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ARTRITIS PSORIÁSICA TRATAMIENTO

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Anti-TNFs



CERTOLIZUMAB PEGOL FOR THE TREATMENT OF PSORIATIC ARTHRITIS: 4-YEAR OUTCOMES FROM THE RAPID-PSA TRIAL

P. J. Mease^{1,*}, R. Fleischmann², J. Wollenhaupt³, A. Deodhar⁴, D. Gladman⁵, B. Hoepken⁶, L. Peterson⁷, D. van der Heijde⁸

- ▶ **Background:** The RAPID-PsA trial (NCT01087788) has investigated the efficacy and safety of certolizumab pegol (CZP) for the treatment of patients (pts) with psoriatic arthritis (PsA). Previous reports have demonstrated CZP to be safe and efficacious over 96 weeks (wks) of treatment.¹
- ▶ **Objectives:** To report 4-year efficacy and safety data from the RAPID-PsA trial of CZP in PsA pts.
- ▶ **Methods:** RAPID-PsA was double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk216. Pts had active PsA and had failed ≥ 1 DMARD. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4) continued on their assigned dose in the OL period. Outcomes assessed included: ACR20/50/70 and PASI75/90 responses, minimal disease activity (MDA), HAQ-DI, pain and patient's global assessment of disease activity (PGADA). Efficacy data are presented for all pts originally randomized to CZP. Data are shown as observed case and with imputation: NRI for categorical and LOCF for continuous measures. The safety set consisted of all pts treated with ≥ 1 dose of CZP to Wk216.
- ▶ **Results:** 409 pts were randomized, of whom 273 received CZP from Wk0. Of CZP-randomized pts, 91% completed to Wk24, 87% to Wk48 and 67% to Wk216. In the OL period, 17 pts (6.2%) withdrew due to an adverse event (AE) and 5 pts (1.8%) due to loss of efficacy.
- ▶ ACR responses were sustained in both dose regimens from Wk24 to Wk216 (Table A). In those 166 CZP pts (60.8%) with $\geq 3\%$ body surface area skin involvement at baseline (BL), PASI75/90/100 responses were maintained to Wk216 (Table A). Improvements in patient-reported outcomes were also maintained through Wk216 (Table B). Pts had further improvements from Wk24 to Wk216 in high-threshold outcomes (ACR70, MDA and PASI100) when either observed case or conservative imputation methods (NRI) were used (Table A).
- ▶ Pts in the safety set (N=393) had total CZP exposure of 1321 patient-years (PY) with an AE rate (ER) per 100 PY of 258.0. No new safety signals were identified from Wk96 to Wk204, and no additional deaths were reported.

Table: A) Clinical outcomes to Week 216 of the RAPID-PsA trial

Outcome, %	CZP 200 mg Q2W (n=138)			CZP 400 mg Q4W (n=135)			CZP dose-combined (n=273)		
	Wk24 (NRI)	Wk216 (NRI)	Wk216 (OC)	Wk24 (NRI)	Wk216 (NRI)	Wk216 (OC)	Wk24 (NRI)	Wk216 (NRI)	Wk216 (OC)
ACR20	63.8	54.3	76.5 [a]	56.3	54.8	85.1 [b]	60.1	54.6	80.5 [c]
ACR50	44.9	42.0	59.2 [a]	41.5	44.4	69.0 [b]	43.2	43.2	63.8 [c]
ACR70	28.3	34.8	49.0 [a]	24.4	34.8	54.0 [b]	26.4	34.8	51.4 [c]
MDA	34.8	37.7	53.1 [a]	34.8	40.7	63.2 [b]	34.8	39.2	57.8 [c]
PASI75 [d]	62.2	60.0	81.8 [e]	60.5	42.1	76.2 [f]	61.4	51.8	79.6 [g]
PASI90 [d]	46.7	44.4	60.6 [e]	35.5	35.5	64.3 [f]	41.6	40.4	62.0 [g]
PASI100 [d]	30.0	32.2	43.9 [e]	13.2	23.7	42.9 [f]	22.3	28.3	43.5 [g]

