

# Rosnilimab Selectively Depletes Pathogenic T Cells and Downregulates Clinically Relevant Immune Pathways in Rheumatoid Arthritis: A Translational Analysis of Blood and Synovial Tissue from the RENOIR Phase 2B Trial

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Cailin Sibley<sup>1</sup>

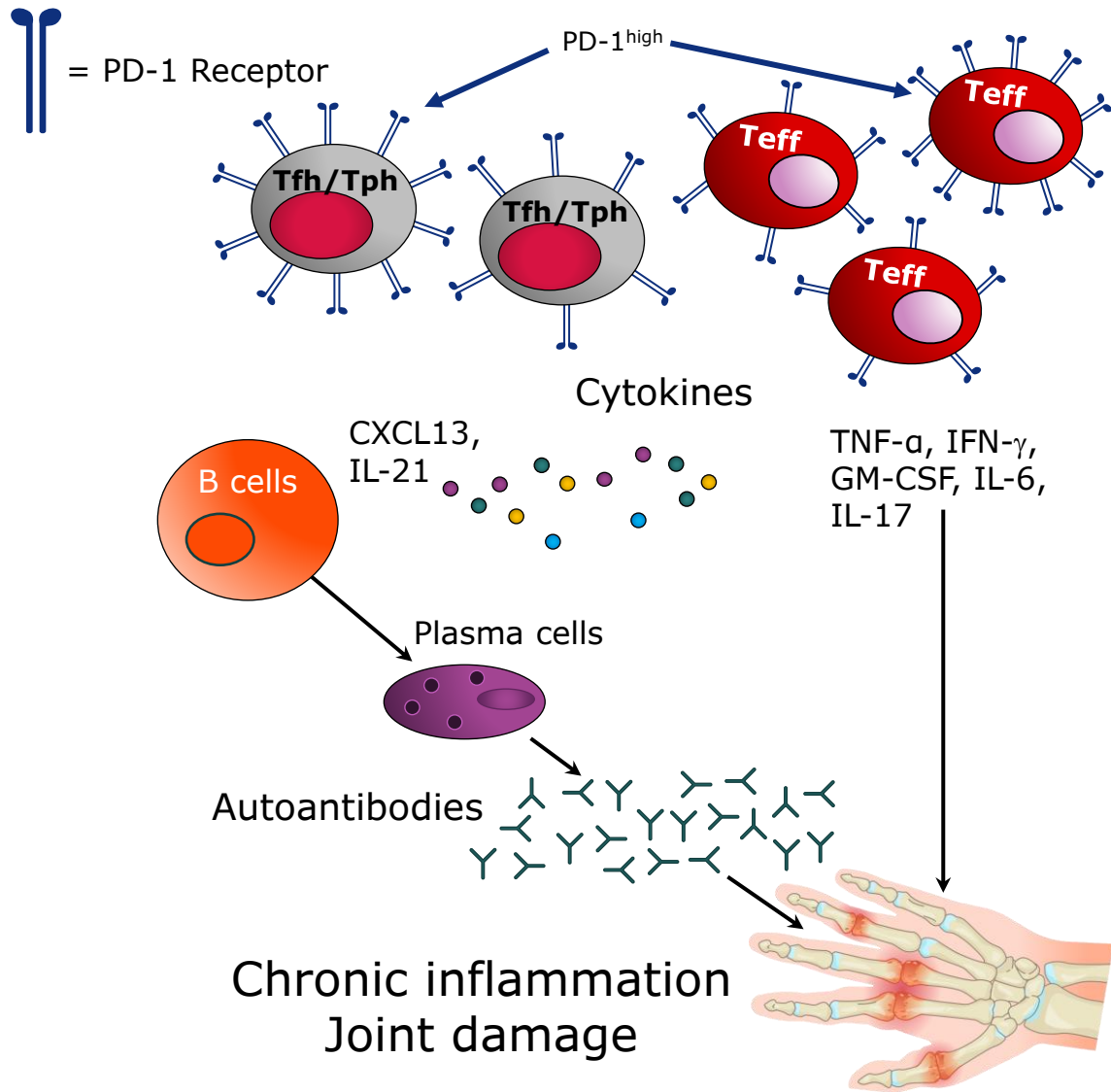
<sup>1</sup>First Tracks Biotherapeutics, Inc., San Diego, CA, USA; <sup>2</sup>QMUL, London, UK

# Disclosures

**C Pitzalis:** consultant for AbbVie/Abbott, First Tracks Bio, Novartis; grant/research support from AbbVie/Abbott, Novartis, Pfizer, Roche, Sanofi; independent contractor for AbbVie/Abbott, First Tracks Bio, Novartis, Roche, Sanofi; speaker for AbbVie/Abbott, Novartis, Roche, Sanofi, and UCB.

