Rosnilimab, a Selective and Potent Depleter of Pathogenic T Cells, Demonstrates Efficacy, Safety and Translational Proof of Mechanism in a Rheumatoid Arthritis Phase 2B Trial

Jonathan Graf,[1] Amy M. Archer,[2] Sergii Kovalenko,[3] Katarzyna Kolossa,[4] John Serpa,[5] Tamta Kobakhidze,[6] Daniela Cepoi,[7] Andrea Everding,[8] Costantino Pitzalis,[9] Catherine Aversa,[2] Martin Dahl,[2] May Hafez,[2] Paul Lizzul,[2] Priya Raina,[2] Bruce Randazzo,[2] Yangsu Ren,[2] Khalil Saikali,[2] Cailin Sibley,[2] Gerd R. Burmester,[10] Jacques-Eric Gottenberg,[11] Iain McInnes,[12] Eduardo Mysler,[13] Lee S. Simon,[14] Josef S. Smolen,[15] Jeffrey A. Sparks,[16] Ronald van Vollenhoven,[17] Michael Weinblatt,[18] **Paul Emery[19]**

[1]UCSF, San Francisco, CA, USA; [2]AnaptysBio, San Diego, CA, USA; [3]Arensia Exploratory Medicine, Kyiv, Ukraine; [4]MICS Centrum Medycze, Bydgoszcz, Poland; [5]Allied Biomedical Research Institute, Miami, FL, USA; [6]Research Institute of Clinical Medicine Todua Clinic, Tbilisi, Georgia; [7]Nicolae Testemitanu State University of Medicine & Pharmacy, Chisinau, Moldova; [8]MVZ Rheumatologie & Autoimmunmedzin Hamburg GmbH, Hamburg, Germany; [9]QMUL, London, UK; [10]Charité University Hospital, Berlin, Germany; [11]Hautepierre Hospital, Strasbourg, France; [12]University of Glasgow, Glasgow, Scotland; [13]Organizacion Medica de Investigatcion, Buenos Aires, Argentina; [14]SDG LLC, West Newton, MA, USA; [15]Medical University of Vienna, Vienna, Austria; [16]Brigham and Women's Hospital, Boston, MA, USA; [17]Amsterdam UMC, Amsterdam, Netherlands; [18]Harvard Medical School, Boston, MA, USA; [19]Leeds NIHR Biomedical Research Centre, LTHT Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

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Disclosures

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S Kovalenko, K Kolossa, T Kobakhidze, D Cepoi, A Everding have nothing to disclose

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Background

- Pathogenic T cells (e.g., PD-1^{high} Tfh/Tph, Teff) play a role in inflammation, are upstream to a broad range of clinically validated targets in RA including TNF-α, IL-6, and B cells and are found in very low levels in healthy individuals[1,2]
  - These cells are enriched in patients with RA (>80% of synovial T cells and 3x higher in peripheral blood)[2,3]
  - Tfh/Tph cells drive B cell activation and maturation, including autoantibody producing cells[1]
  - Activated Teff cells proliferate and secrete inflammatory cytokines (e.g., IFNγ)

- **Rosnilimab**, an investigational monoclonal antibody, is a **selective and potent depleter of pathogenic T cells** that has the potential advantage of restoring immune homeostasis

1. Rao D, et al. *Nature* 2017;542:7639. 2. Guo Y, et al. *PLOS ONE* 2018;1:e0192704. 3. Chen Y-j, et al. *Clin Translational Immunol* 2024;13:e70006.

Objective

Report complete study results for safety and efficacy of rosnilimab in a Phase 2B study in patients with moderate-to-severe rheumatoid arthritis

Global, Randomized, Placebo-controlled Phase 2B Trial with Rosnilimab in Moderate-to-Severe Rheumatoid Arthritis

Key Inclusion Criteria

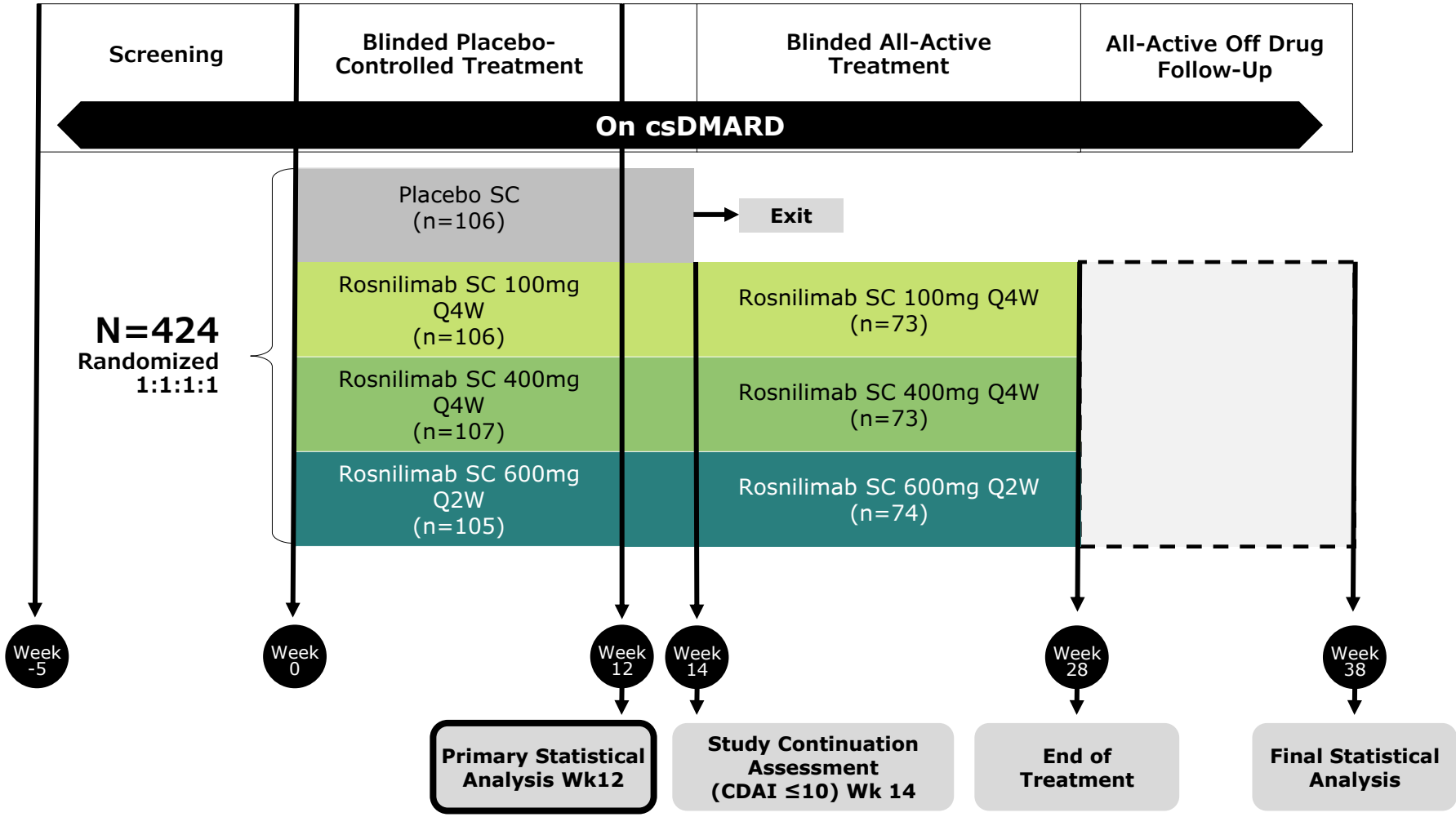
- Seropositive RA
- ≥6 swollen and ≥6 tender joints
- hs-CRP ≥ 3mg/L during Screening
- Concurrent use of 1 or 2 csDMARDs that were initiated at least 3 months before screening