B) Patient-reported outcomes to Week 216 of the RAPID-PsA trial

Outcome, mean	CZP 200 mg Q2W (n=138)			CZP 400 mg Q4W (n=135)			CZP dose-combined (n=273)		
	BL	Wk24 (LOCF)	Wk216 (LOCF)	BL	Wk24 (LOCF)	Wk216 (LOCF)	BL	Wk24 (LOCF)	Wk216 (LOCF)
HAQ-DI	1.3	0.8	0.8	1.3	0.9	0.8	1.3	0.8	0.8
Pain	59.7	31.1	29.1	61.1	32.7	27.3	60.4	31.9	28.3
PGADA	60.2	31.1	28.3	60.2	32.5	27.0	60.2	31.7	27.7

All patients received CZP loading dose of 400mg at Weeks 0, 2 and 4. [a] n=98; [b] n=87; [c] n=185; [d] PASI response rates reported in patients with $\geq 3\%$ body surface area skin involvement at baseline (CZP 200mg Q2W, n=90; CZP 400 mg Q4W, n=76); [e] n=66; [f] n=42; [g] n=108. BL: baseline; LOCF: last observation carried forward; MDA: minimal disease activity; NRI: non-responder imputation; OC: observed case; PGADA: patient's global assessment of disease activity.

Conclusions:
CZP efficacy was maintained in PsA pts over 4 years of treatment, with no new safety signals identified. Additional improvements in high-threshold outcomes were seen from Wk24 to Wk216.

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Secukinumab



SECUKINUMAB PROVIDES SUSTAINED IMPROVEMENTS IN THE SIGNS AND SYMPTOMS OF ACTIVE PSORIATIC ARTHRITIS: 2-YEAR EFFICACY AND SAFETY RESULTS FROM THE PHASE 3 RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL, FUTURE 1

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- ▶ **Background:** Secukinumab, an anti-interleukin-17A monoclonal antibody, provided rapid and significant improvements in multiple clinical domains of psoriatic arthritis (PsA) including, signs and symptoms, joint structural damage, physical function, and quality of life, through 52 weeks (wks) in the Phase 3 FUTURE 1 study (NCT01392326).¹
- ▶ **Objectives:** To assess the long-term efficacy and safety of secukinumab in patients (pts) with PsA treated for up to 104 wks in FUTURE 1.
- ▶ **Methods:** 606 adults with active PsA were randomised to secukinumab or placebo (PBO). Secukinumab pts received a 10 mg/kg i.v. loading dose at baseline (BL), Wks 2 and 4, followed by 150 mg s.c. (IV→150 mg) or 75 mg s.c. (IV→75 mg) every 4 wks from Wk 8. PBO was given on the same dosing schedule. At Wk 16, PBO-treated pts were re-randomised to receive secukinumab 150 or 75 mg s.c. from either Wk 16 or Wk 24, based on clinical response. Clinical assessments at Wk 104 included: ACR 20/50/70, PASI 75/90, DAS28-CRP, SF-36 PCS, HAQ-DI, mTSS, dactylitis, and enthesitis. Efficacy variables are presented from those pts originally randomised to secukinumab. Multiple imputation (binary variables) and a mixed-effect model repeated measures (continuous variables) were used for analyses at Wk 104. mTSS data are as observed.
- ▶ **Results:** Overall, 476 pts (78.5%) completed 104 wks of study (167 [82.7%] pts in IV→150 mg group; 155 [76.7%] in IV→75 mg group). At Wk 104, ACR 20/50/70 response rates were 66.8/39.0/22.4% with IV→150 mg and 58.6/29.7/17.6% with IV→75 mg, respectively. Sustained clinical improvements with secukinumab through Wk 104 were observed across other clinically important domains of PsA (Table). Responses were sustained through Wk 104 in pts naïve to anti-TNF therapy and in those with an inadequate response or intolerance to these agents (anti-TNF-IR). ACR20 response rates at Wk 104 in anti-TNF-naïve pts were 75.2% and 63.7% with IV→150 mg and IV→75 mg, respectively; corresponding rates in anti-TNF-IR pts were 48.0% and 46.9%. No radiographic disease progression (≤ 0.5 change in mTSS) was observed between BL and Wk 104 in 84.6% of x-ray completers in the IV→150 mg and 83.9% in the IV→75 mg groups. Over the entire study period (mean exposure to secukinumab of 627.1 days) the type, incidence and severity of AEs were consistent with that reported previously. Infections and infestations were the most common AEs observed with secukinumab (67.9 per 100 pt-years). No cases of TB were reported. Malignant/unspecified tumours and major adverse cardiac events occurred at a rate of 0.6 and 0.7 per 100 pt-years, respectively with secukinumab. No suicides were recorded in secukinumab-treated patients.

