Efficacy and Safety Results from a Phase 2 Trial of Risankizumab, a Selective IL-23p19 Inhibitor, in Patients with Active Psoriatic Arthritis

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PJ Mease has received research grants, consulting fees, and/or speaker's fees from AbbVie, Amgen, Bristol Myers, Celgene, Genentech, Janssen, Leo, Lilly, Merck, Novartis, Pfizer, Sun Pharma, and UCB.

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S Aslanyan and **B Berner** are full-time employees of Boehringer Ingelheim.

K Chen and **A Eldred** are full-time salaried employees of AbbVie and may own stock/options.

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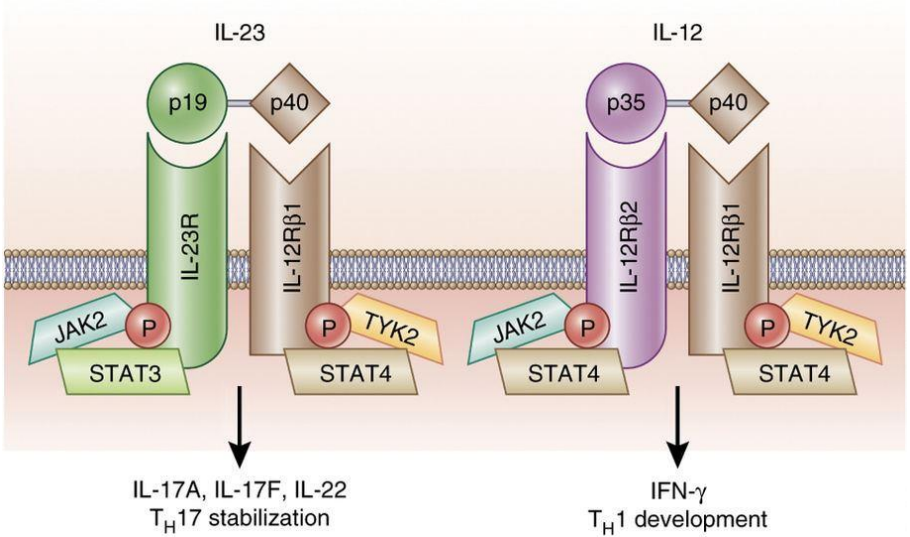
Background

- Interleukin-23 (IL-23), a key regulator of multiple effector cytokines, has been implicated in psoriatic skin lesions, synovitis, enthesitis, and bone remodeling
- Risankizumab (RZB) is a potent humanized IgG1 monoclonal antibody that inhibits IL-23 by specifically binding to its p19 subunit

IL-23 and IL-12 Signaling[1]



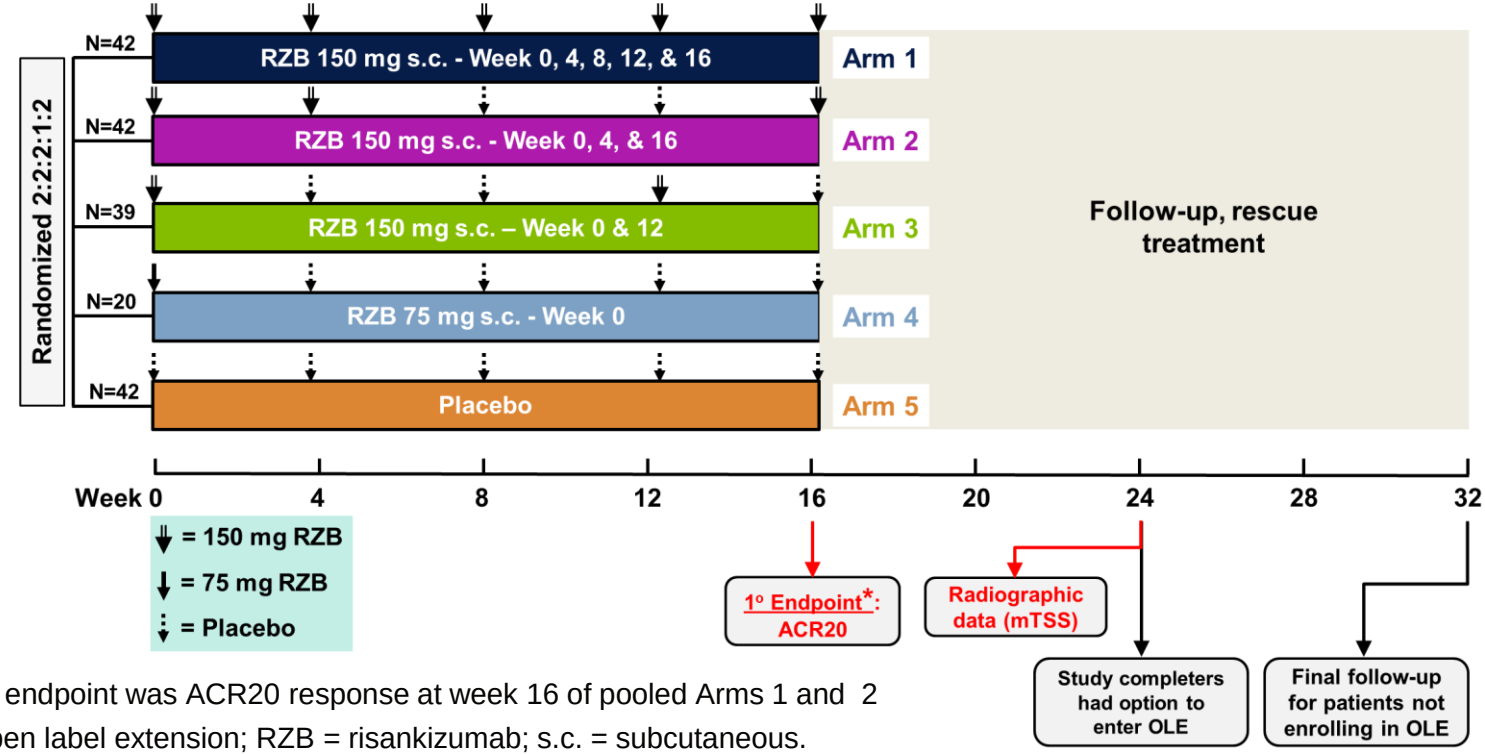
1. Teng et al., *Nat. Med.* 2015;21(7):19-29.

Objective

- The purpose of this dose-ranging Phase 2 study was to provide proof-of-concept and evaluate the safety and efficacy of risankizumab in patients with active psoriatic arthritis (PsA)

Methods: Study Design

185 adult patients with active PsA who met Classification Criteria for Psoriatic Arthritis (CASPAR) were stratified at randomization by **prior TNFi use** and **concurrent MTX use**



*Primary endpoint was ACR20 response at week 16 of pooled Arms 1 and 2

OLE = open label extension; RZB = risankizumab; s.c. = subcutaneous.

Methods: Patients Entry Criteria

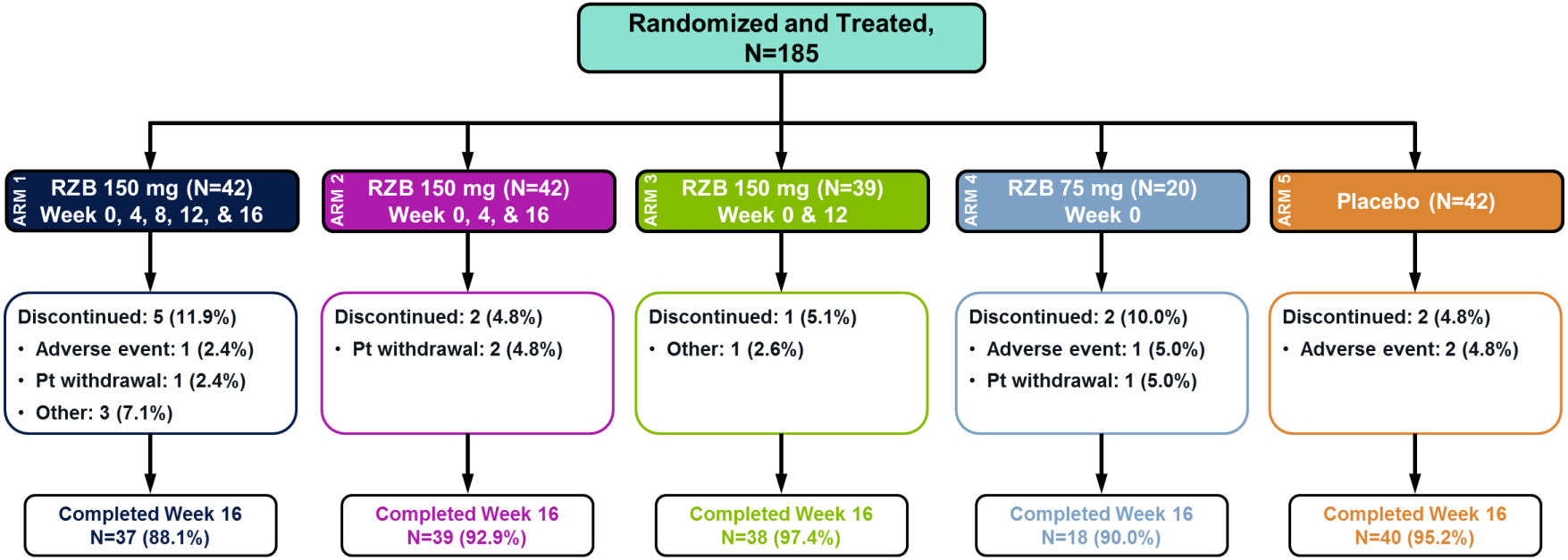
Key Inclusion Criteria:

- Active PsA, defined as ≥5 tender joints and ≥5 swollen joints
- At least one psoriatic lesion or a documented history of psoriasis
- Inadequate response or intolerance to standard doses of NSAIDs (≥4 weeks), or csDMARDs (≥3 months), or TNFi
- Must be on stable dose if receiving concomitant medications (MTX, oral corticosteroids, NSAIDs)

Key Exclusion Criteria:

- Prior exposure to any therapeutic agent targeting IL-12/23, IL-23, or IL-17
- Prior exposure to >2 different TNFi
- Exposure to TNFi within 8–12 weeks prior to randomization
- Exposure to csDMARDs (except MTX) within 4 weeks prior to randomization
- Exposure to topical psoriasis medication or phototherapy within 4 weeks prior to randomization

Results: Patient Disposition



Pt = Patient; RZB = risankizumab.