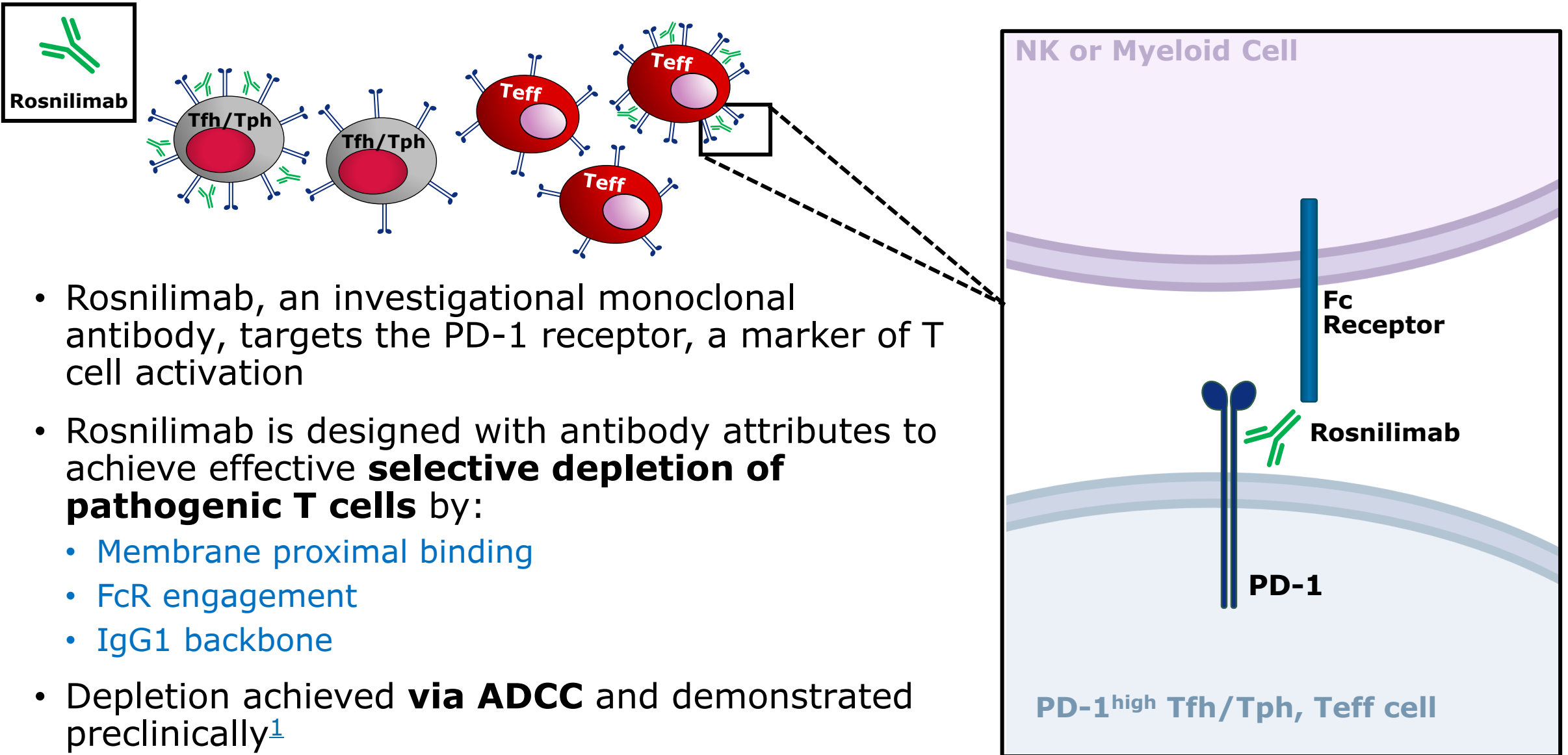
**C Aversa, Y Ren, E Hare, M Dahl, P Lizzul, C Sibley** are employees and shareholders of First Tracks Bio

# Pathogenic T Cells Drive Inflammation and Joint Damage in RA



- Pathogenic T cells (PD-1<sup>high</sup> Tfh/Tph, Teff):
  - Play a major role in inflammation
  - Are enriched in patients with RA (>80% of synovial T cells and 3x higher in peripheral blood) and **low levels in healthy individuals**<sup>2,3</sup>
  - T cell activation leads to upregulation of PD-1 and the production of a broad range of chemokines & cytokines **upstream of clinically validated targets** such as TNF- $\alpha$ , IL-6, and B cells<sup>1,2</sup>
- Tfh/Tph cells drive B cell activation and maturation, including autoantibody producing cells<sup>1</sup>
- Activated Teff cells proliferate and secrete proinflammatory cytokines

# Rosnilimab Characteristics & Mechanism of Action



- Rosnilimab, an investigational monoclonal antibody, targets the PD-1 receptor, a marker of T cell activation
- Rosnilimab is designed with antibody attributes to achieve effective **selective depletion of pathogenic T cells** by:
  - Membrane proximal binding
  - FcR engagement
  - IgG1 backbone
- Depletion achieved **via ADCC** and demonstrated preclinically<sup>1</sup>

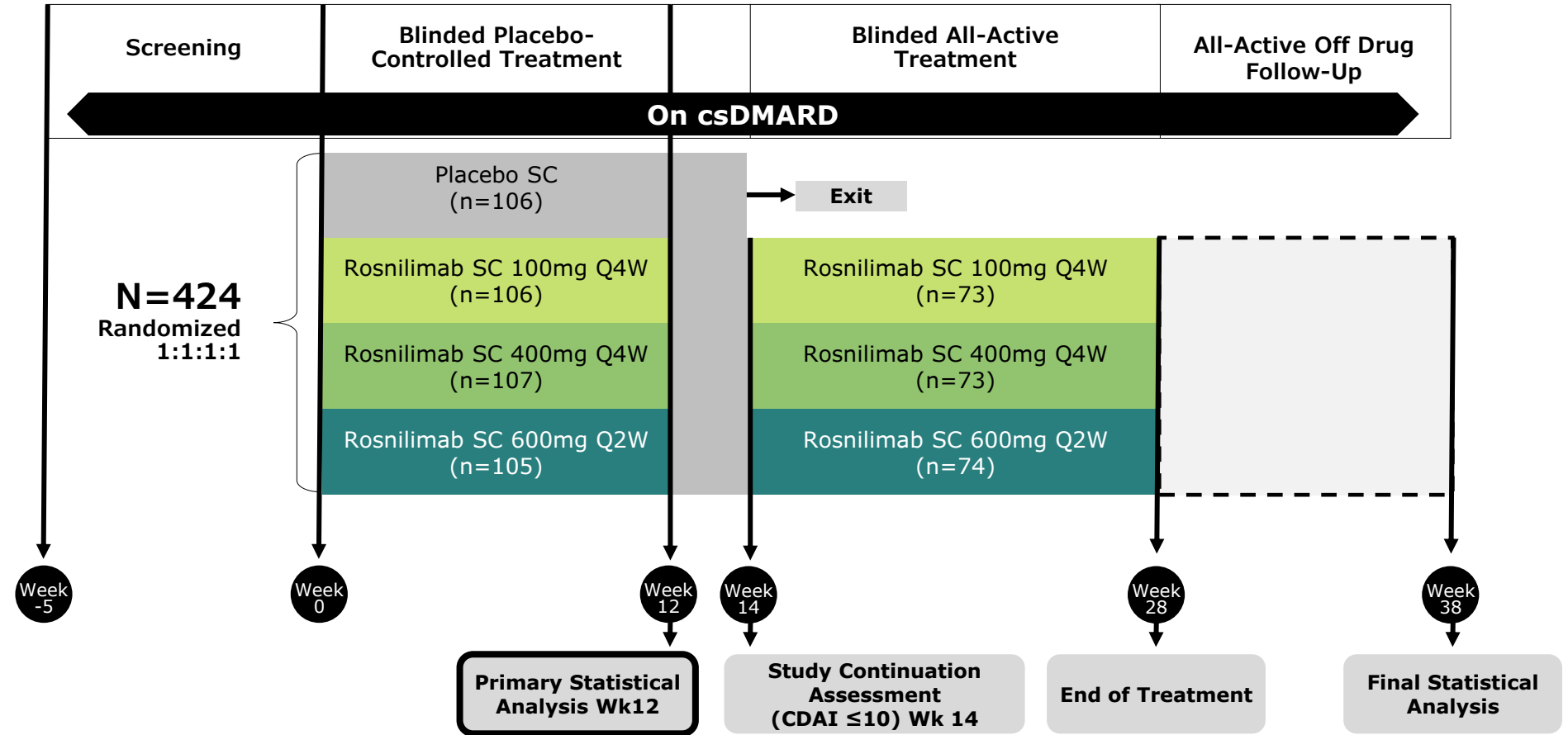
# RENOIR: Global, Randomized, Placebo-controlled Phase 2B Trial Investigating Effectiveness and Tolerability of Rosnilimab in Moderate-to-Severe Rheumatoid Arthritis

