon cells to total Treg cells post-treatment. No effect was observed on any of the aforementioned cell types in placebo-dosed subjects. In addition, an antigen-specific functional T cell assay measuring ex vivo interferon-gamma released in response to antigen challenge, was inhibited to a maximum of approximately 90% relative to baseline within 30 days following single Rosnilimab dose, while placebo administration had no effect. Based upon these data, we believe Rosnilimab’s in vivo mechanism has the potential to treat T-cell driven human inflammatory diseases.

Introduction
Rosnilimab: PD-1 Agonist Antibody

Activated T cells are down regulated by PD-L1-mediated negative signaling, leading to suppressed immune responses in healthy individuals

Insufficient negative signaling, which could occur due to low PD-L1 expression, leads to excess T cell activity and inflammatory diseases

Rosnilimab mimics the function of PD-L1, restoring PD-1 mediated negative signaling on activated T cells, and has the potential to suppress human inflammatory diseases

Pharmacodynamics: PD-1 High Reduction Following Dosing
A. PD-1 high expressing T cells reduced >90% at Day 15 following Rosnilimab administration in cohort 11. B. Data from all dosed subjects from cohort 11 concatenated 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. C. Near complete reduction of high-expressing PD-1+ cells following Rosnilimab administration persisted for >30 days, with 50% reduction as soon as day 1, and >90% reduced at day 5 and after. Conventional T cells expressing PD-1 reduced 50% and persisted for >30 days following Rosnilimab administration.

Change in T Cells PD-1 Expression Following Rosnilimab Dosing

Conclusions
- Rosnilimab’s pharmacodynamic activity resulted in rapid and sustained reduction in the quantity and functional activity of PD-1+ T cells
- Conventional T (Tcon) cells (CD3+ CD25 low) expressing PD-1 were reduced by 50%, including in both CD4+ and CD8+ subsets in a dose-dependent manner and in correlation with receptor occupancy.
- PD-1 high expressing Tcon cells, which represented approximately 5% of peripheral T cells had a 95% reduction relative to baseline.
- An antigen-specific functional T cell recall response measured as ex vivo IFNγ release in response to tetanus toxoid challenge, was inhibited in a receptor occupancy dependent manner and was consistent with the observed reduction of PD-1+ Tcon cells, to a maximum of approximately 90% relative to baseline within 30 days following single Rosnilimab dose.
- Based upon these data, we believe Rosnilimab’s in vivo mechanism has the potential to treat T-cell driven human inflammatory diseases.