Results: Baseline Demographics and Disease Characteristics

Characteristic	Risankizumab (RZB)				Placebo N=42
	150 mg W 0, 4, 8, 12, & 16 N=42	150 mg W 0, 4, & 16 N=42	150 mg W 0 & 12 N=39	75 mg W 0 N=20	
Age, years, mean (SD)	51.8 (14.6)	50.1 (12.3)	51.6 (11.9)	53.8 (11.0)	49.0 (11.2)
Female, n (%)	21 (50.0)	14 (33.3)	17 (43.6)	10 (50.0)	18 (42.9)
Race, White, n (%)	35 (85.4)	37 (92.5)	34 (89.5)	15 (78.9)	36 (85.7)
Weight, mean (SD)	86.0 (17.5)	83.3 (19.7)	84.6 (13.0)	83.8 (17.4)	84.8 (20.6)
BMI (Kg/m^2), mean (SD)	29.4 (5.6)	27.8 (5.3)	29.1 (3.9)	30.1 (5.3)	29.4 (6.7)
PsA duration[a], years, mean (SD)	6.0 (7.6)	6.1 (7.0)	7.4 (8.3)	7.9 (7.8)	7.0 (8.8)
PsO affecting ≥3% BSA, n (%)	16 (41.0)	20 (48.8)	23 (59.0)	9 (47.4)	21 (50.0)
Presence of dactylitis, n (%)	13 (31.7)	13 (31.0)	14 (35.9)	6 (30.0)	10 (23.8)
Presence of enthesitis (LEI), n (%)	20 (47.6)	21 (51.2)	20 (47.6)	23 (59.0)	20 (47.6)
Presence of enthesitis (SPARCC), n (%)	28 (66.7)	25 (59.5)	26 (66.7)	13 (65.0)	25 (59.5)
Prior exposure to TNFi, n (%)	11 (26.2)	11 (26.2)	9 (23.1)	4 (20.0)	10 (23.8)
Concurrent exposure to MTX, n (%)	24 (57.1)	24 (57.1)	23 (59.0)	11 (55.0)	24 (57.1)

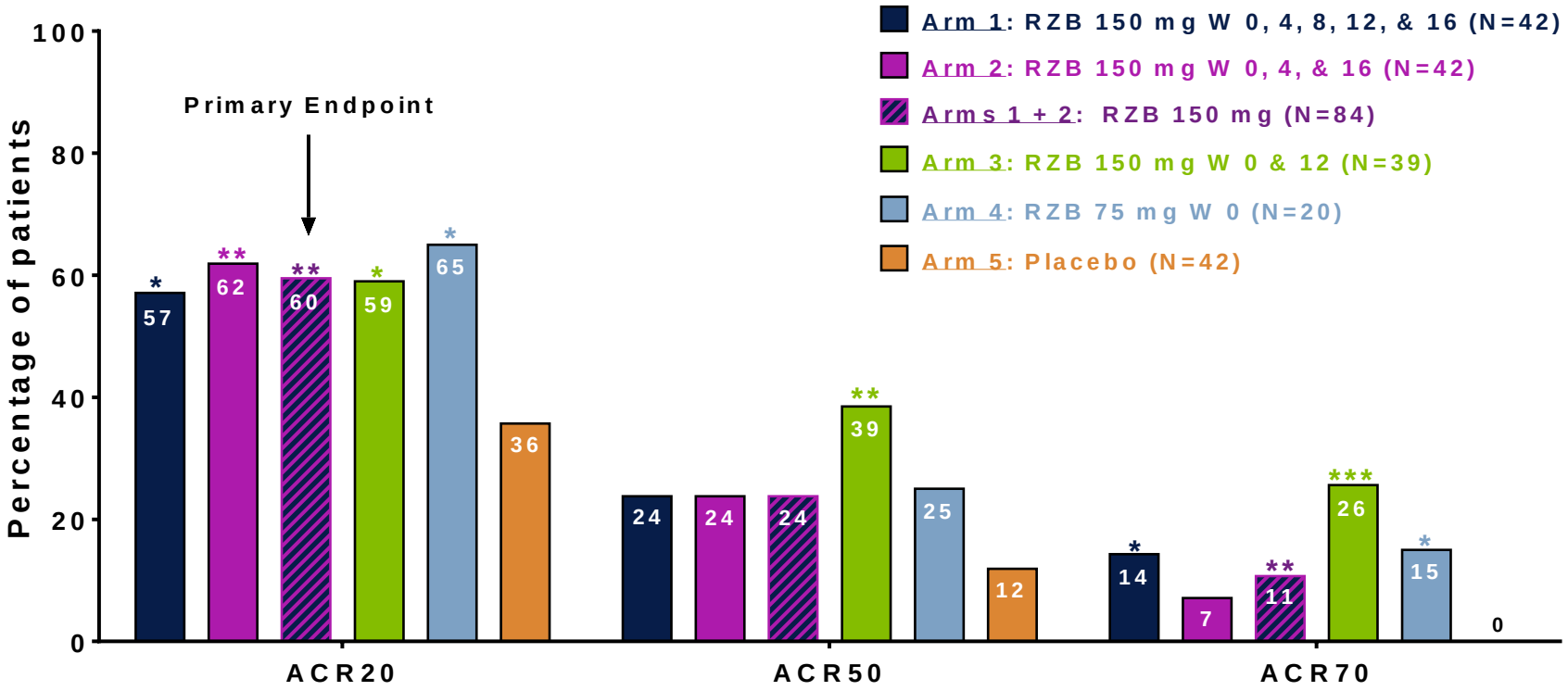
[a]Duration since diagnosis. SD = standard deviation; W = week.

Results: Baseline Demographics and Disease Characteristics

Characteristic, mean (SD)	Risankizumab (RZB)				Placebo N=42
	150 mg W 0, 4, 8, 12, & 16 N=42	150 mg W 0, 4, & 16 N=42	150 mg W 0 & 12 N=39	75 mg W 0 N=20	
DAS28(CRP)	4.6 (1.1)	4.7 (1.1)	4.8 (0.8)	4.9 (0.8)	4.6 (1.3)
CRP, mg/L	9.5 (11.5)	12.1 (31.0)	7.6 (12.0)	9.5 (10.7)	10.2 (14.3)
Dactylitis Count[a]	3.0 (2.3)	3.9 (4.2)	4.1 (4.5)	3.3 (2.7)	4.5 (4.5)
SPARCC enthesitis Index[b]	4.4 (4.1)	4.4 (4.2)	4.5 (3.0)	6.5 (4.3)	4.7 (3.9)
Leeds enthesitis Index[b]	1.9 (1.9)	1.9 (1.7)	2.0 (1.5)	2.7 (2.2)	2.2 (1.7)
PASI[c]	7.2 (9.5)	7.7 (7.3)	9.8 (8.9)	8.0 (11.8)	6.2 (5.8)
BSA (%)	4.8 (10.0)	6.9 (12.9)	9.4 (13.6)	6.6 (13.8)	6.0 (10.5)
Swollen joint count, 66 joints	12.0 (11.3)	13.1 (10.0)	11.3 (7.3)	8.7 (4.3)	10.4 (7.2)
Tender joint count, 68 joints	20.0 (14.5)	20.8 (14.9)	20.7 (13.4)	17.2 (14.6)	19.4 (15.4)
Pain-VAS	56.4 (23.1)	52.5 (26.9)	59.4 (23.6)	60.2 (26.6)	57.6 (22.6)
HAQ-DI	1.1 (0.7)	1.1 (0.7)	1.0 (0.6)	1.1 (0.7)	1.0 (0.7)