## Key Inclusion Criteria

- Seropositive RA
- $\geq 6$  swollen and  $\geq 6$  tender joints
- hs-CRP  $\geq 3$ mg/L during Screening
- Concurrent use of 1 or 2 csDMARDs that were initiated at least 3 months before screening

## Key Exclusion Criteria

- Inadequate response, loss of response, or intolerance to any combination of  $\geq 3$  b/tsDMARD classes



## Clinical Outcomes

**Primary Endpoint:** Mean change in DAS28-CRP from baseline to week 12, **statistically significant at all doses**

**Select Secondary:** All dose arms showed **statistically significant changes for ACR20**

**Exploratory:** All dose arms had **statistically significant changes for hs-CRP as early as week 2**

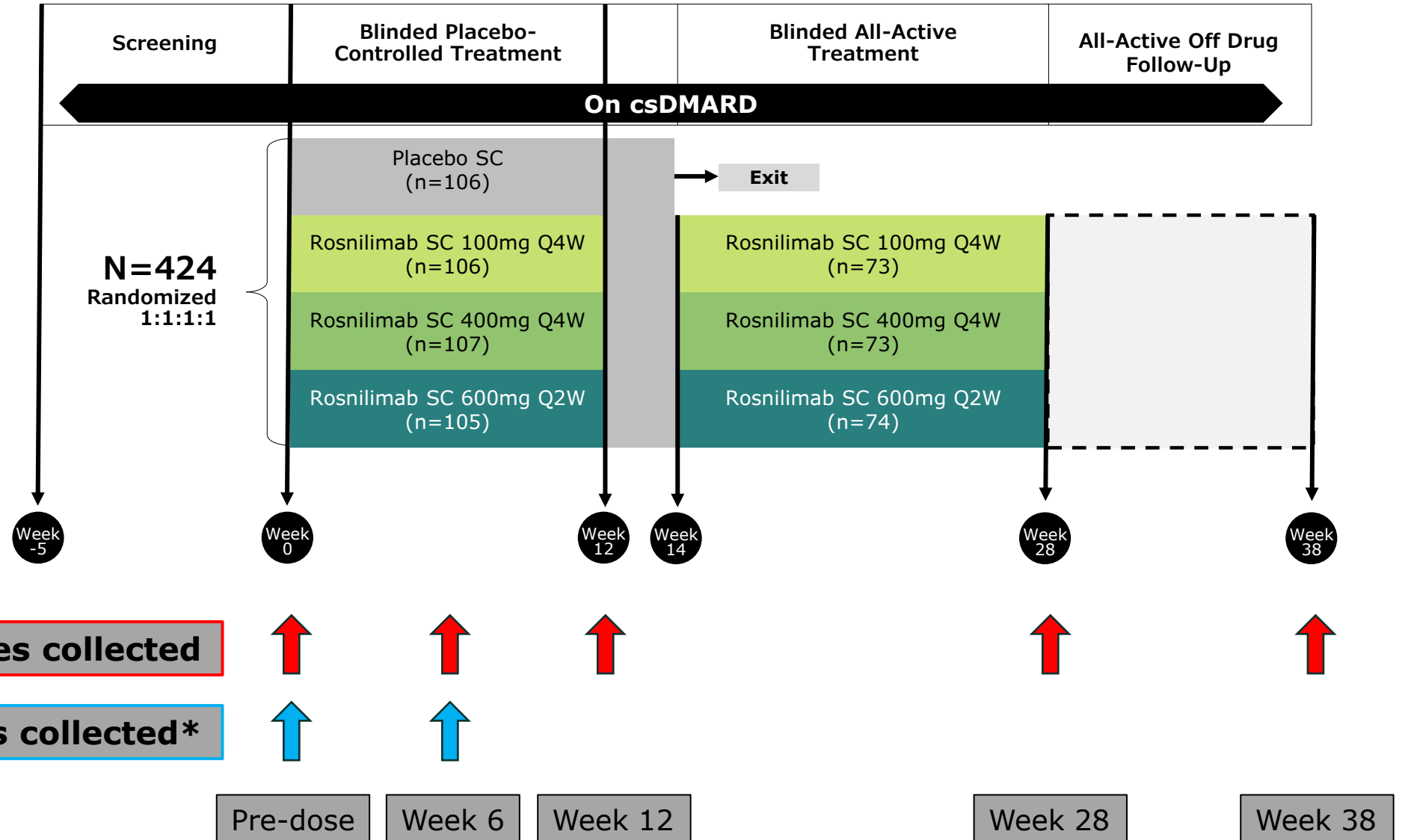
# RENOIR Translational Investigation Sample Collection

## Key Inclusion Criteria

- Seropositive RA
- $\geq 6$  swollen and  $\geq 6$  tender joints
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## Key Exclusion Criteria

- Inadequate response, loss of response, or intolerance to any combination of  $\geq 3$  b/tsDMARD classes



# RENOIR: Translational Objective

To elucidate the pharmacodynamic and mechanistic effects of rosnilimab in adults with moderate-to-severe RA through peripheral blood flow cytometry and serum protein analyses, as well as synovial tissue histopathology and molecular profiling

## Blood samples

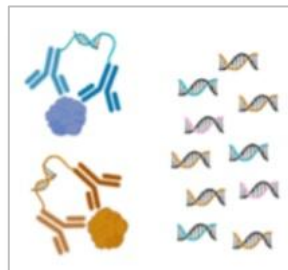
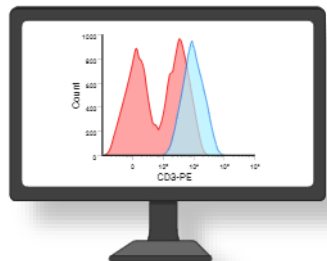


### Flow cytometry:

Total T cells, Treg, PD1+/-hi (n=145\*) and Tph (n=132\*) analysis

### Serum biomarkers:

Olink® Target 96 Immuno-Oncology Panel (n=420\*)