Figure 2. ACR20 Response Rates through Week 104

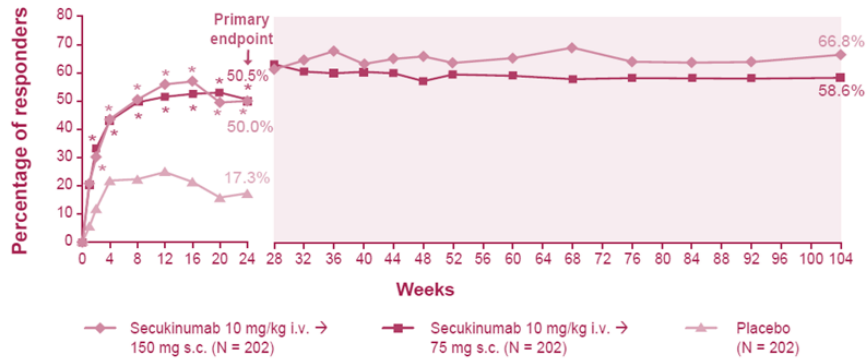
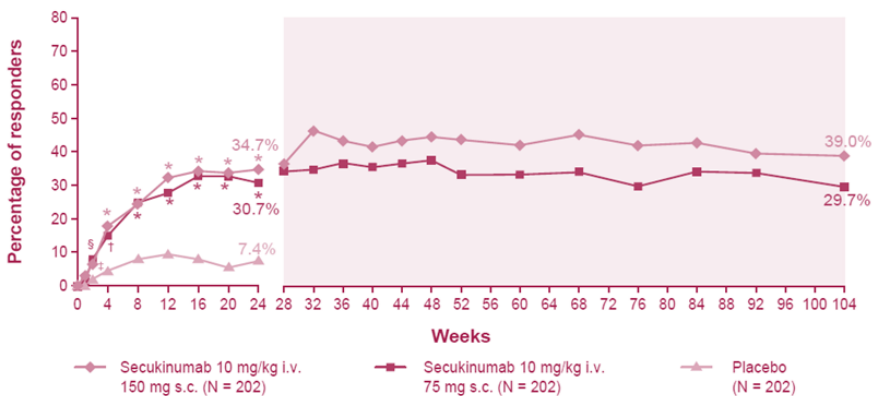
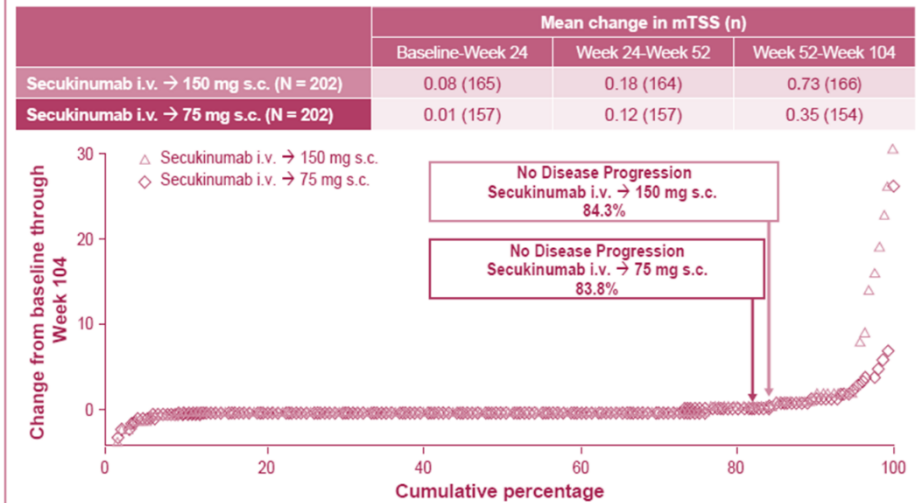