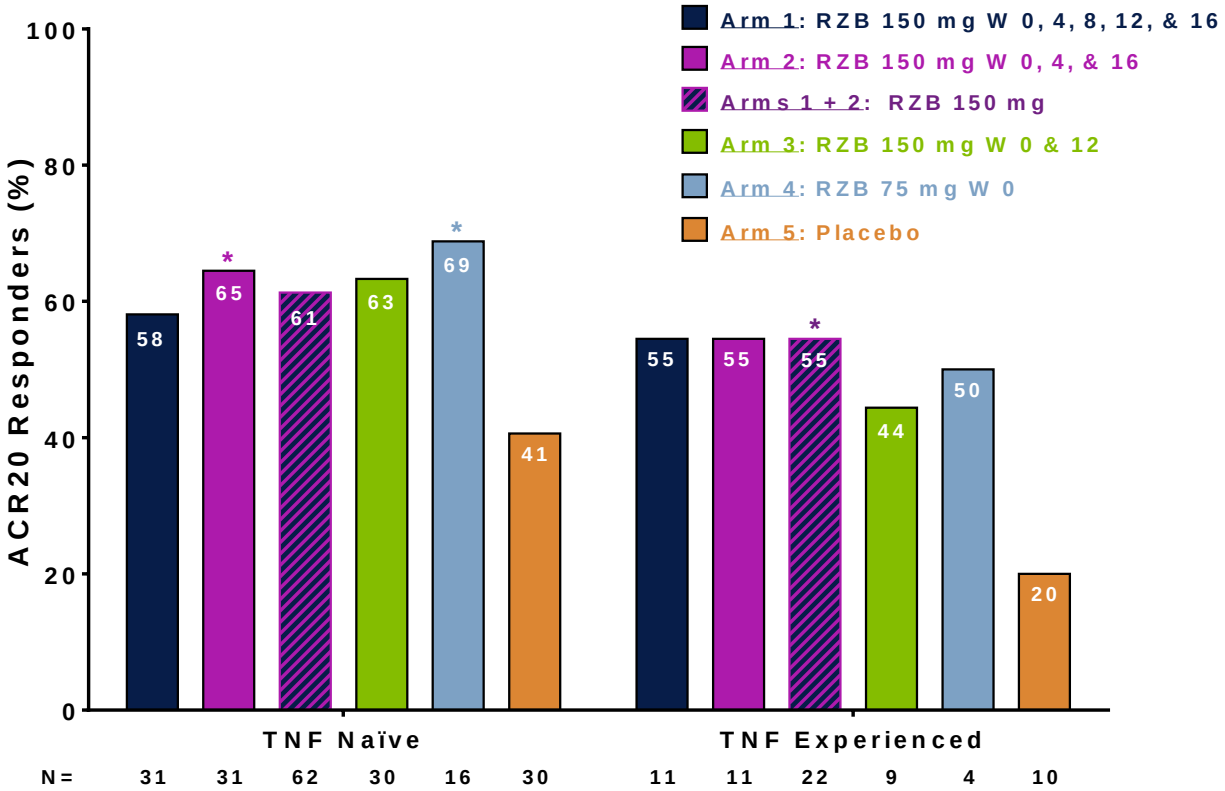
[a]Dactylitis count in patients with dactylitis at baseline; [b]SPARCC and Leeds enthesitis index in patients with enthesitis at baseline based on LEI or SPARCC; [c]PASI assessed in patients with psoriasis affecting ≥3% BSA at baseline. SD = standard deviation; W = week.

Results: ACR Responses at Week 16 (NRI)



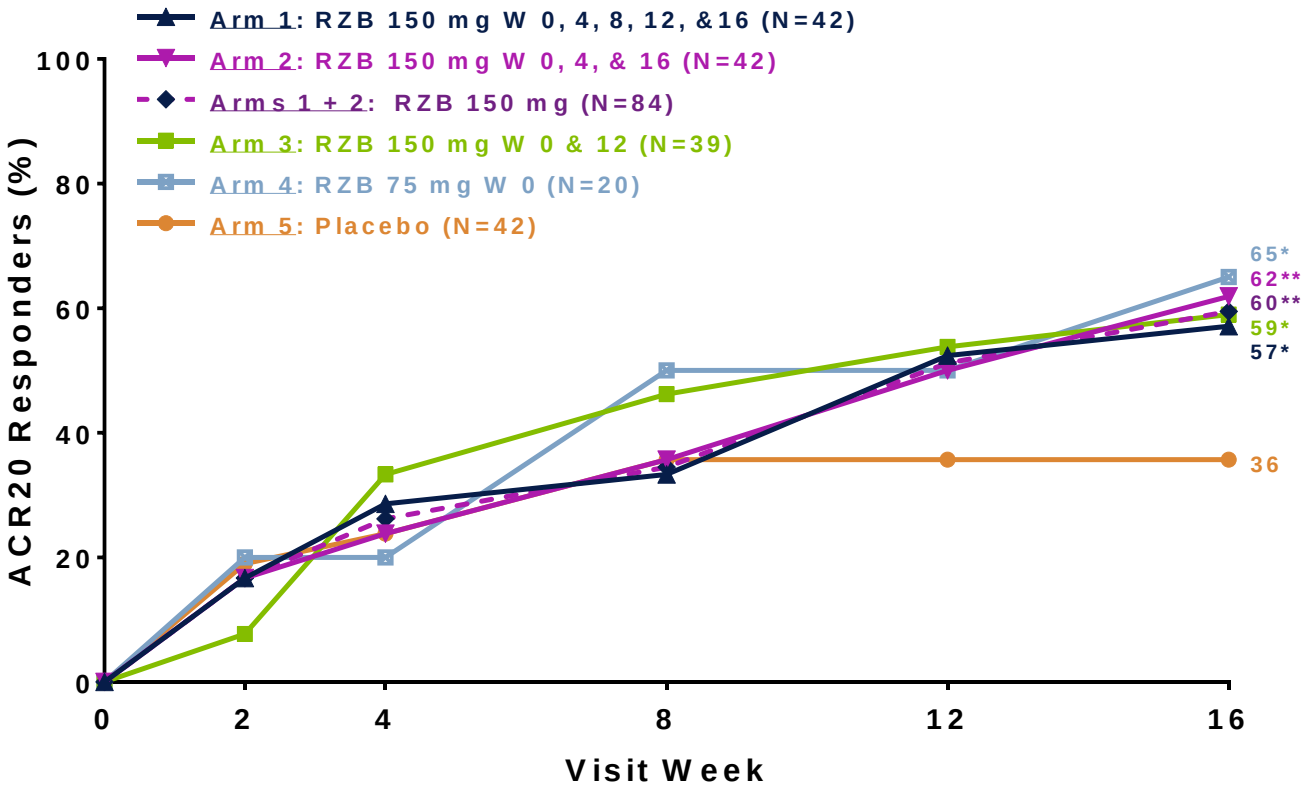
P-values for comparison vs placebo: ***, P <0.001; **, P <0.01; *, P <0.05; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: ACR20 Responses by TNFi Exposure at Week 16 (NRI)



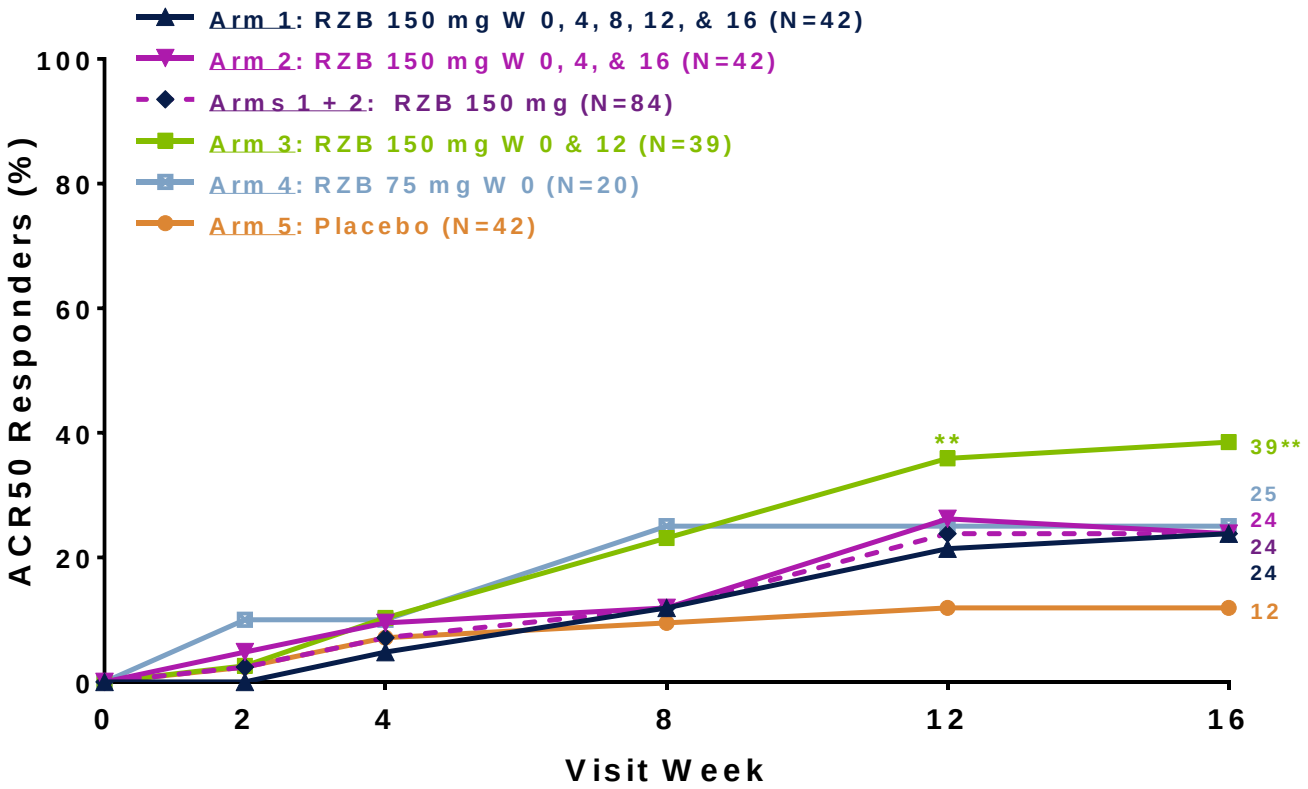
P-values for comparison vs placebo: *, P <0.05; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: Time Course of ACR20 Responses (NRI)