\* n=Day 1 samples

## Synovial biopsies



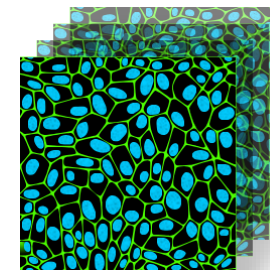
### H&E-stained FFPE

Krenn synovitis score  
n=80 total samples assessed



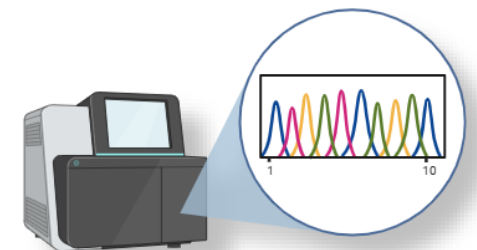
### Multiplex IHC:

Ayoka platform,  
6-plex IF panels  
n=39 evaluable  
paired biopsies



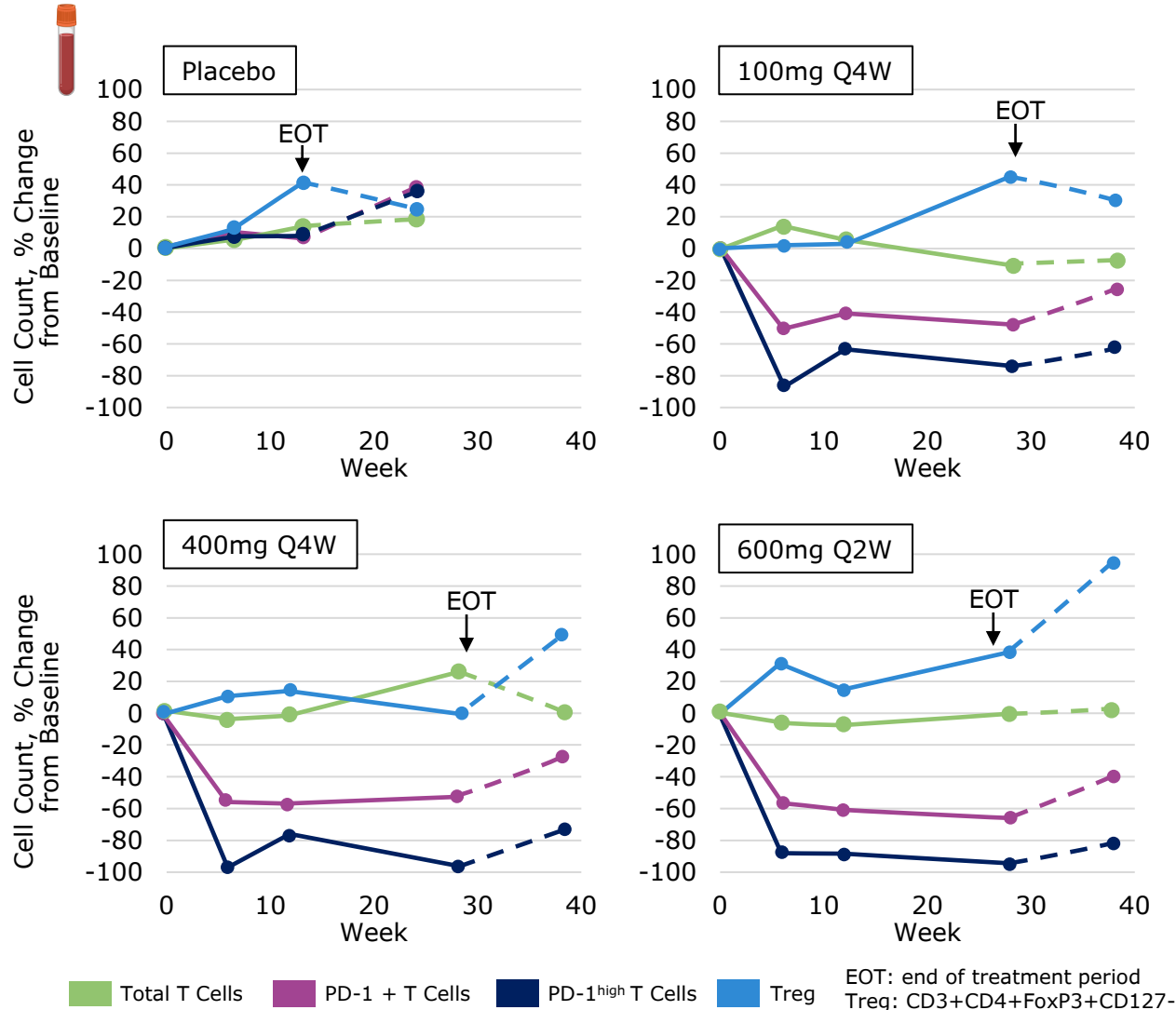
### RNA Later (bulk RNA-seq)

n=24 evaluable  
paired biopsies



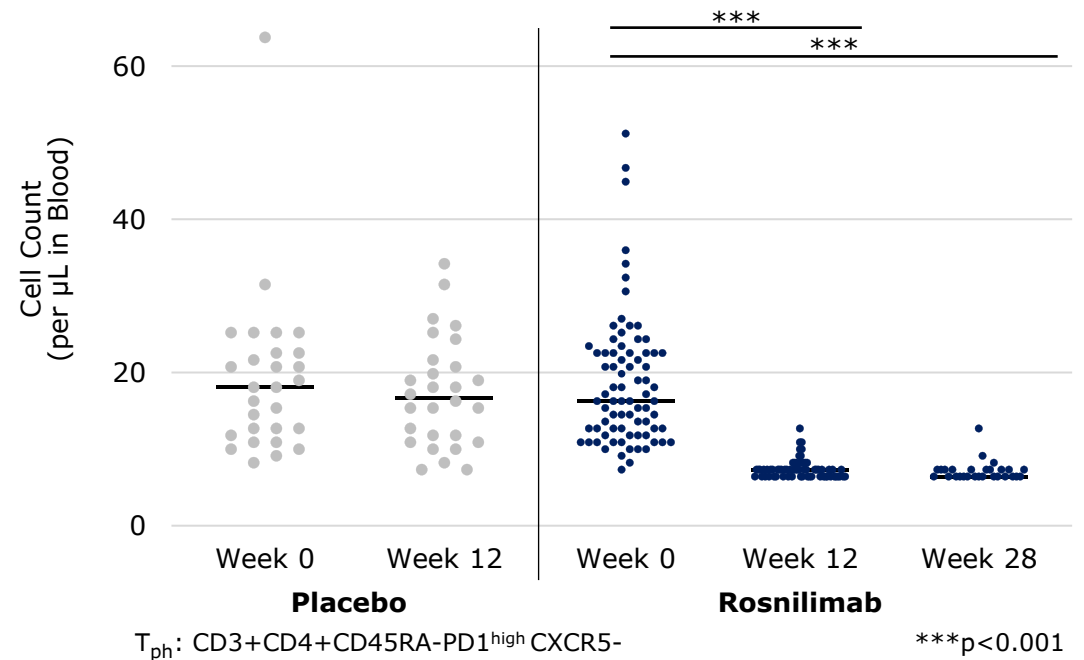
# Rosnilimab Potently Reduced Pathogenic T Cells in Blood