Key Exclusion Criteria

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

Primary Endpoint

- Mean change from baseline at week 12 for DAS28-CRP



ClinicalTrials.gov: NCT06041269

Statistical Analysis

Analysis populations and associated imputation

- ITT population (all randomized)
  - Dichotomous outcomes
    - NRI at Week 12
    - NRI at Week 28
      - Participants with CDAI>10 at Week 14 could not continue in the all-active period regardless of meeting ACR20, ACR50 or ACR70
      - Thus, in the Week 28 NRI analysis were imputed as nonresponders
  - Continuous measures
    - MMRM for Primary Analysis through Week 12
    - MI-LMCF for all analyses that include a timepoint beyond Week 12
- Completer population
  - Subjects with at least one efficacy measure at Week 38
- Safety population
  - Those randomized that received at least one dose of study drug matching the ITT population (all randomized)

ITT = Intent to Treat (all randomized); MMRM = Mixed model repeated measures; MI-LMCF = Multiple imputations with last mean carried forward;
NRI = Nonresponder imputation

Baseline Demographics

Baseline Characteristic	Placebo (N=106)	Rosnilimab 100mg Q4W (N=106)	Rosnilimab 400mg Q4W (N=107)	Rosnilimab 600mg Q2W (N=105)	Overall (N=424)
Age, years, mean (SD)	58 (11)	57 (10)	57 (12)	56 (11)	57 (11)
Female, n (%)	83 (78%)	79 (75%)	79 (74%)	80 (76%)	321 (76%)
Weight (kg), mean (SD)	78 (17)	78 (19)	81 (19)	77 (16)	78 (18)
Geographic region, n (%) US and Canada Europe	 37 (35%) 69 (65%)	 35 (33%) 71 (67%)	 36 (34%) 71 (66%)	 28 (27%) 77 (73%)	 136 (32%) 288 (68%)
Race, n (%) White Black or African American Asian Other	 102 (96%) 3 (3%) 0 (0%) 2 (2%)	 102 (96%) 1 (<1%) 0 (0%) 5 (5%)	 103 (96%) 4 (4%) 0 (0%) 0 (0%)	 101 (96%) 4 (4%) 0 (0%) 0 (0%)	 408 (96%) 12 (3%) 0 (0%) 7 (2%)

SD- standard deviation, N – total number of subjects in analysis set, n – number of subjects in specific category; ITT population

Baseline Disease Characteristics

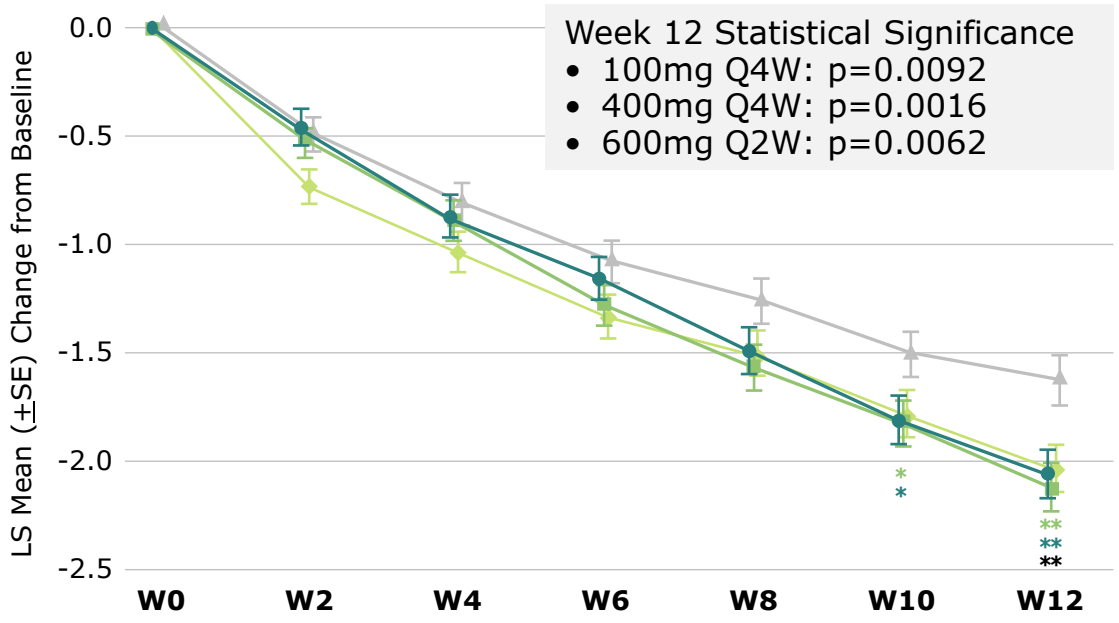
Baseline Characteristic	Placebo (N=106)	Rosnilimab 100mg Q4W (N=106)	Rosnilimab 400mg Q4W (N=107)	Rosnilimab 600mg Q2W (N=105)	Overall (N=424)
Duration of disease, years, mean (SD)	11 (9)	11 (10)	9 (8)	10 (9)	10 (9)
Prior b/tsDMARD, n (%)	44 (41.5%)	44 (41.5%)	45 (42.1%)	41 (39.0%)	174 (41.0%)
>1 b/tsDMARD classes, n (%)	5 (11.4%)	7 (15.9%)	5 (11.1%)	8 (19.5%)	25 (14.4%)
JAK inhibitor, n (%)	12 (27.3%)	10 (22.7%)	15 (33.3%)	13 (31.7%)	50 (28.7%)
RF positive, n (%)	101 (95.3%)	102 (96.2%)	99 (92.5%)	101 (96.2%)	403 (95.0%)
CCP positive, n (%)	96 (90.6%)	96 (90.6%)	84 (78.5%)	91 (86.7%)	367 (86.6%)
DAS28-CRP, mean (SD)	5.7 (0.8)	5.6 (0.8)	5.7 (0.9)	5.7 (0.8)	5.6 (0.8)
CDAI, mean (SD) **CDAI >22, n (%)**	37.9 (10.2) 101 (95%)	37.2 (10.6) 101 (95%)	37.1 (10.6) 102 (95%)	38.6 (11) 100 (95%)	37.7 (10.6) 404 (95%)
TJC68, mean (SD)	23 (13)	22 (12)	22 (12)	23 (13)	22 (12)
SJC66, mean (SD)	14 (7)	15 (7)	14 (7)	16 (9)	15 (8)
hs-CRP, mean (SD) mg/L	16 (22)	17 (20)	21 (26)	19 (28)	18 (24)