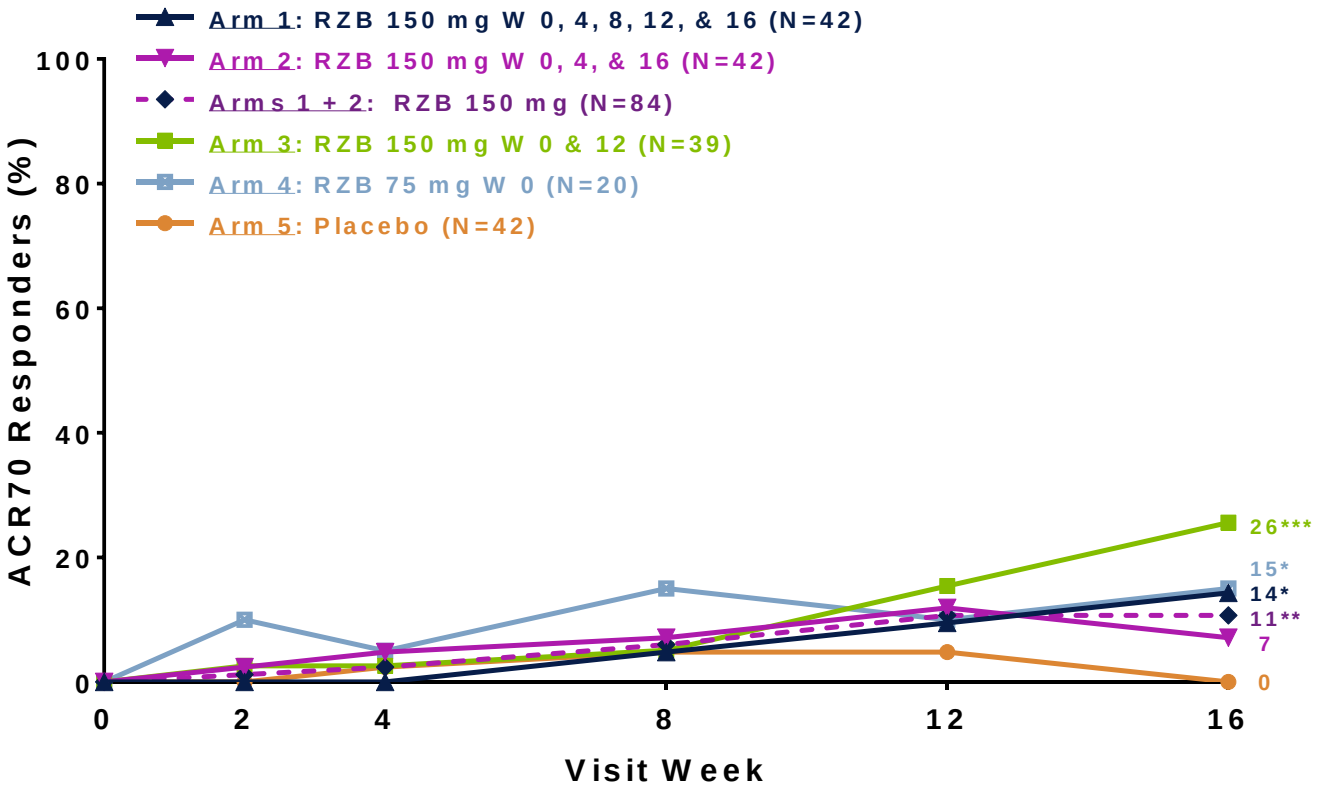
P-values for comparison vs placebo: **, P <0.01; *, P <0.05; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: Time Course of ACR50 Responses (NRI)



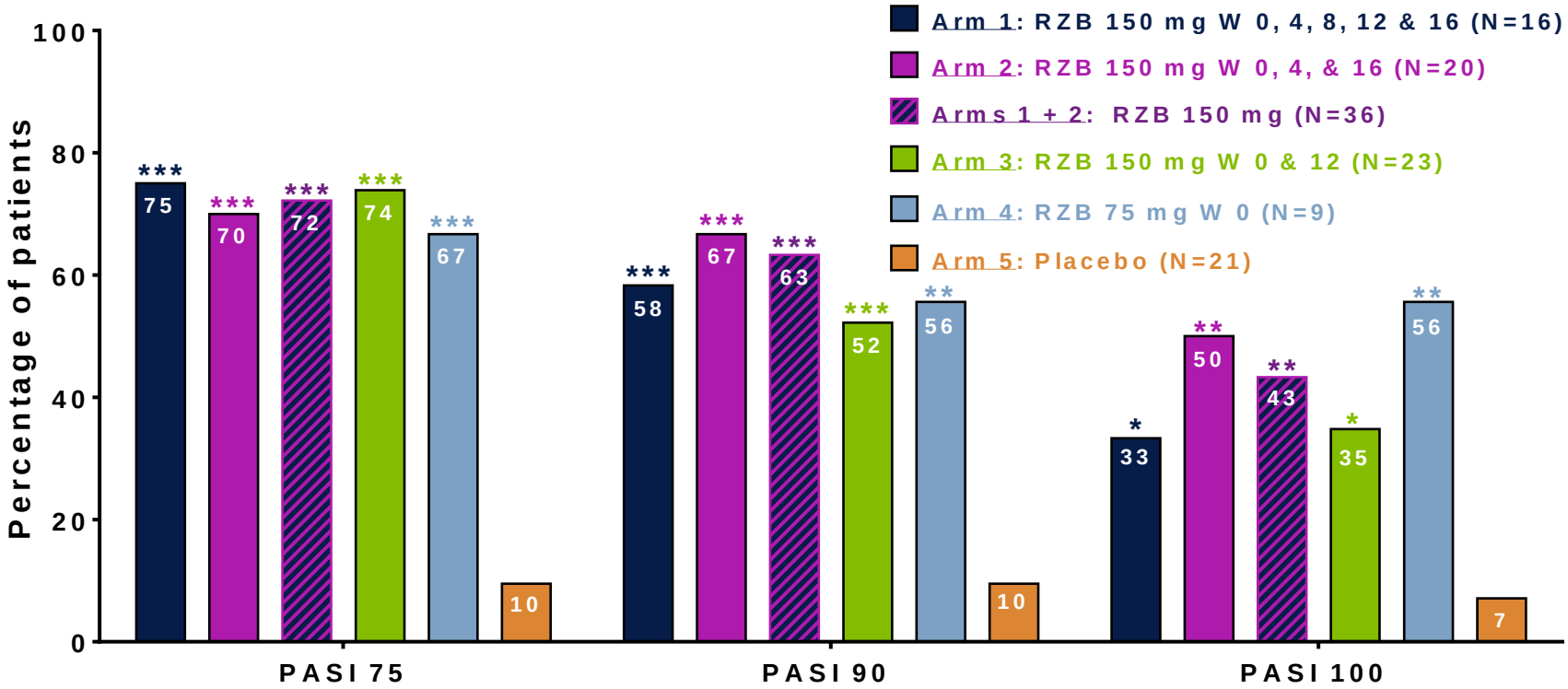
P-values for comparison vs placebo: **, P <0.01; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: Time Course of ACR70 Responses (NRI)



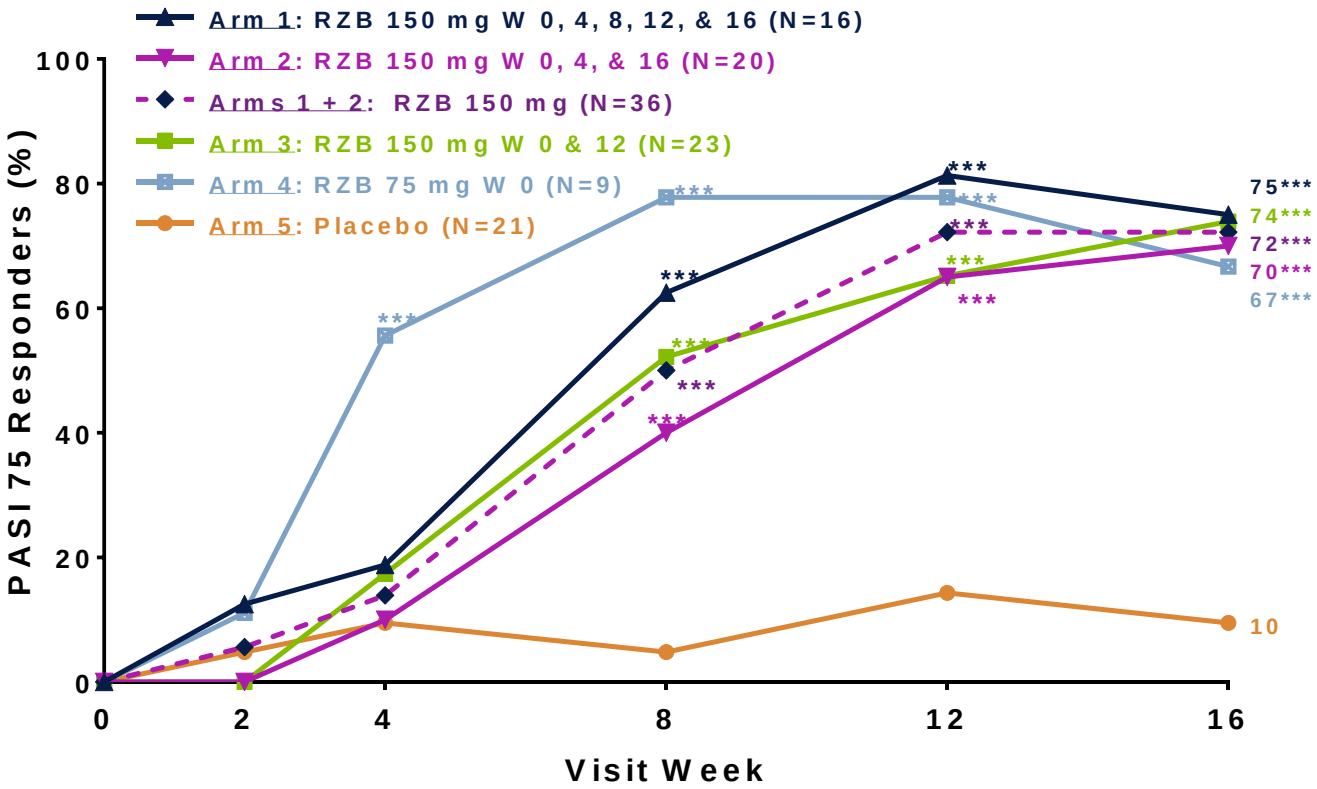
P-values for comparison vs placebo: ***, P <0.001; **, P <0.01; *, P <0.05; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: PASI Responses[a] at Week 16 (NRI)