## Peripheral T Cell Changes Over Time



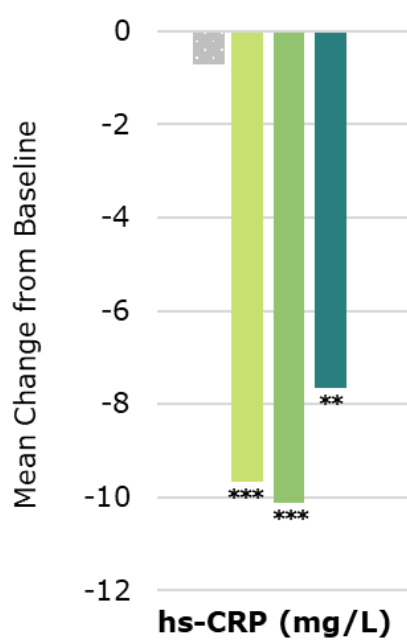
- >90% reduction in PD-1<sup>high</sup> T cell numbers (including Tph cells) at highest doses
  - Reductions persist 12 Weeks after last dose
- No changes in overall T cell numbers
  - PD-1<sup>high</sup> T cells ~5% of total T cells
- Treg numbers unchanged to increased
- Overall results in a favorable T cell composition reflective of healthy immune homeostasis

## Rosnilimab T<sub>ph</sub> Impact - Pooled Doses



# Rosnilimab Reduced Pro-inflammatory Serum Biomarkers

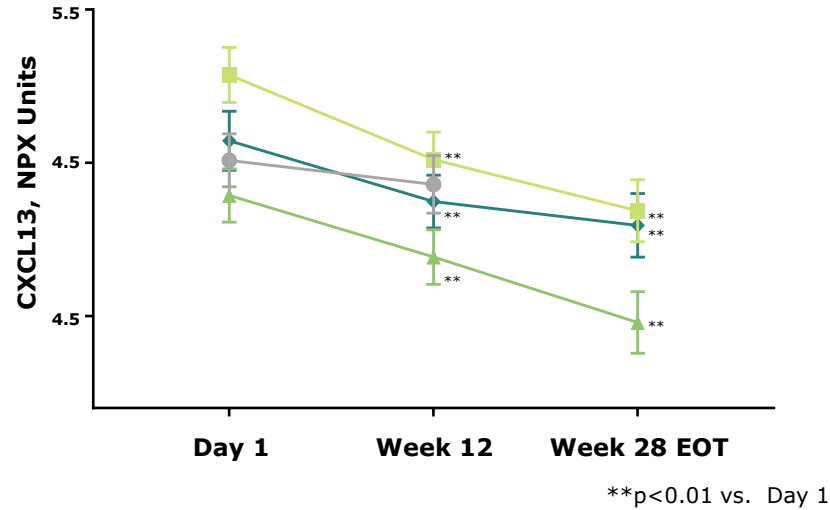
## hs-CRP, Week 12



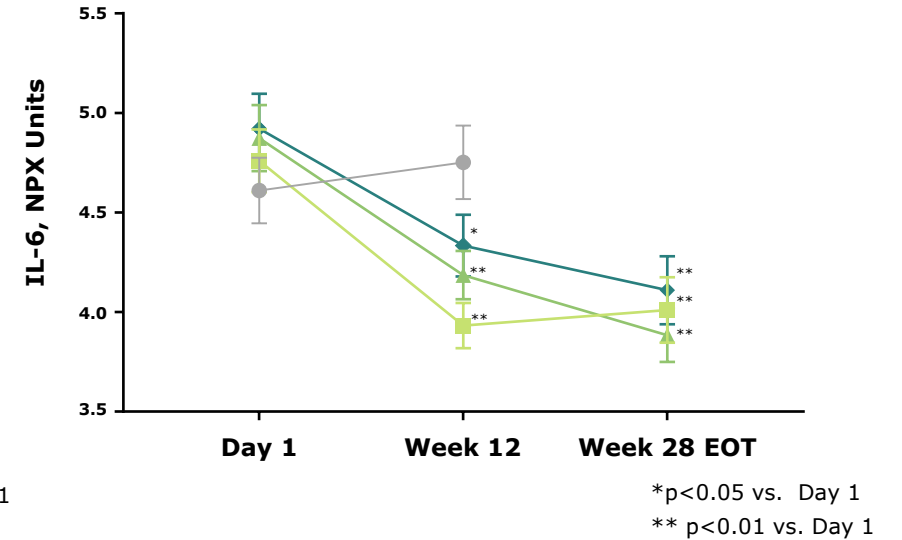
All dose arms had statistically significant changes for hs-CRP

Statistically significant differentiation of hs-CRP occurred as early as Week 2

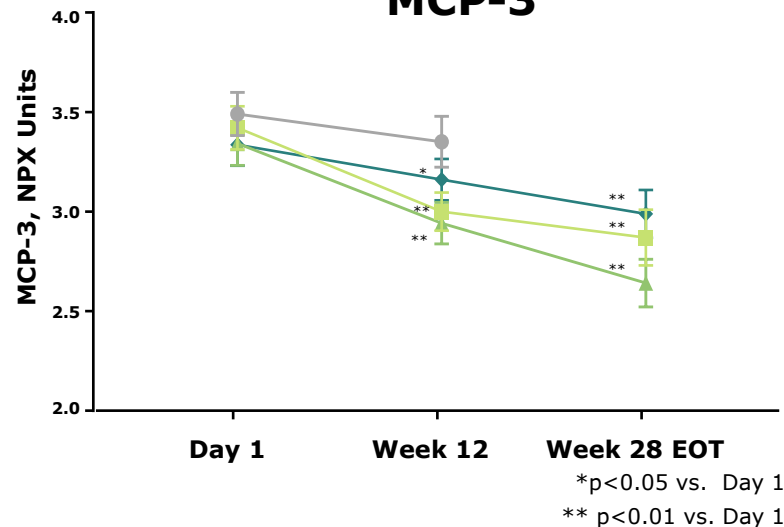
## CXCL13



## IL-6



## MCP-3



Depletion of pathogenic T cells in the periphery was accompanied by significant decreases in systemic inflammatory (IL-6, CRP), Tph/Tfh/B cell-associated (CXCL13) and myeloid-associated (MCP-3) biomarkers in serum