DAS28-CRP – Disease Activity Score 28-C-reactive protein; CDAI – Clinical Disease Activity Index; TJC68 – tender joint count, 68 joints; SJC66 – swollen joint count, 66 joints; hs-CRP – high-sensitivity C-reactive protein, SD- standard deviation, N – total number of subjects in analysis set, n – number of subjects in specific category; b/tsDMARD - biologic/targeted synthetic Disease Modifying Antirheumatic Drugs

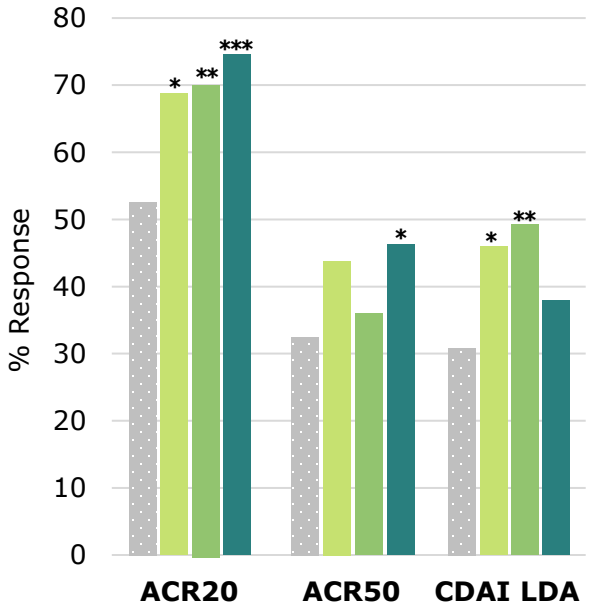
Primary and Select Secondary and Exploratory Endpoints Show Statistical Significance at Week 12

ITT population, MMRM and NRI analysis

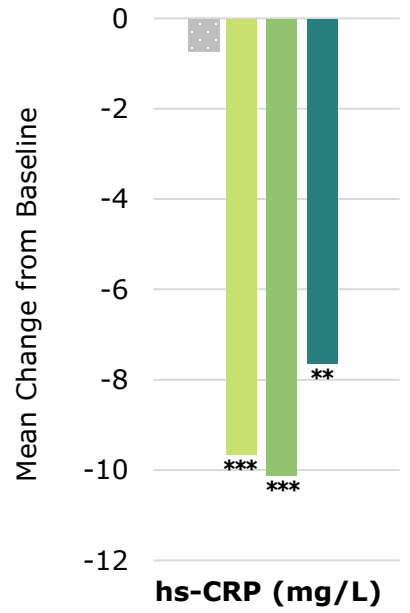
Primary Endpoint: Mean Change from Baseline in DAS28-CRP at Week 12



Secondary Endpoints at Week 12



Exploratory Endpoint at Week 12



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

All dose arms demonstrated statistically significant changes in DAS28-CRP

All dose arms showed statistically significant changes for traditional FDA regulatory endpoint (ACR20)

More stringent endpoints showed numerical, if not statistically significant, responses versus placebo at Week 12

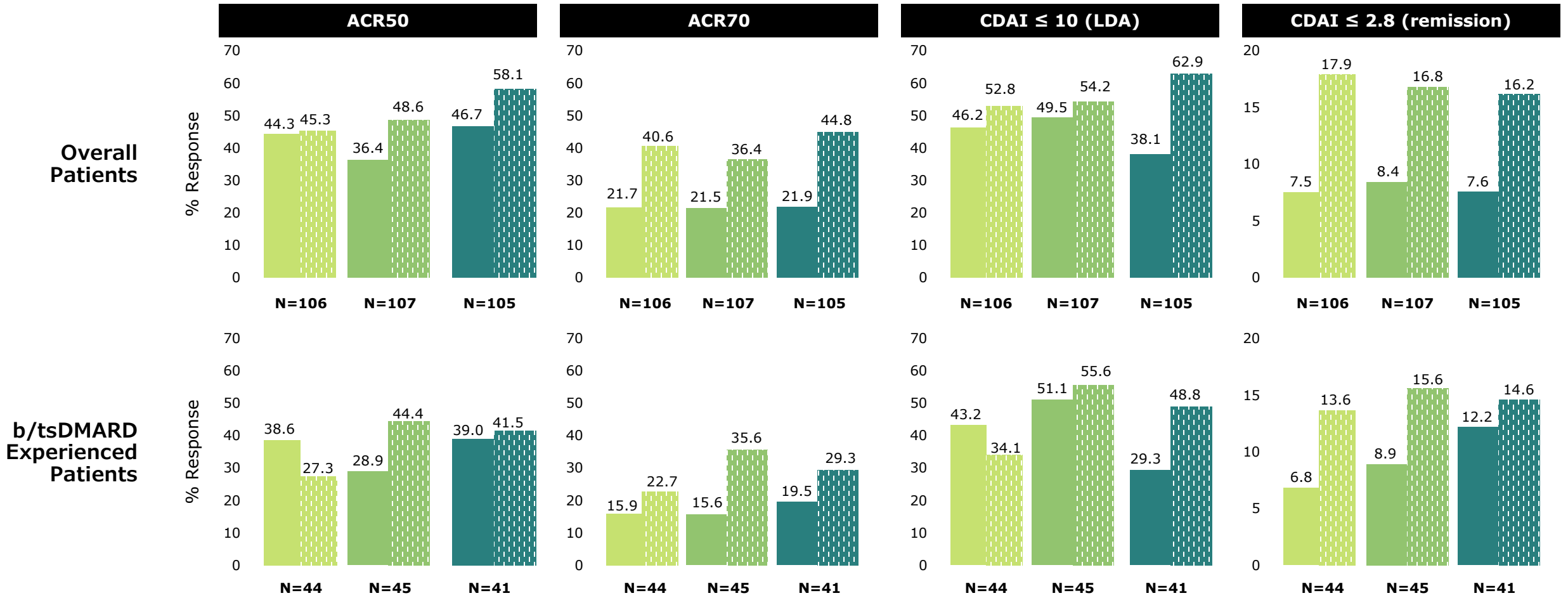
All dose arms had statistically significant changes for hs-CRP