Figure 3. ACR50 Response Rates through Week 104



* $P < 0.0001$; † $P < 0.001$; ‡ $P < 0.01$; § $P < 0.05$ versus placebo (P -values at Week 24 adjusted for multiplicity of testing)
Non-responder imputation through Week 24 and multiple imputation from Week 28 to Week 104 (shaded)

Figure 6. Radiographic Progression (vdH-mTSS) through Week 104



Non-progression defined as a change in mTSS from baseline ≤ 0.5 . Data from full analysis set with evaluable cases
Week 24 values are from Week 24 assessment, if available, or Week 16 assessment with linear extrapolation
Includes all patients who have a Week 104 reading; n, number of evaluated patients

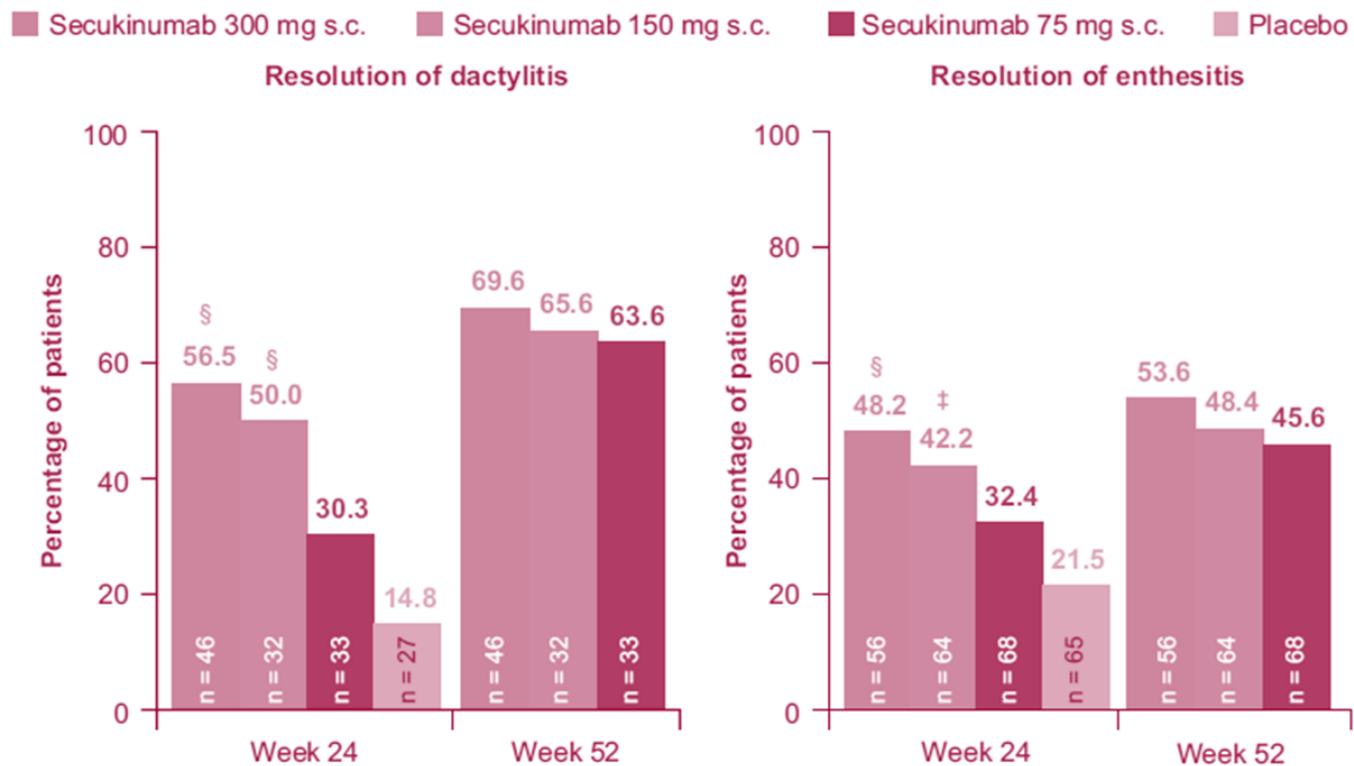
Conclusions: Secukinumab provided sustained improvements in signs and symptoms and multiple clinical domains of active PsA in pts who completed 2 years of therapy. Secukinumab was well tolerated with a safety profile consistent with that previously reported.