Placebo
  Rosnilimab 100mg Q4W
  Rosnilimab 400mg Q4W
  Rosnilimab 600mg Q2W

# Rosnilimab Decreased Krenn Scores, Depleted Pathogenic T Cells and Downregulated T cell Activation Pathways in Synovium

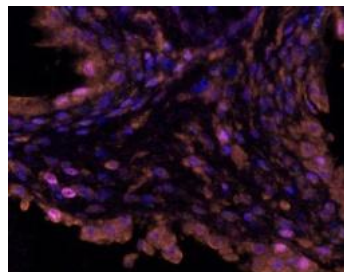
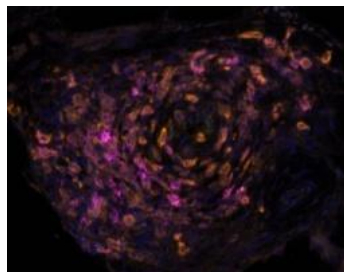
## Synovial Immunohistochemistry

n= 39 paired samples

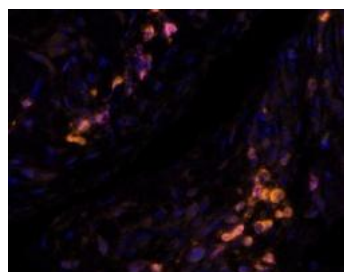
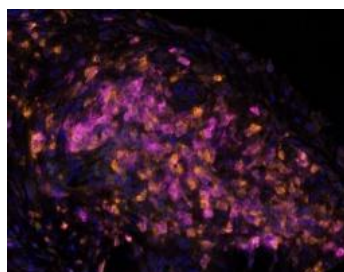
Baseline

Week 6

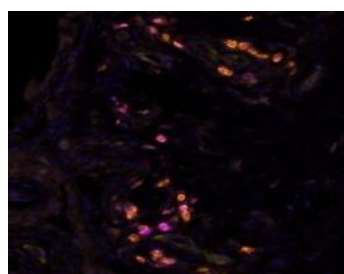
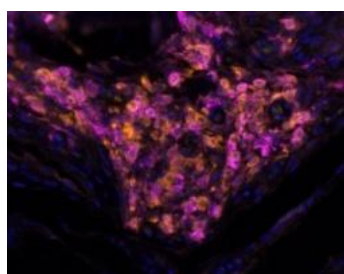
**Placebo**  
No change/  
increased



**Rosnilimab 400mg Q4W**  
~90% reduction



**Rosnilimab 600mg Q2W**  
~90% reduction

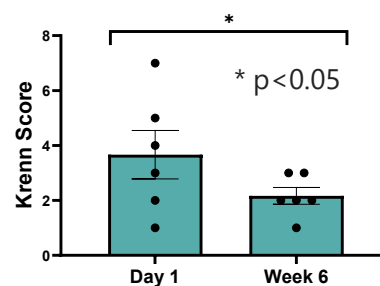


PD-1 CXCR5 CD3 DAPI

Representative IHC samples from synovial biopsies.  
T<sub>ph</sub>: PD-1+CD3+CD4+CXCR5-

## Krenn Score

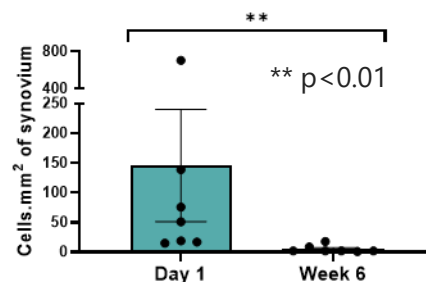
400 Q4W+600 mg Q2W



Krenn scores at baseline ranged from 0 to 7 in evaluable samples. Samples from the 400 and 600 mg dose groups showed a mean Krenn score reduction of 41%. Placebo and 100 mg Q4W were ns.

## Synovial IHC:

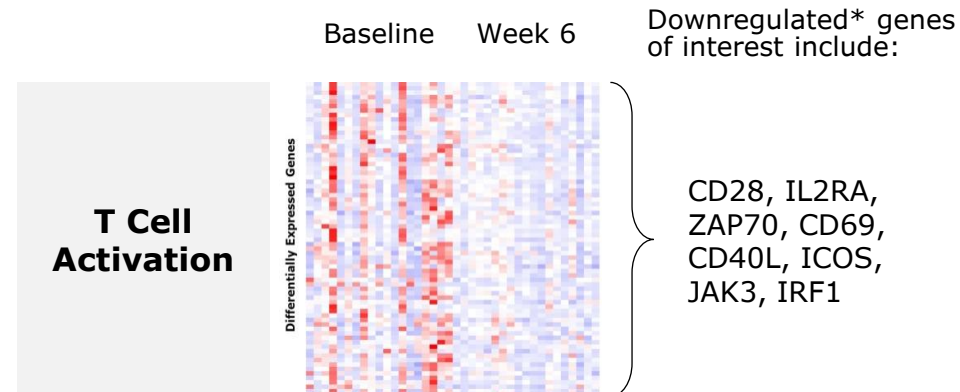
CD4+PD-1+ T cells,  
400 Q4W+600 mg Q2W



In tissue samples with Day 1 cell counts >10 cells/mm<sup>2</sup>, ~90% reduction in CD4+PD1+T cells was observed. Placebo and 100 mg Q4W were ns.

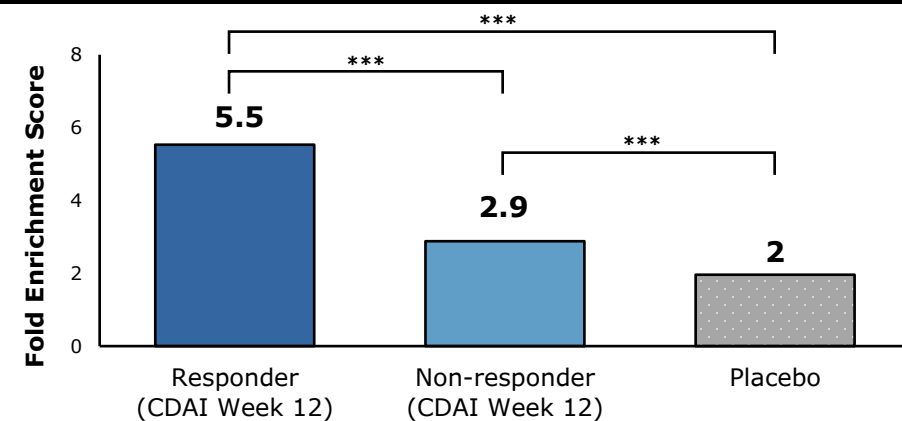
## Synovial Bulk RNA-seq (Rosnilimab Pooled Doses)

n= 24 paired samples, responders & nonresponders



Gene ontology (GO) pathway analysis performed on samples with evidence of inflammation at baseline. Fold enrichment T cell activation 4.03, p=1.09e-24