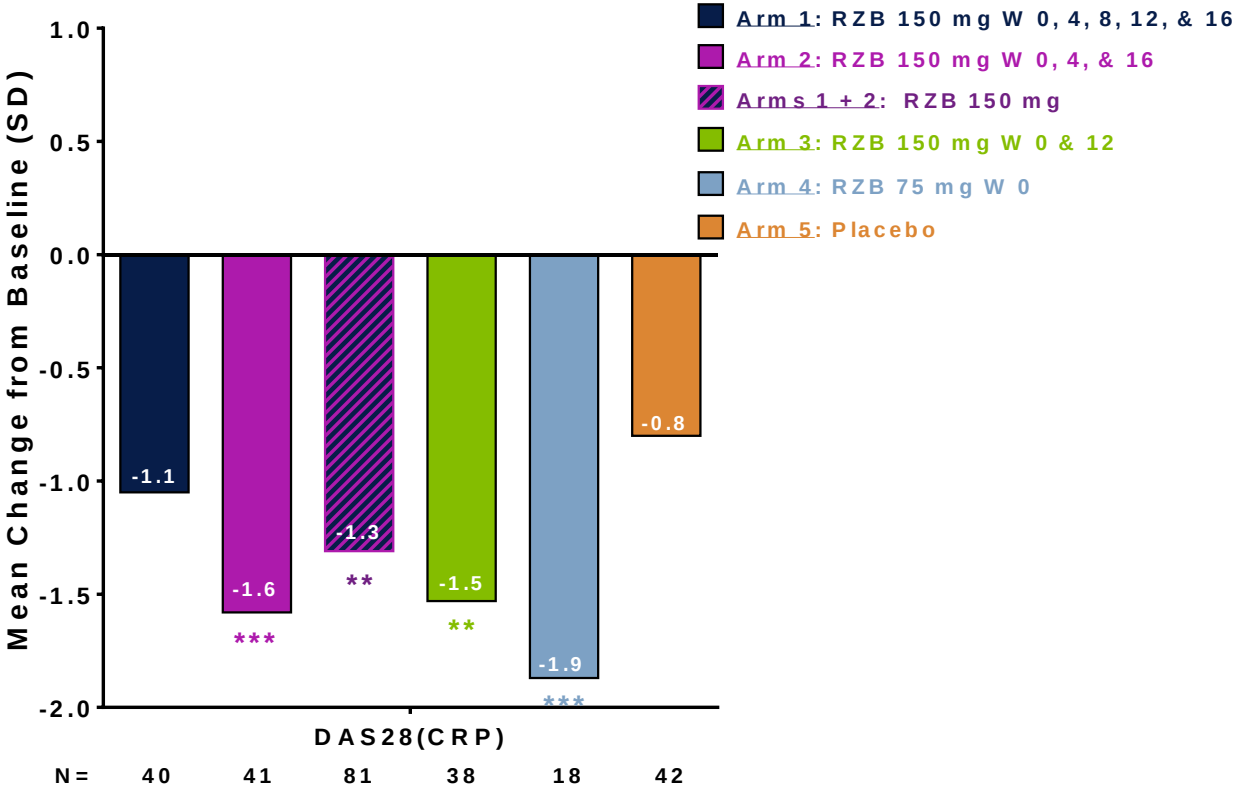
[a]PASI assessed in patients with psoriasis affecting ≥3% BSA at baseline; P-values for comparison vs placebo: ***, P <0.001; **, P <0.01; *, P <0.05; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: Time Course of PASI 75 Responses[a] (NRI)



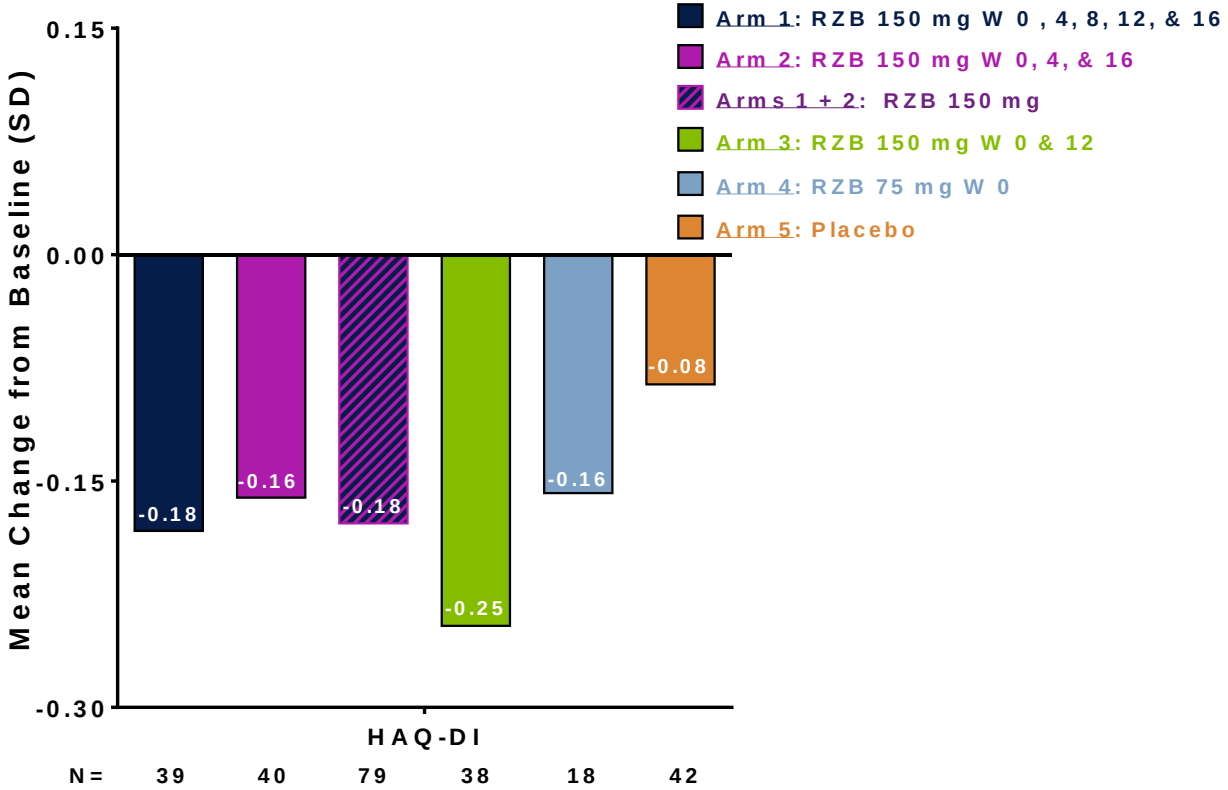
[a]PASI assessed in patients with psoriasis affecting ≥3% BSA at baseline; P-values for comparison vs placebo: ***, P <0.001; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: ΔDAS28(CRP) at Week 16 (MMRM)



P-values for comparison vs placebo: ***, P <0.001; **, P <0.01; no multiplicity adjustment; MMRM = mixed model repeated measures; W = week.