SECUKINUMAB PROVIDES RAPID AND SUSTAINED REDUCTIONS IN DACTYLITIS AND ENTHESITIS IN PATIENTS WITH PSORIATIC ARTHRITIS: ANALYSIS OF DATA FROM THE PHASE 3 RANDOMISED, MULTICENTRE, DOUBLE-BLIND, PLACEBO-CONTROLLED FUTURE 2 STUDY

B. Kirkham^{1,*}, P. Mease², I. McInnes³, V. Bhosekar⁴, S. Mpofu⁵, K. Gandhi⁶, C. Gaillez⁵

- ▶ **Background:** Dactylitis and enthesitis are common debilitating manifestations of psoriatic arthritis (PsA).¹ Secukinumab has previously been reported to reduce the number of dactylitic digits and enthesitis sites in patients (pts) with PsA, with a greater proportion of pts achieving complete resolution of dactylitis and enthesitis than placebo (PBO) at Week (Wk) 24.^{2,3}
- ▶ **Objectives:** To evaluate the effects of secukinumab on dactylitis and enthesitis through Wk 52 in FUTURE 2 (NCT01752634).
- ▶ **Methods:** The study design from FUTURE 2 has been reported previously.² The proportions of pts with resolution of dactylitis and enthesitis at Wk 24 and Wk 52 were secondary and exploratory endpoints, respectively; additional measures were dactylitic digit and enthesitis counts. Post-hoc analyses included Kaplan Meier (KM) analysis to achieve resolution of enthesitis and dactylitis and proportion of pts with resolution of dactylitis and enthesitis by baseline (BL) severity.
- ▶ **Results:** Of the 397 pts randomized, 138 (35%) and 253 (64%) had dactylitis and enthesitis, respectively, at BL. KM curves indicate that median time to resolution in dactylitis and enthesitis was Wk 4 for secukinumab 300 and 150 mg. At Wk 24, a greater proportion of secukinumab-treated pts achieved complete resolution of dactylitis and enthesitis than PBO ($P < 0.05$); more secukinumab-treated pts had complete resolution of symptoms at Wk 52 than Wk 24. Improvements at Wk 24 and 52 were observed regardless of BL severity. A sustained decrease in mean changes from BL to Wk 24 and 52 in dactylitis and enthesitis count were shown in those pts with symptoms at BL (Table), with improvements versus PBO observed by Wk 4 ($P < 0.05$).

Figure 2. Resolution of Dactylitis and Enthesitis at Weeks 24 and 52



[§]P < 0.01; [‡]P < 0.05 versus placebo

Resolution of dactylitis and enthesitis in patients with these symptoms respectively at baseline