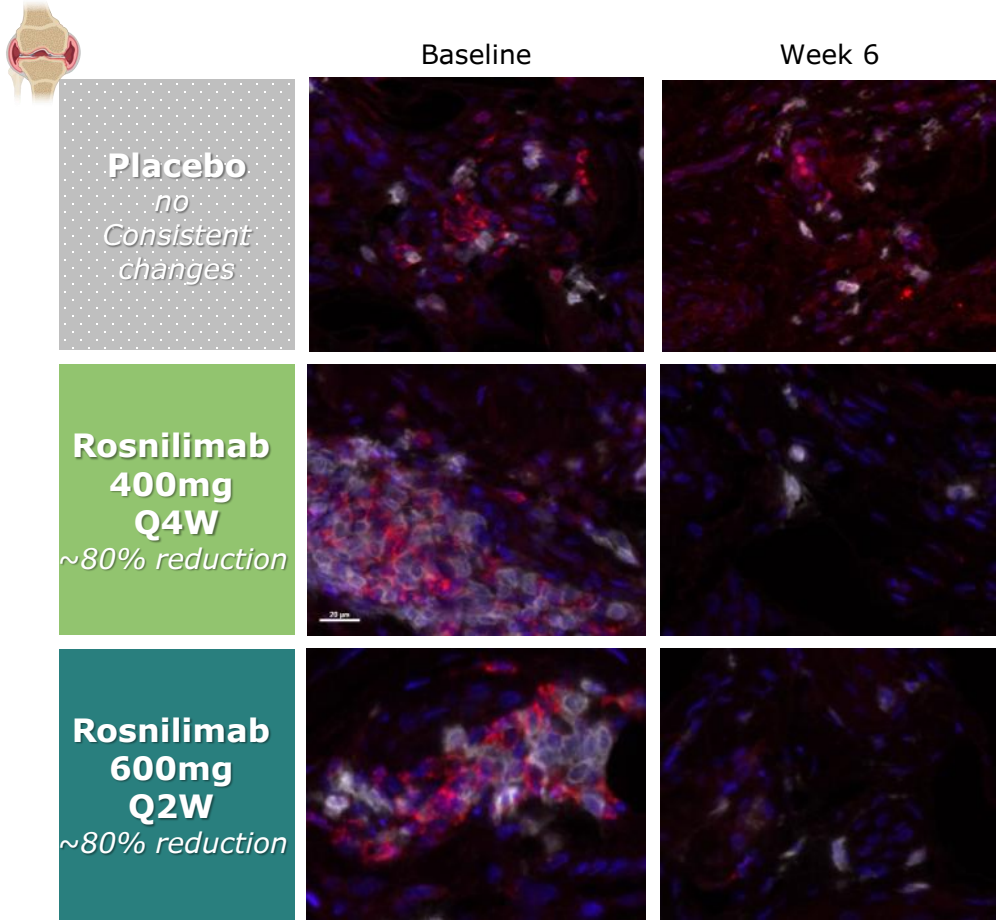
## CDAI LDA Responders Showed Significantly Greater Reductions in T cell Activation Pathway (RNA-seq) vs Non-Responders



\* p<0.05, \*\* p<0.01, \*\*\* p<0.001

# Rosnilimab Reduced Synovial B Cells and Downregulated B cell Activation Pathways in Synovium

## Synovial Immunohistochemistry: B cells n= 39 paired samples

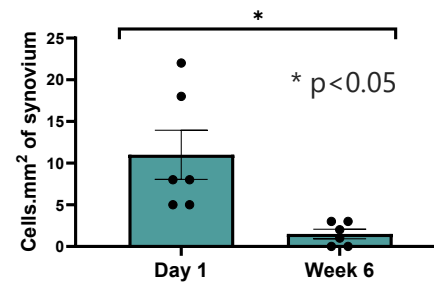


■ CD20 □ CD3 ■ DAPI

Representative IHC samples from synovial biopsies.

## Synovial IHC

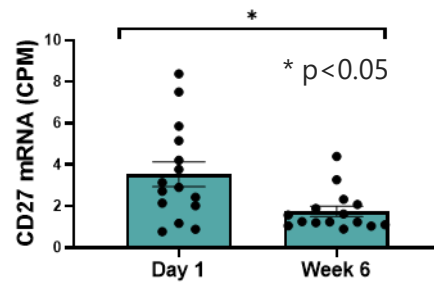
CD20+ B cells, 400 Q4W+600 mg Q2W



In tissue samples with Day 1 cell counts >5 cells/mm<sup>2</sup>, ~80% reduction in CD4+PD1+T cells was observed. Placebo and 100 mg Q4W were ns.

## Synovial RNA-Seq

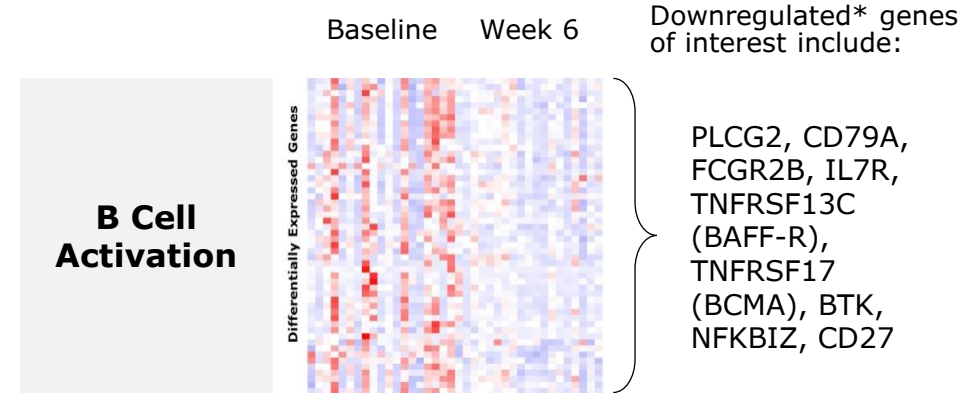
CD27 mRNA, 400 Q4W+600 mg Q2W



Reductions in mRNA transcripts associated with activated, memory B cells (e.g. CD27) were also observed.