Results: ΔHAQ-DI at Week 16 (MMRM)

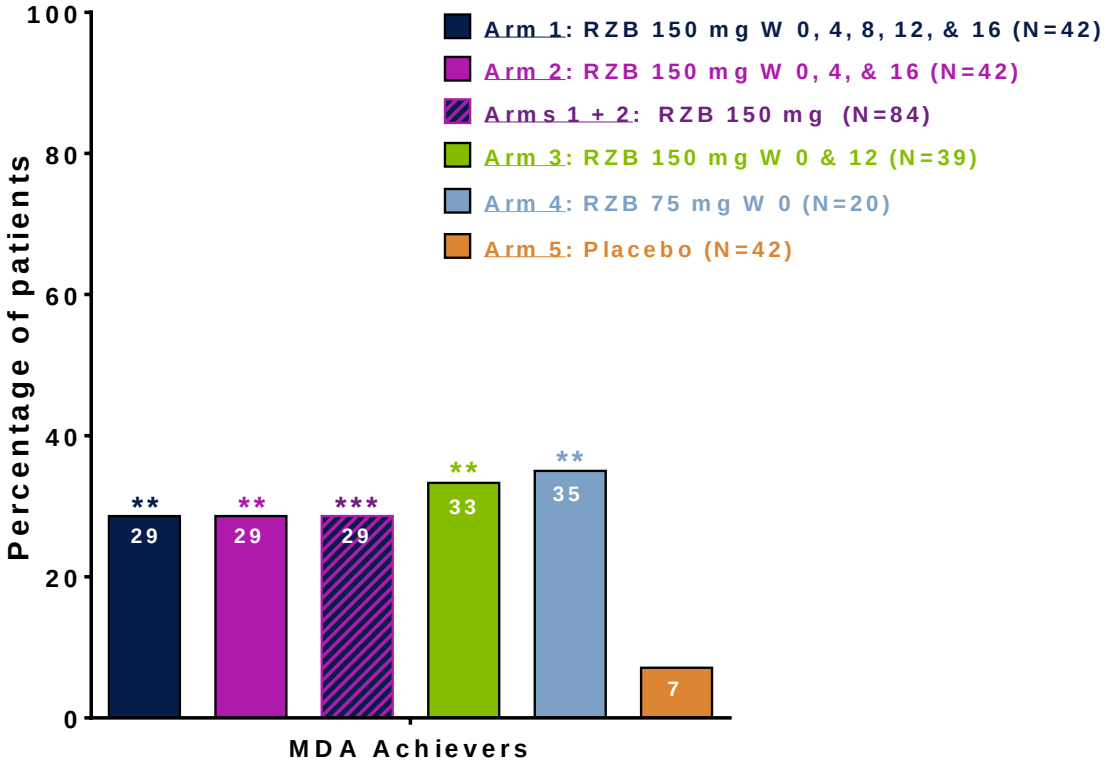


MMRM = mixed model repeated measures; W = week.

Results: MDA Achievers at Week 16 (NRI)

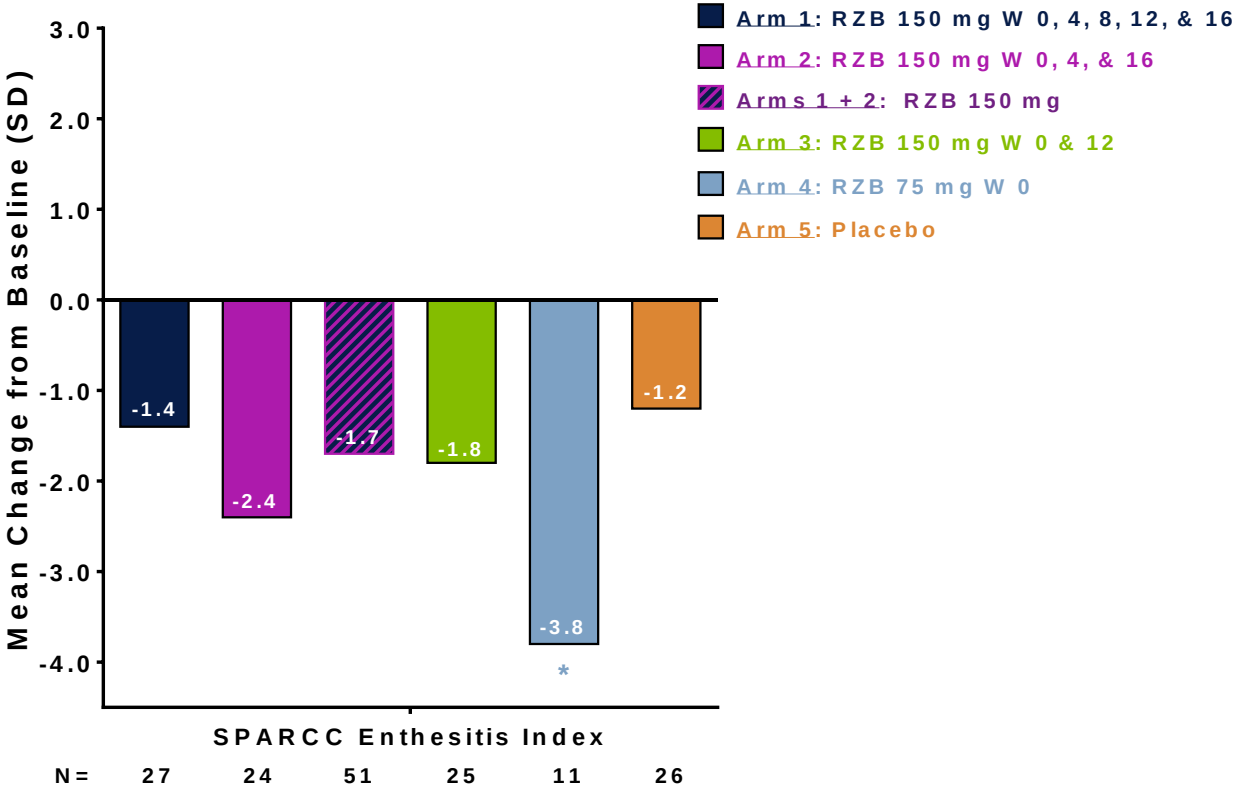
Minimal Disease Activity defined as achieving ≥5 of the following 7 criteria:

- TJC68 ≤1
- SJC66 ≤1
- PASI ≤1 or BSA ≤3%
- Pain VAS ≤15
- PtGA VAS ≤20
- HAQ-DI ≤0.5
- Tender entheseal points ≤1



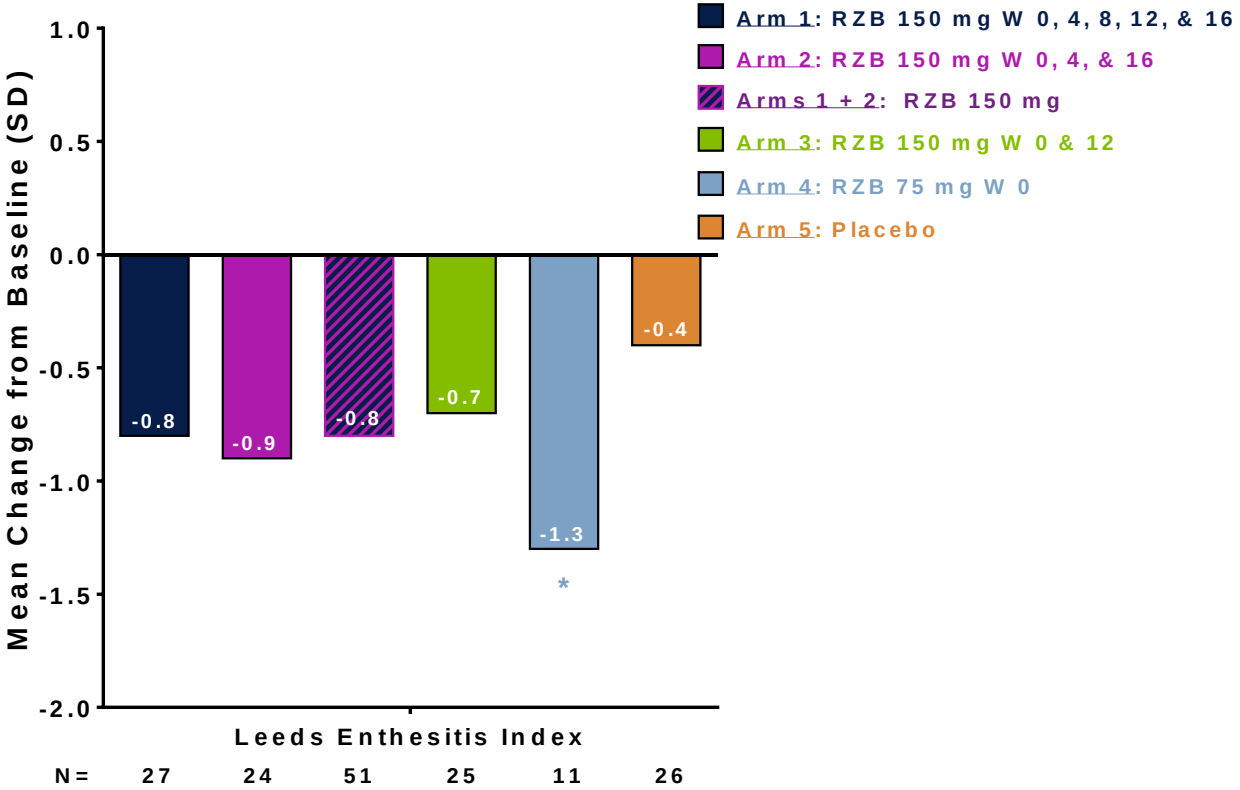
P-values for comparison vs placebo: ***, P <0.001; **, P <0.01; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: ΔSPARCC Enthesitis Index[a] at Week 16 (MMRM)