Missing values were imputed as non-response (non-responder imputation) at Weeks 24 and 52

n, number of evaluable patients

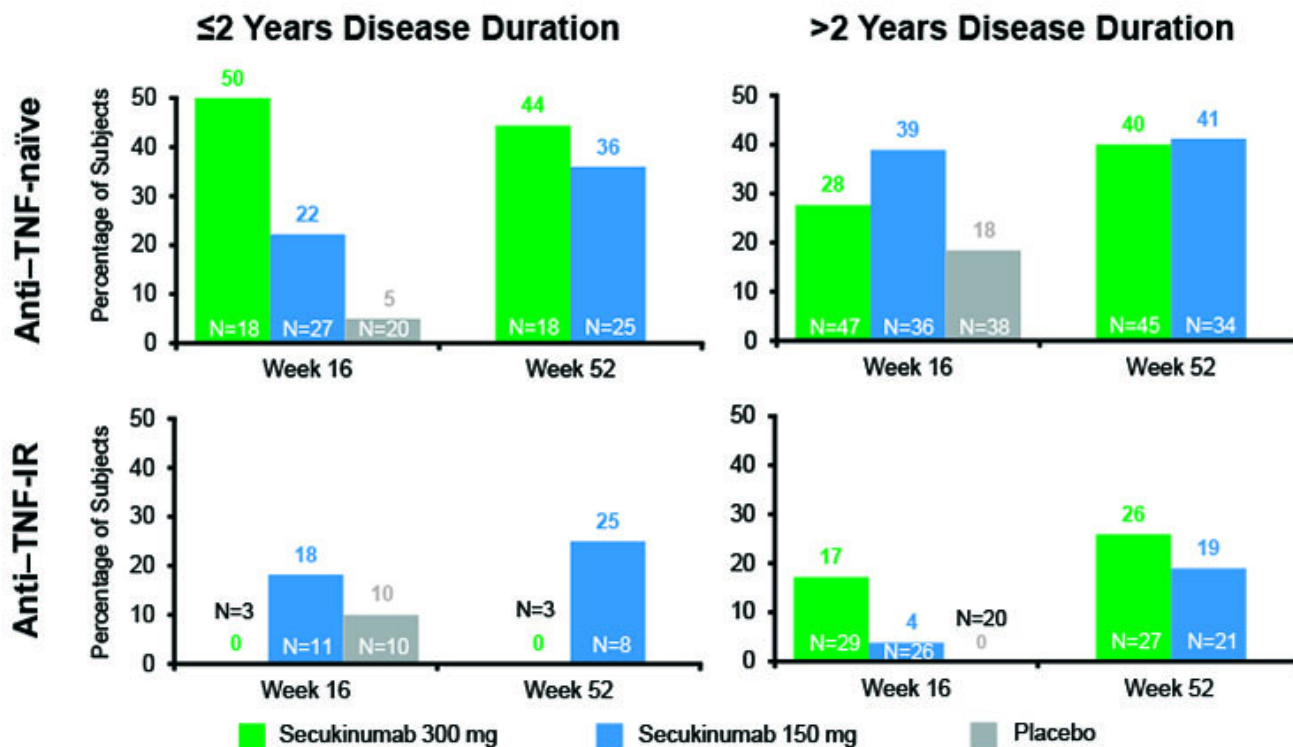
Conclusions: Secukinumab demonstrated a rapid resolution of dactylitis and enthesitis as early as Wk 4 and this was sustained up to Wk 52. A higher proportion of pts achieved complete resolution and reduced mean counts of dactylitis and enthesitis at Wk 52 than Wk 24.

SECUKINUMAB IMPROVES MINIMAL DISEASE ACTIVITY RESPONSE RATES IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS: DATA FROM THE RANDOMIZED PHASE 3 STUDY, FUTURE 2