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

*p < 0.05; **p < 0.01; ***p < 0.001; ITT population; MMRM for continuous endpoints, NRI for dichotomous endpoints

Responses Increase from Week 12 to Week 28 in Overall and b/tsDMARD Experienced Population

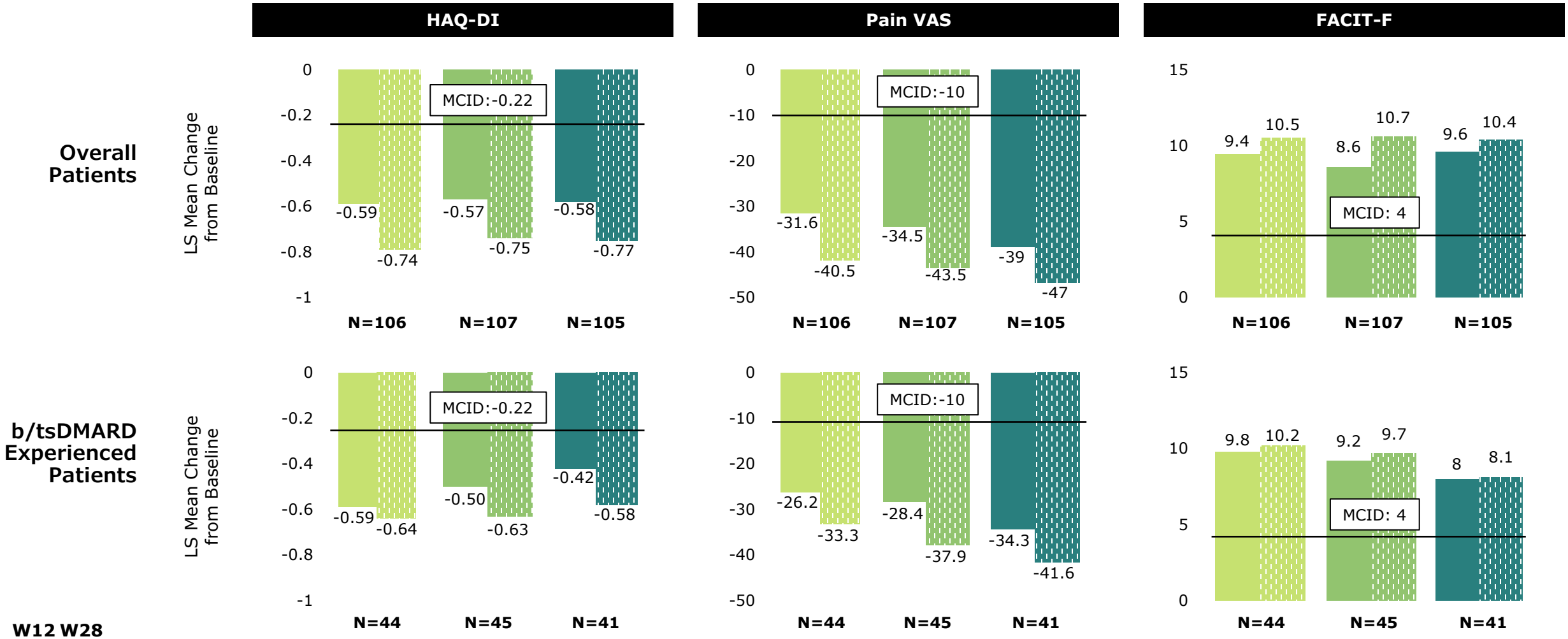
ITT population, NRI analysis



- Consistent improvement across endpoints and populations in the 400mg and 600mg dose arms
- These improvements were despite 14 ACR50 and 3 ACR70 responders at the mandated study continuation visit being imputed as nonresponders at Week 28

Improvement in Patient Reported Outcome Measures from Week 12 to Week 28 in Overall and b/tsDMARD Experienced Population