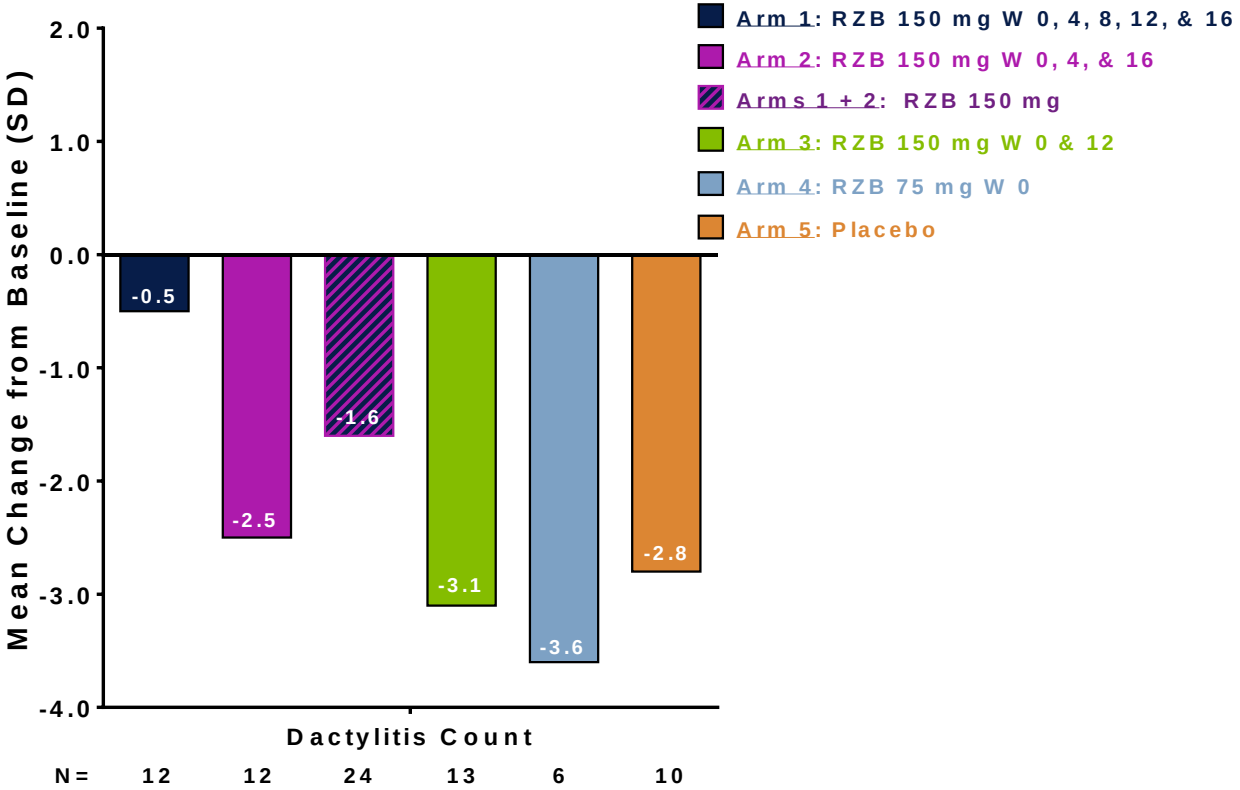
[a]SPARCC enthesitis index in patients with enthesitis at baseline based on LEI or SPARCC; P-values for comparison vs placebo: *, P <0.05; no multiplicity adjustment; MMRM = mixed model repeated measures; W = week.

Results: ΔLeeds Enthesitis Index at Week 16 (MMRM)



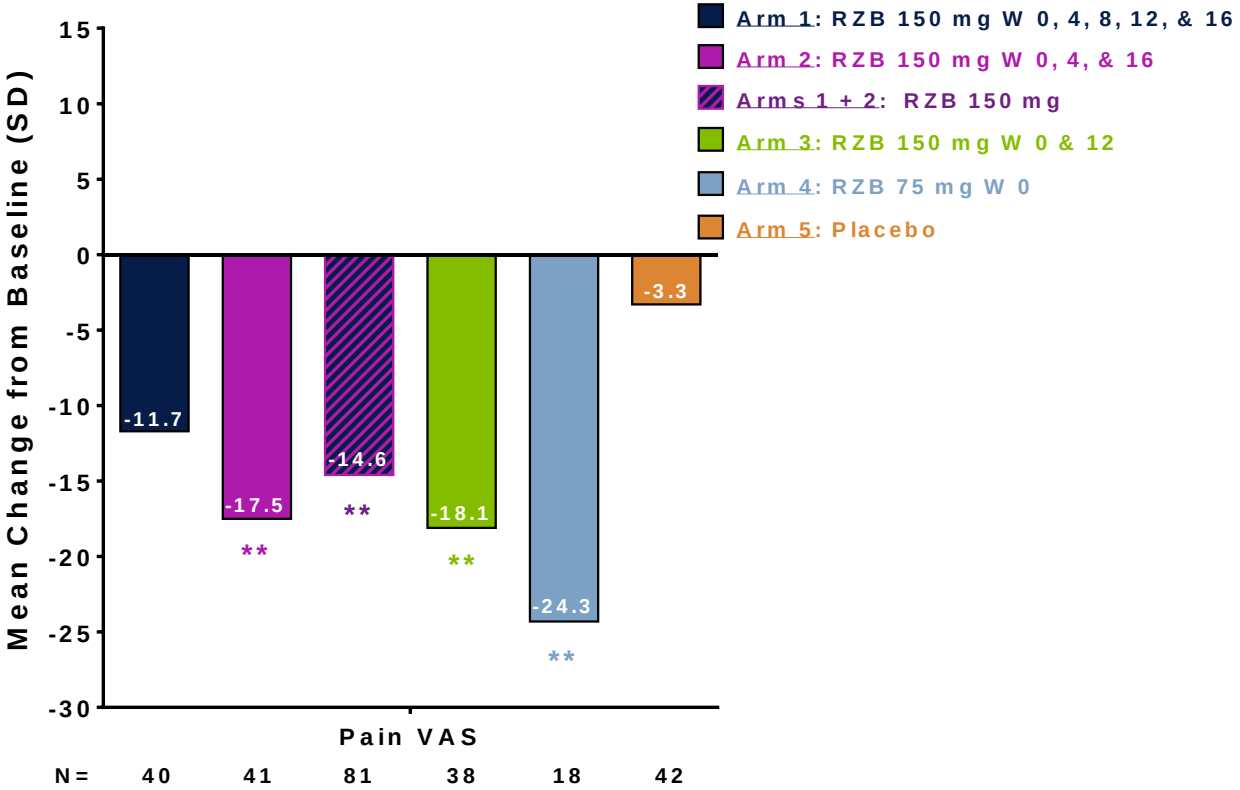
[a]Leeds enthesitis index in patients with enthesitis at baseline based on LEI or SPARCC; P-values for comparison vs placebo: *, P <0.05; no multiplicity adjustment; MMRM = mixed model repeated measures; W = week.

Results: ΔDactylitis Count[a] at Week 16 (MMRM)



[a]Dactylitis count in patients with dactylitis at baseline; MMRM = mixed model repeated measures; W = week.

Results: ΔPain VAS at Week 16 (MMRM)



P-values for comparison vs placebo: **, P <0.01; no multiplicity adjustment; MMRM = mixed model repeated measures; W = week.

Results: Safety Summary – TEAEs Over 16 Weeks

TEAEs, n (%)	Risankizumab (RZB)				Placebo N=42
	150 mg W 0, 4, 8, 12, & 16 N=42	150 mg W 0, 4, & 16 N=42	150 mg W 0 & 12 N=39	75 mg W 0 N=20	
Any AE	27 (64.3)	22 (52.4)	27 (69.2)	12 (60.0)	29 (69.0)
Drug related AEs[a]	8 (19.0)	7 (16.7)	7 (17.9)	4 (20.0)	8 (19.0)
Serious AE[b]	3 (7.1)	0	2 (5.1)	2 (10.0)	2 (4.8)
Drug related serious AE[a]	1 (2.4)	0	2 (5.1)	1 (5.0)	0
Severe AE	3 (7.1)	0	2 (5.1)	1 (5.0)	4 (9.5)
AE leading to drug discontinuation	3 (7.1)	0	0	1 (5.0)	2 (4.8)

[a]Investigator assessed AE as possibly related to study drug.

[b]No serious adverse event type was reported in more than one patient.

TEAEs = treatment-emergent adverse events; W = week.

Results: Safety Summary – Areas of Special Interest Over 16 Weeks

TEAEs, n (%)	Risankizumab (RZB)				Placebo N=42
	150 mg W 0, 4, 8, 12, & 16 N=42	150 mg W 0, 4, & 16 N=42	150 mg W 0 & 12 N=39	75 mg W 0 N=20	
Infection[a]	16 (38.1)	13 (31.0)	16 (41.0)	6 (30.0)	12 (28.6)
Serious infection	0	0	0	2 (10.0)[b]	0
Serious hypersensitivity	1 (2.4)[c]	0	0	0	0
Adjudicated MACE	0	0	0	1 (5.0)[d]	0
Malignancy	0	0	0	1 (5.0)[e]	0
Depression[f]	0	0	2 (5.1)	0	0

[a]The most frequently reported AE was upper respiratory tract infection.
[b]1 patient with urinary tract infection, influenza, and sepsis (also reported ovarian cancer stage IV); 1 patient with gastroenteritis and pyelonephritis.
[c]An event of investigator reported anaphylactic reaction occurred after the first injection of risankizumab in a biologic naïve patient. The sponsor assessed the event as not consistent with IgE-mediated anaphylaxis.
[d]1 patient with myocardial infarction reported as Non-STEMI (Non-ST-elevation myocardial infarction).
[e]1 patient with Ovarian cancer stage IV reported on study day 184.
[f]1 patient reported depressed mood on study day 1 while 1 patient reported depression on study day 71.
AEs = adverse events; MACE = major adverse cardiovascular event; W = week.