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- ▶ **Background:** Minimal disease activity (MDA), a validated composite measure in PsA, is gaining acceptance as a target for achieving substantial disease control.
- ▶ **Objectives:** Secukinumab (SEC), an anti-IL-17A monoclonal antibody, significantly improved the signs and symptoms of PsA over 52 wks in the FUTURE 2 study. This post-hoc exploratory analysis assessed MDA response rates through 52 wks.
- ▶ **Methods:** 397 patients (pts) with active PsA were randomized to subcutaneous (SC) SEC (300 mg, 150 mg, or 75 mg) or placebo (PBO) at baseline (BL), Wks 1, 2, and 3, and every 4 wks (q4w) from Wk 4. PBO pts were re-randomized to SEC 300 or 150 mg SC q4w from Wk 16 or 24, depending upon clinical response. Pts were considered in MDA when they met at least 5 of the following 7 criteria: 1) tender joint count ≤ 1 ; 2) swollen joint count ≤ 1 ; 3) Psoriasis Activity and Severity Index ≤ 1 or psoriasis affecting $< 3\%$ body surface area at BL; 4) pt pain VAS ≤ 15 ; 5) pt global disease activity VAS ≤ 20 ; 6) HAQ-DI ≤ 0.5 ; 7) tender enthesal points ≤ 1 . MDA was assessed in the overall population and in pts stratified by prior anti-tumor necrosis factor (anti-TNF) therapy use (anti-TNF-naïve and inadequate response/intolerance to these agents [anti-TNF-IR]) and disease duration (≤ 2 yrs vs > 2 yrs since diagnosis). Observed data are shown. 75 mg data are not reported as this was not considered an effective dose (no secondary endpoints were met).
- ▶ **Results:** In the overall population, 23/100 (23%) and 27/97 (28%) pts achieved MDA at Wk 16 with SEC 150 mg and 300 mg, respectively, vs 9/88 (10%) pts with PBO; these response rates were sustained through Wk 52 (150 mg: 29/88 [33%]; 300 mg: 33/93 [35%]). In the anti-TNF-naïve cohort, a higher proportion of pts achieved MDA at Wk 16 with SEC 150 mg (20/63 [32%]) or 300 mg (22/65 [34%]) vs PBO (8/58 [14%]), with response rates sustained through Wk 52 (150 mg: 23/59 [39%]; 300 mg: 26/63 [41%]). Lower rates were observed in anti-TNF-IR pts (SEC vs PBO at Wk 16: 150 mg, 3/37 [8%]; 300 mg, 5/32 [16%]; PBO, 1/30 [3%]; Wk 52: 150 mg, 6/29 [21%]; 300 mg, 7/30 [23%]). The proportion of pts achieving MDA at Wk 16 and Wk 52 in the overall population was greater for those ≤ 2 yrs since diagnosis vs those > 2 yrs since diagnosis for both SEC 150 mg and 300 mg. The proportion of pts achieving MDA with SEC at Wk 16 was higher in anti-TNF-naïve pts with low disease duration vs pts with longer disease duration, and higher in the anti-TNF-naïve cohort than the anti-TNF-IR cohort at all times (Figure).

Figure. MDA by Anti-TNF Status (naïve and -IR) and Disease Duration (≤ 2 and >2 Years Since Diagnosis)