ITT population, MI-LMCF analysis



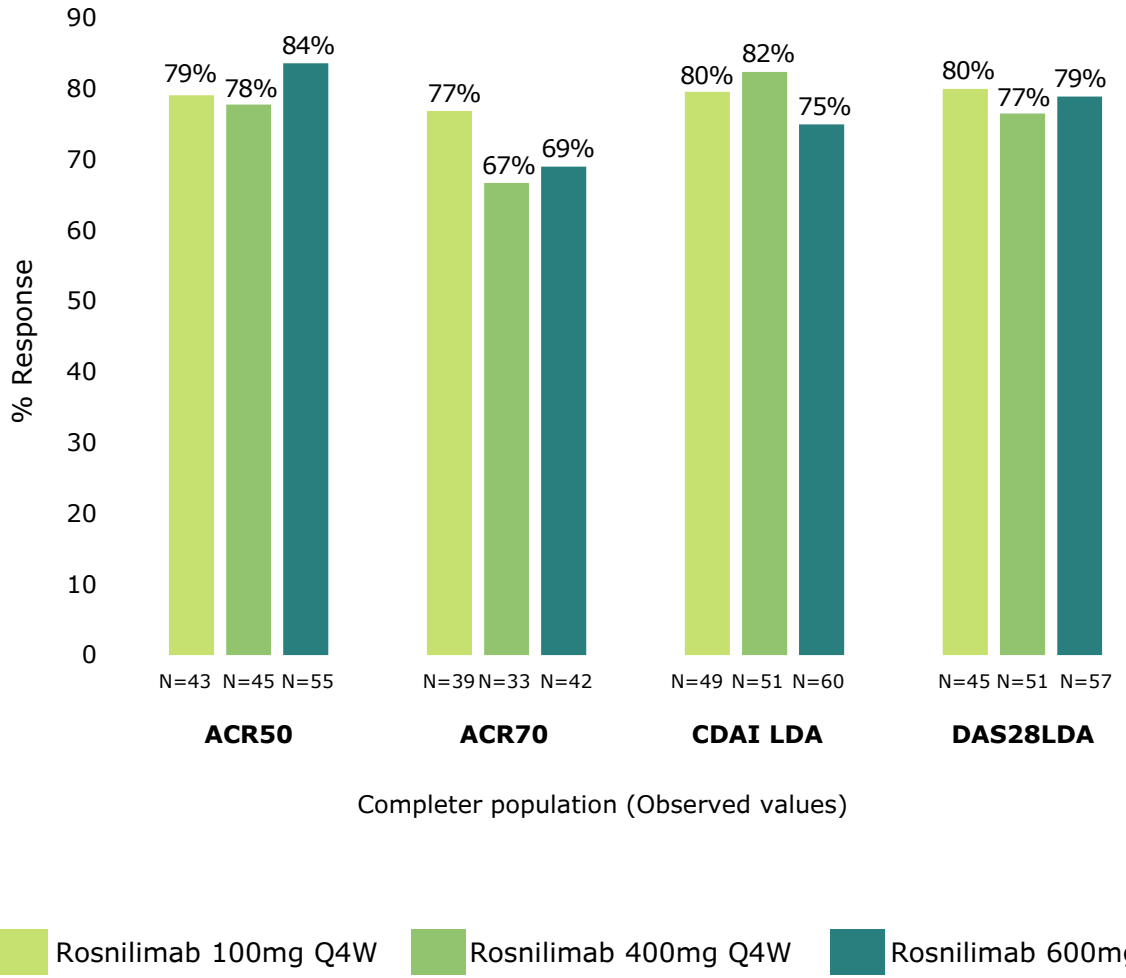
Responses exceed MCID in HAQ-DI, Pain VAS and FACIT-F

PRO responses improve over time

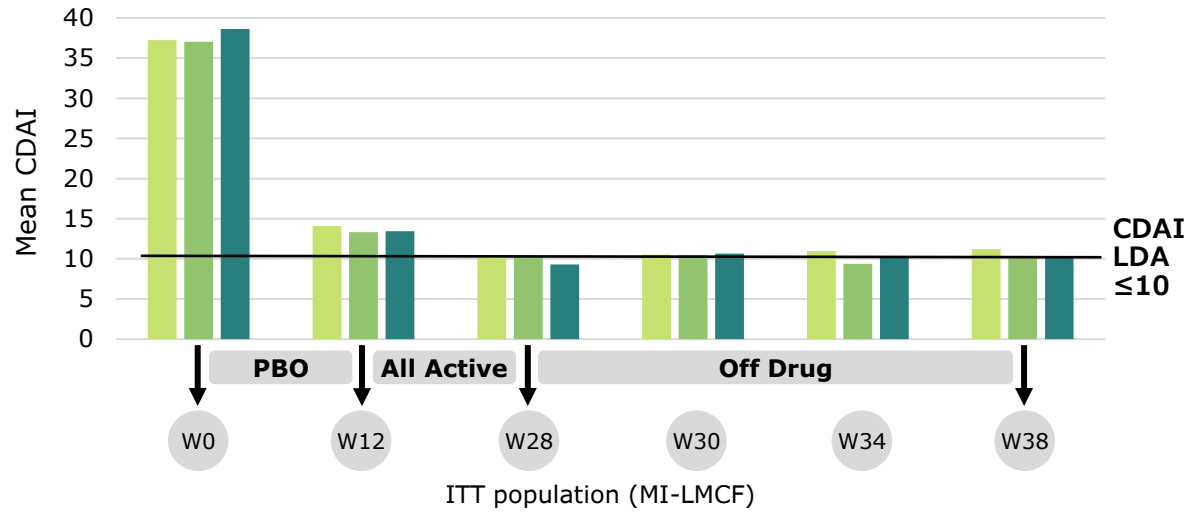
MCID = minimum clinically important difference

Responses Were Durable Off Study Drug for 3 Months

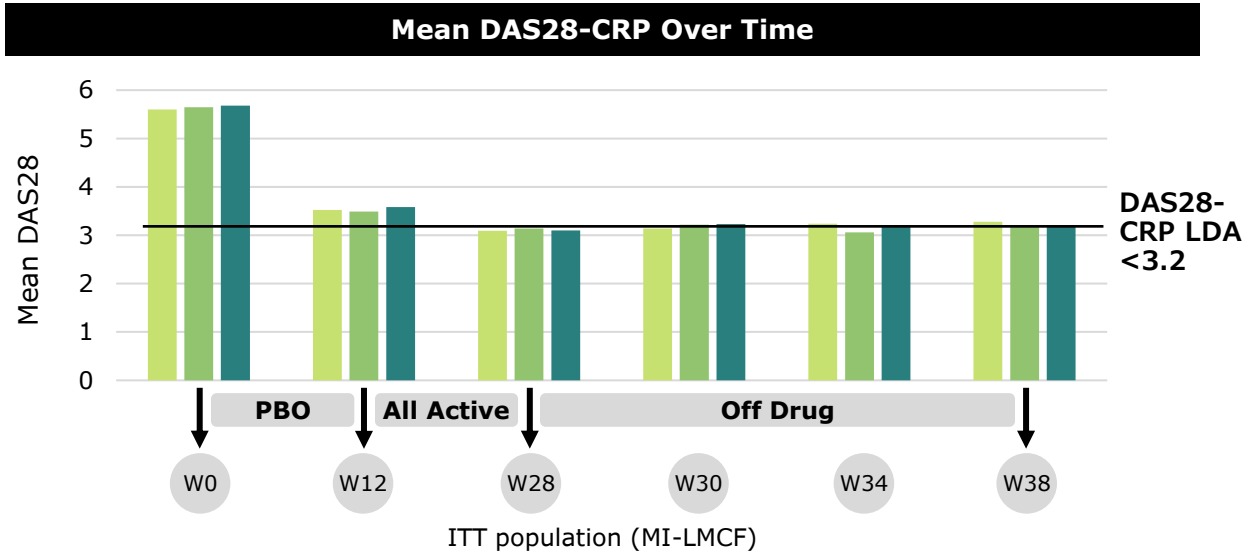
Week 28 Responders Maintaining Response Off-Drug (Week 38)