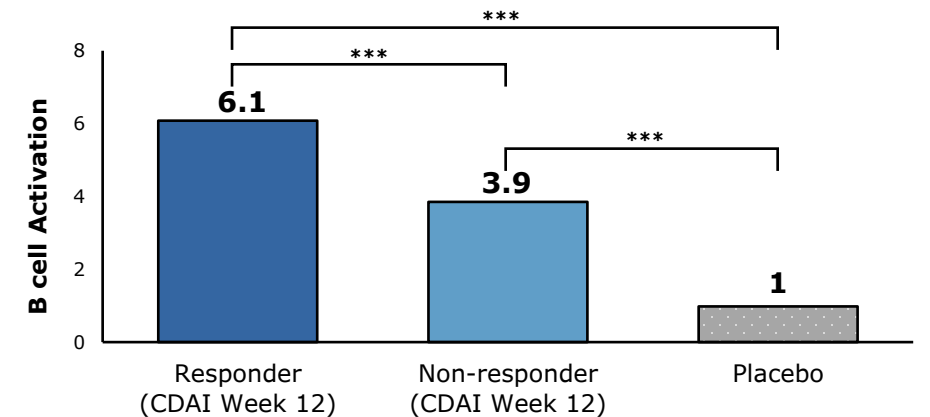
## Synovial Bulk RNA-seq (Rosnilimab Pooled Doses)

n= 24 paired samples, responders & nonresponders



Gene ontology (GO) pathway analysis performed on samples with evidence of inflammation at baseline. Fold enrichment B cell activation 4.06, p=1.77e-18

## CDAI LDA Responders Showed Significantly Greater Reductions in B cell Activation Pathway (RNA-seq) vs Non-Responders

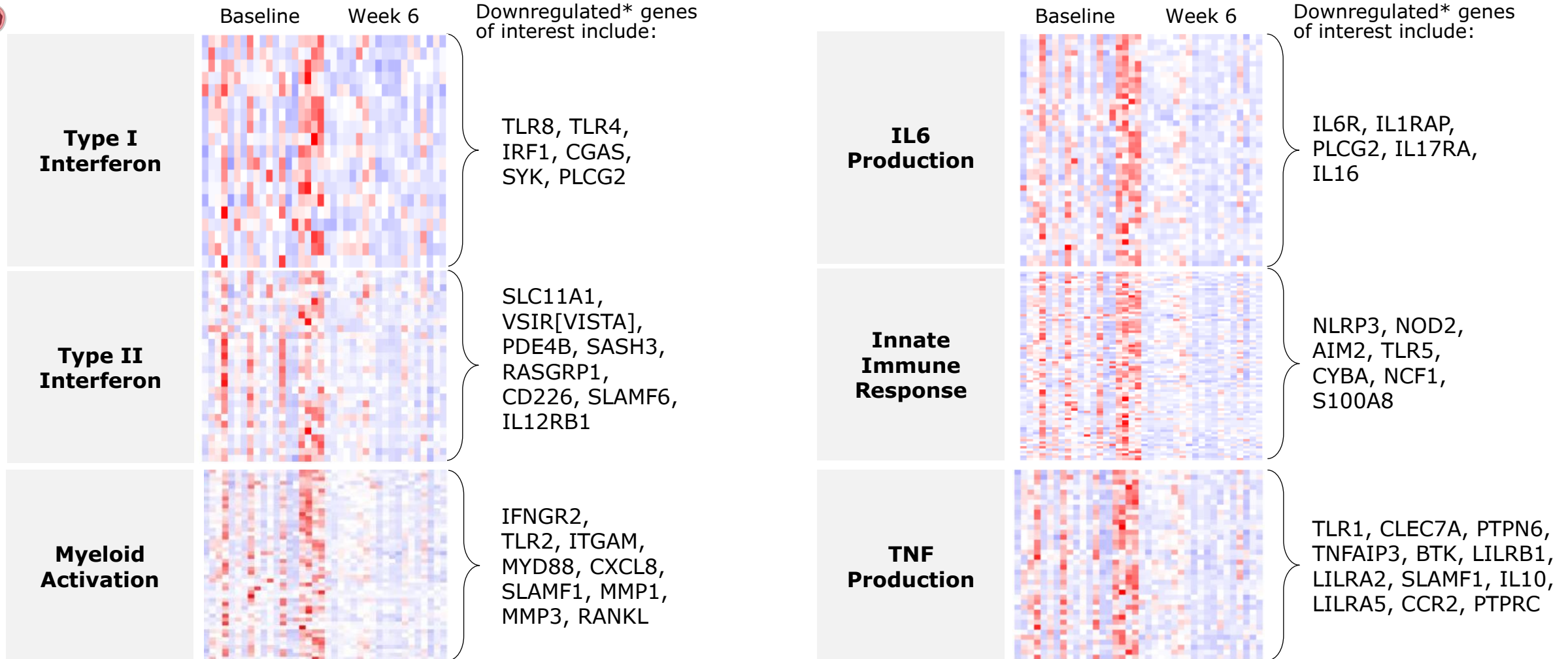


\* p<0.05, \*\* p<0.01, \*\*\* p<0.001

# Broad Downregulation of Innate and Adaptive Immune Pathways Observed in Synovium

## Synovial Bulk RNA-seq (Rosnilimab Pooled Doses)

n= 24 paired samples, responders & nonresponders



Gene ontology (GO) pathway analysis performed on samples with evidence of inflammation at baseline. Fold enrichment Type I interferon 3.60, p=1.34e-05; Type II interferon 5.52, p=4.45e-14; myeloid activation 4.15, p=6.44e-18; IL6 production 5.63, p=2.61e-21; Innate immune response 3.68, p=5.47e-25; TNF production 3.38, p=4.39e-15; \*p<0.05

# Conclusions

- Rosnilimab selectively depleted pathogenic T PD-1<sup>high</sup> cells including Tph, Tfh and Teff cells in blood, key drivers of systemic and synovial inflammation, without reducing the total number of T cells and Tregs
- Rosnilimab potently reduced pathogenic T and B cells in synovium, resulting in downregulation of a wide range of innate, adaptive and inflammatory pathways
- The results generated from this novel, comprehensive translational study support the concept that these pathogenic T cells function as upstream mechanistic drivers in RA
- These findings highlight rosnilimab as a novel therapeutic approach that targets fundamental mechanisms of disease in RA and other autoimmune and inflammatory conditions and enable durable disease control
- Continued investigations of synovial cell phenotypes and functional states are on-going



**Thank  
You!**

*to*  
**Patients  
Caregivers  
Investigators  
Study Staff  
& Everyone**  
*involved in this study!*

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