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- Statistical support was provided by Su Chen and Andrew Topp, both of Abbvie
- Medical writing support was provided by Deepa Venkitaramani, PhD, of AbbVie

Conclusions

- In this Phase 2 study, Risankizumab, a selective IL-23p19 inhibitor, significantly improved joint and skin symptoms compared with PBO in patients with active PsA
- The safety and tolerability profile was consistent with observations from previous risankizumab trials

Back-up Slides

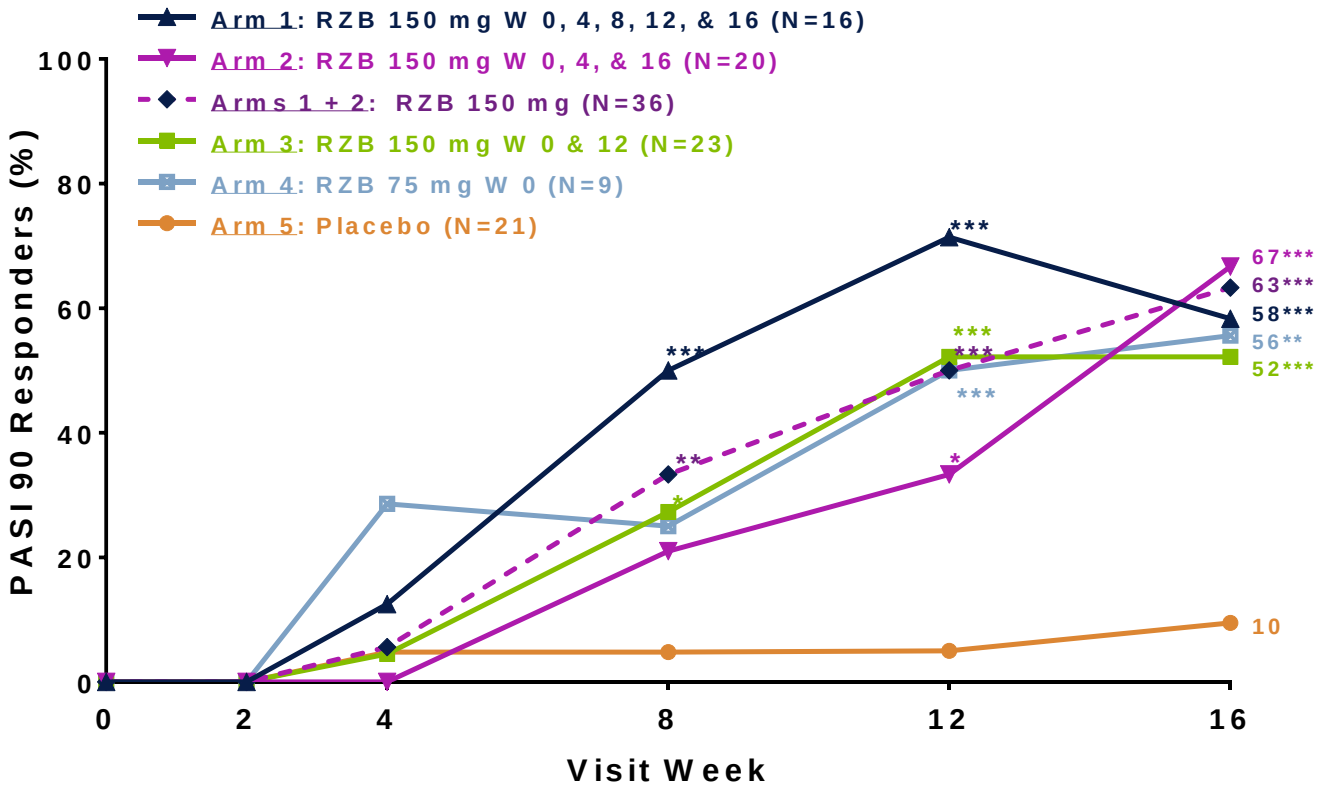
Methods: Efficacy and Safety Assessments

- The primary efficacy endpoint was ACR20 response versus PBO at Week 16
- Additional efficacy endpoints included:
  - ACR50/70
  - PASI responses in patients with psoriasis affecting ≥3% BSA at baseline
  - DAS28(CRP)
  - Minimal disease activity (MDA)
  - Dactylitis count
  - SPARCC enthesitis index
  - Leeds enthesitis index
  - Pain on visual analog scale (VAS)
  - HAQ-DI
- Treatment-emergent adverse events (TEAEs), defined as any adverse events with an onset date on or after the first dose of study drug and up to 105 days after the last dose of study drug, were assessed

Methods: Statistical Analyses

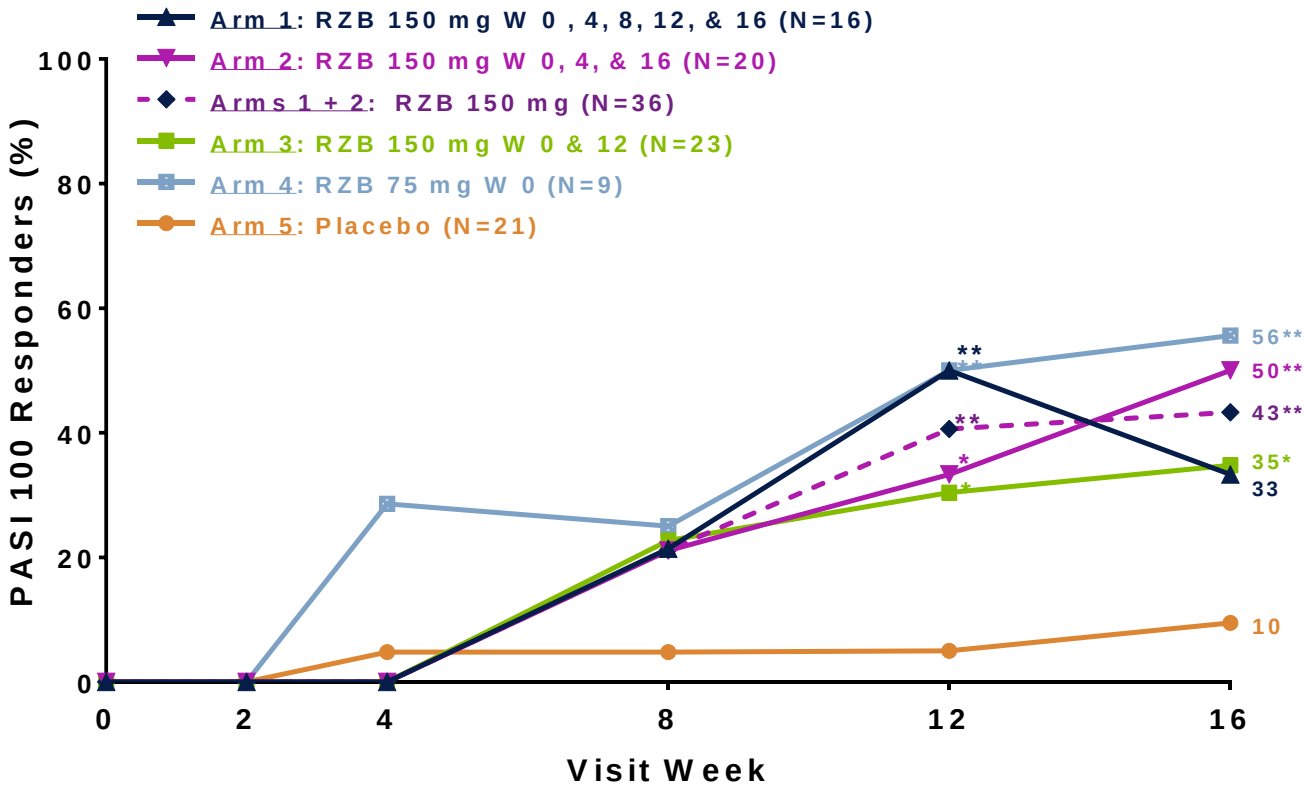
- The baseline and efficacy analysis was conducted on the Full Analysis Set (all randomized patients who received at least one dose of study drug)
  - For categorical variables, pairwise comparisons were conducted using the same Cochran-Mantel-Haenszel methods
  - Missing efficacy data for categorical variables was handled using Non-responder imputation (NRI)
  - For continuous variables, the mixed model repeated measurement (MMRM) model with treatment regimen, clinical visit, and stratification factors as fixed factors, and baseline score as a fixed continuous covariate, were used
  - There were no adjustments for multiplicity in this study
- Safety analyses were conducted on the Safety Analysis Set (all patients who received at least one dose of study drug)

Results: Time Course of PASI 90 Responses[a] (NRI)



[a]PASI assessed in patients with psoriasis affecting ≥3% BSA at baseline; P-values for comparison vs placebo: ***, P <0.001; **, P <0.01; *, P <0.05; no multiplicity adjustment; NRI = non-responder imputation; W = week.

Results: Time Course of PASI 100 Responses[a] (NRI)



[a]PASI assessed in patients with psoriasis affecting ≥3% BSA at baseline; P-values for comparison vs placebo: **, P <0.01; *, P <0.05; no multiplicity adjustment; NRI = non-responder imputation; W = week.