Mean CDAI Over Time



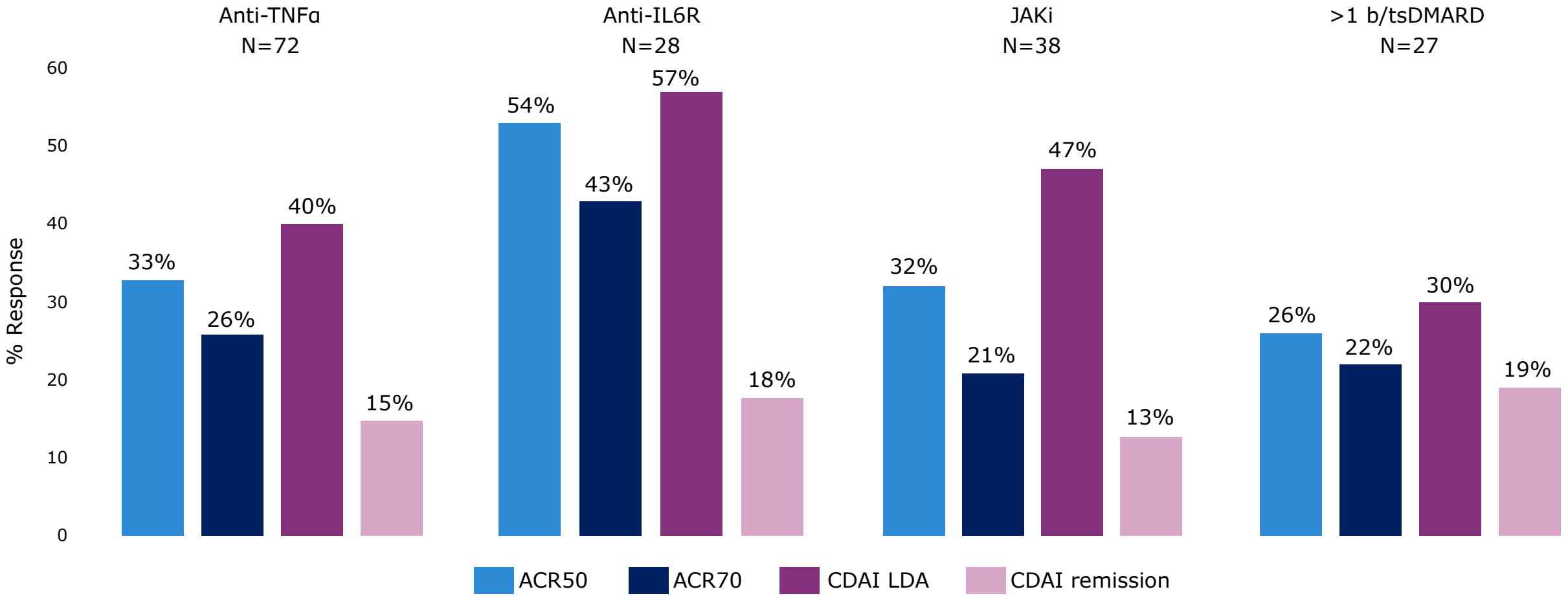
Mean DAS28-CRP Over Time



Responses Across Endpoints Based on Prior Therapeutic Agent (Rosnilimab Pooled Doses)

ITT population, NRI analysis

Week 28



Similar effects observed in more stringent endpoints regardless of prior therapy type, including JAKis

Safety and Tolerability: Treatment Initiation Through Week 38 (End of Follow Up)

	Placebo** N=106 n (Rate)	Rosnilimab 100mg q4w N=106 n (Rate)	Rosnilimab 400mg q4w N=107 n (Rate)	Rosnilimab 600mg q2w N=105 n (Rate)	All Rosnilimab N=318 n (Rate)
Subjects with at least one AE	47 (152.72)	75 (238.29)	69 (190.35)	57 (140.09)	201 (185.41)
Subjects with at least one AE related to study treatment	19 (51.15)	17 (29.07)	28 (49.50)	20 (35.38)	65 (37.89)
Subjects with at least one severe AE	3 (7.12)	4 (6.00)	3 (4.38)	4 (6.13)	11 (5.49)
Subjects with at least one severe study treatment-related AE	1 (2.35)	0	1 (1.45)	0	1 (0.49)
Subjects with at least one SAE	1 (2.35)	3 (4.46)	5 (7.34)	4 (6.14)	12 (5.98)
Subjects with at least one SAE related to study treatment	1 (2.35)	0	0	0	0
Subjects with at least one AE leading to study treatment discontinuation	1 (2.35)	1 (1.48)	3 (4.36)	2 (3.01)	6 (2.95)
Subjects with at least one SAE leading to study treatment discontinuation	1 (2.35)	0	0	0	0
Infections and infestations	23 (60.22)	43 (87.34)	43 (83.83)	35 (64.74)	121 (78.27)
Serious (SAE) infections	1 (2.35)	1 (1.48)	1 (1.45)	1 (1.50)	3 (1.48)
Opportunistic infections*	2 (4.75)	1 (1.48)	1 (1.45)	1 (1.50)	3 (1.47)
MACE	0	1 (1.47)	0	0	1 (0.49)
Malignancies	0	0	0	0	0
Deaths	0	0	0	0	0

- Rosnilimab was well tolerated with no safety dose effect
  - Low rates of treatment discontinuation on account of TEAEs
- Serious infections and opportunistic infections (herpes zoster) were balanced with no dose response
- 1 MACE in 100 mg group was ischemic stroke in participant with stenosis in common carotid artery
- There were no malignancies or deaths

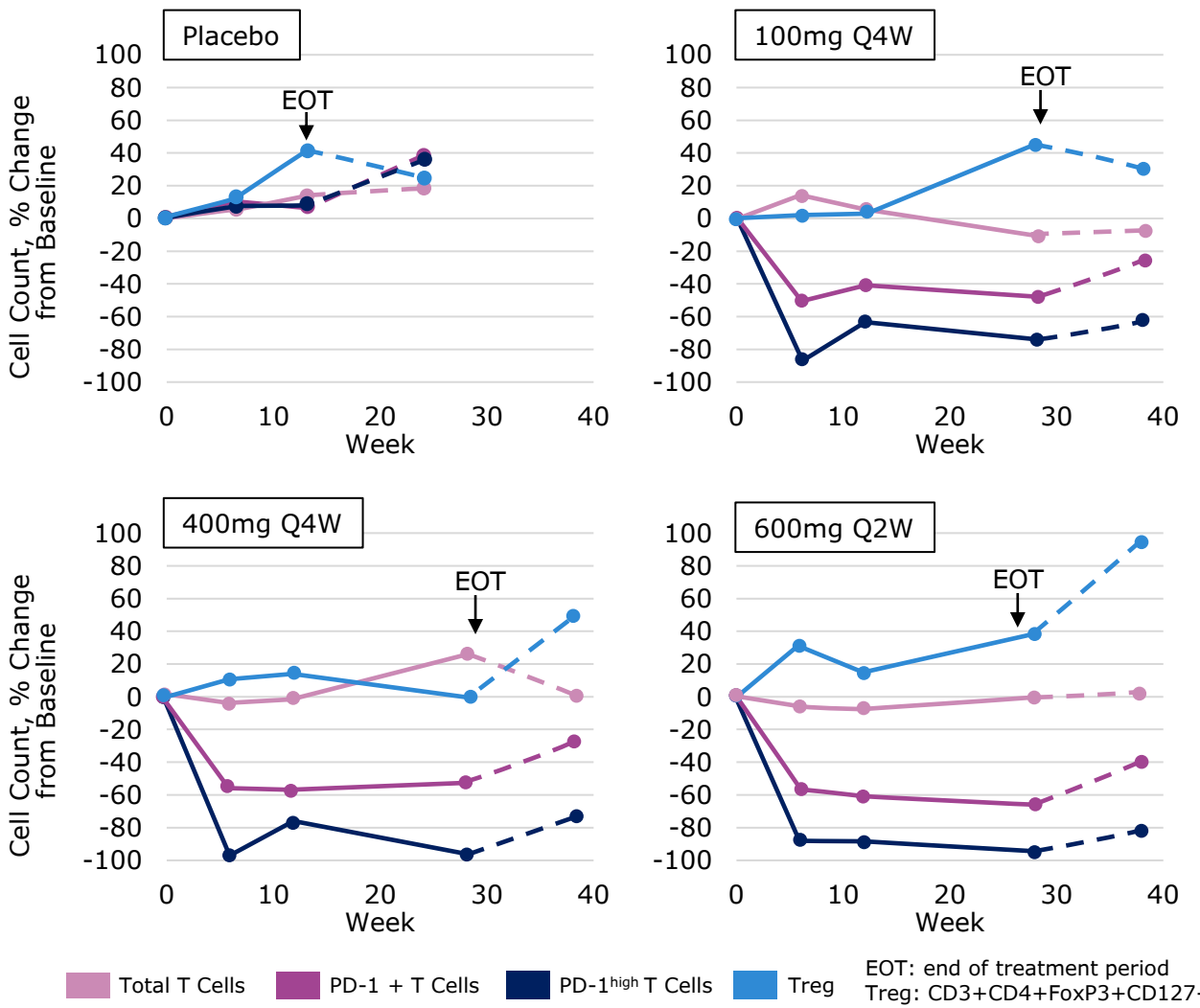
*Herpes zoster is the only opportunistic infection. **Placebo participants received treatment through week 12.

Exposure adjusted incidence rate per 100 person-year = 100 x (Number of subjects with AE in the given period / Total years of exposure in the given period across all subjects at risk for the treatment). All adverse events (AEs) that are summarized above are treatment emergent adverse events. SAE=serious adverse event. N – total number of subjects in analysis set, n – number of subjects in specific category

Translational Data

Rosnilimab Potently Reduced Pathogenic T Cells in Blood

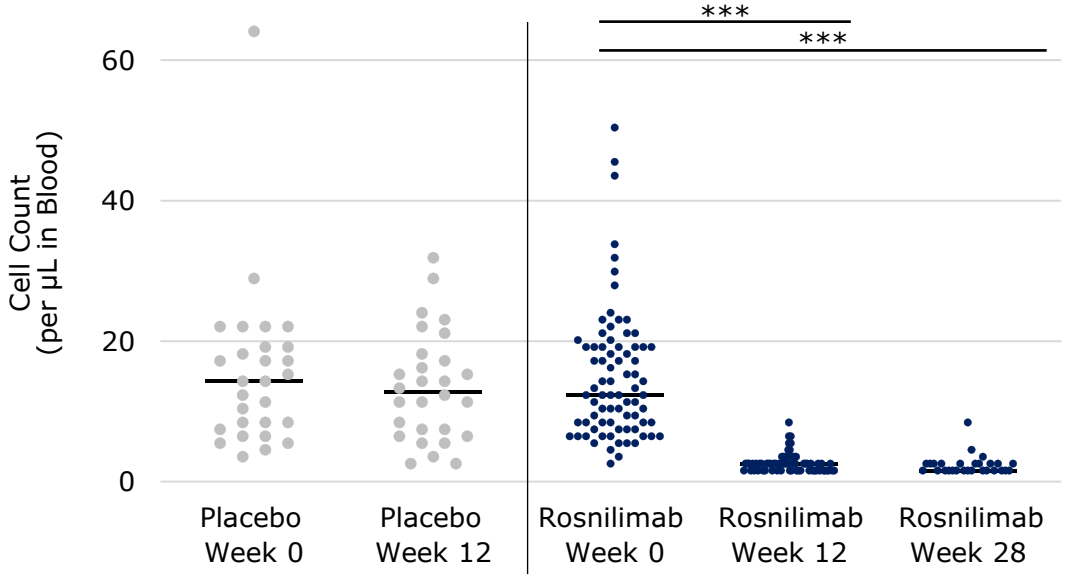
Peripheral T Cell Changes Over Time



EOT: end of treatment period
Treg: CD3+CD4+FoxP3+CD127-

- >90% reduction in PD-1^{high} 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^{high} 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

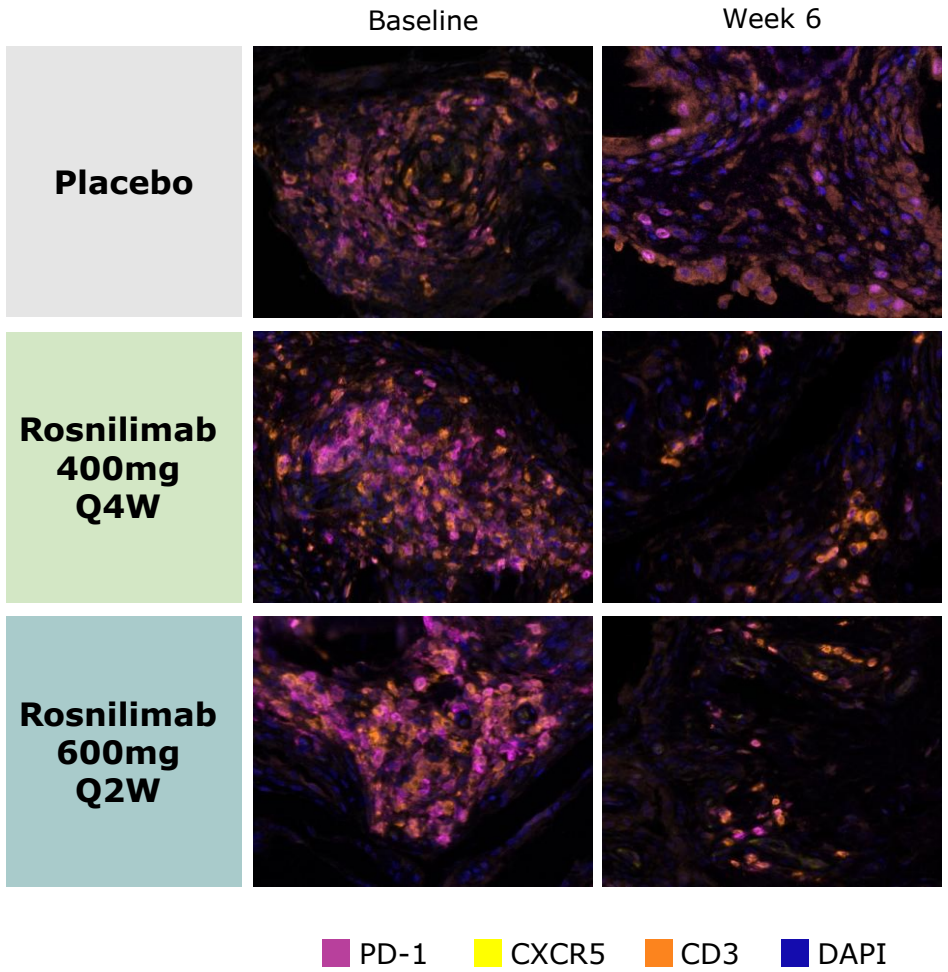
Rosnilimab T_{ph} Impact - Pooled Doses



T_{ph}: CD3+CD4+CD45RA-PD1^{high} CXCR5-
***p<0.001

Rosnilimab Demonstrated Pathogenic T cell Depletion and Broad Downregulation of T cell, B cell and Myeloid Pathways in Synovium

Synovial immunohistochemistry
n= 39 paired samples



Representative IHC samples from synovial biopsies. % change calculated for synovial samples with ≥10cells/mm² in baseline biopsy.
T_{ph}: PD-1+CD3+CD4+CXCR5-

Impact on Synovial PD-1+ T cells

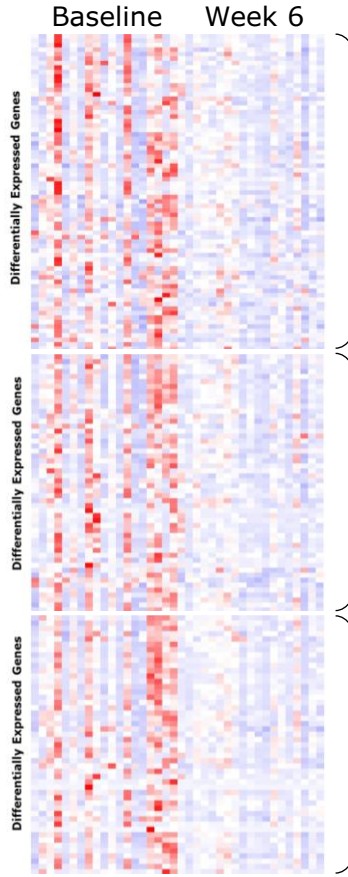
Placebo
increased

100mg dose
no consistent changes

400mg dose
~90% reduction

600mg dose
~90% reduction

Synovial bulk RNA-seq (rosnilimab pooled doses)
n= 24 paired samples, responders & nonresponders



Downregulated* genes of interest include:

T Cell Activation
CD28, IL2RA, ZAP70, CD69, CD40L, ICOS, JAK3, IRF1

B Cell Activation
PLCG2, CD79A, FCGR2B, IL7R, TNFRSF13C (BAFF-R), TNFRSF17 (BCMA), BTK

Myeloid Activation
IFNGR2, TLR2, FCGR2B, ITGAM, MYD88, CXCL8, SLAMF1, MMP1, MMP3, RANKL

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; B cell activation 4.06, p=1.77e-18; myeloid activation 4.15, p=6.44e-18 *p<0.05

CDAI LDA responders showed greater reductions in T cell and B cell activation ($p < 0.0001$ for both)

Summary

- At Week 12, the primary endpoint of mean change in DAS28-CRP was achieved across all doses of rosnilimab compared to placebo, as was ACR20
- At Week 28, improvements observed in ACR50/70, CDAI LDA and CDAI remission
  - Responses independent of prior therapy type (including JAKi)
- At Week 38, 3 months off study drug, clinical responses were sustained
- Safety data through Week 38 demonstrated rosnilimab was well tolerated, including no malignancies and no deaths
- Rosnilimab potently reduced pathogenic T cells in the blood and synovium resulting in downregulation of a wide range of inflammatory pathways

Conclusions

- Rosnilimab, with a novel MoA, demonstrated a meaningful and durable clinical benefit along with a favorable safety profile in this large Phase 2B rheumatoid arthritis trial

- Clinical proof-of-concept for pathogenic T cell depletion was achieved and corroborated by translational validation in the blood and synovium

- Based on these data and the unmet need in RA, further clinical development of rosnilimab is warranted

Thank You!

to

Patients
Caregivers
Investigators
Study Staff
& Everyone

involved in this study!

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