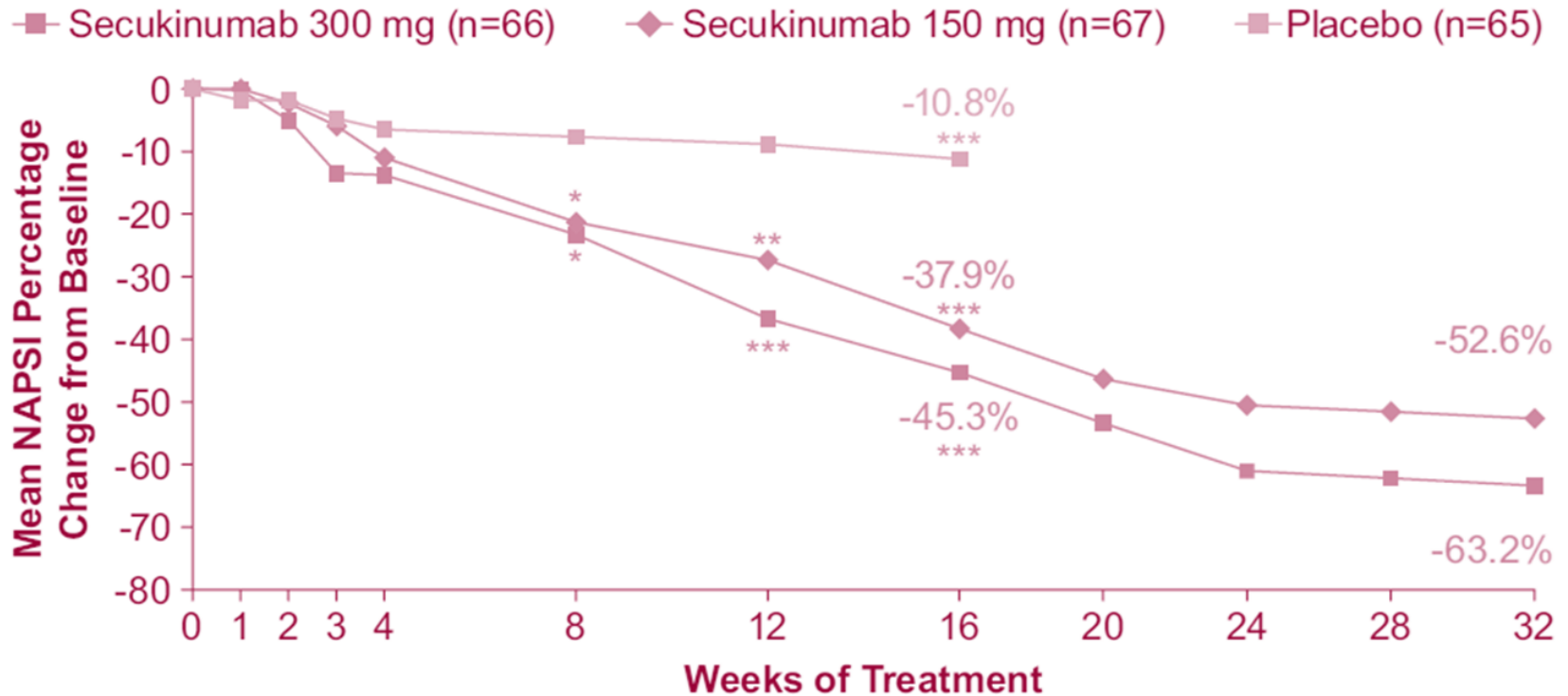
Conclusions: SEC pts had higher MDA response rates vs PBO pts at Wk 16, with response rates sustained through Wk 52. Response rates were consistent with those previously reported with anti-TNF therapies in comparable pt populations. This study is the first to report MDA in anti-TNF-IR pts. The finding that greater MDA can be achieved in early anti-TNF-naïve PsA pts warrants further research.

SECUKINUMAB SHOWS SIGNIFICANT EFFICACY IN NAIL PSORIASIS: WEEK 32 RESULTS FROM THE TRANSFIGURE STUDY

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- ▶ **Background:** Nail psoriasis is associated with decreased finger mobility, functional impairment, pain and reduced quality of life [1] and is often resistant to available therapies.[2] It correlates with more severe psoriatic disease and is an important predictor of psoriatic arthritis (PsA).[3] The incidence of nail psoriasis in PsA patients is up to 80%.[4]
- ▶ **Objectives:** We assessed superiority of secukinumab 300 mg and/or 150 mg vs. placebo (PBO) in treating subjects with moderate to severe psoriasis and significant nail involvement, as assessed by NAil Psoriasis Severity Index (NAPSI) at Week (Wk) 16 and Wk 32 and Psoriasis Area and Severity Index (PASI) at Wk 32. Impact on quality of life was assessed by Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) Patient Benefit Index (-PBI) and Quality of Life (-QOL) at Wk 16.
- ▶ **Methods:** TRANSFIGURE is a double-blind, randomized, PBO-controlled, parallel-group multicentre phase 3b study. Subjects (N = 198) were randomized 1:1:1 to receive either secukinumab 300 mg, secukinumab 150 mg or PBO subcutaneously up to Wk 128. At Wk 16, all subjects receiving PBO were re-randomized 1:1 to receive 300 mg or 150 mg secukinumab.
- ▶ **Results:** The primary objective of this study was met. Both doses of secukinumab were superior to PBO at Wk 16 with a mean percentage NAPSI improvement from Baseline of -45.3%, -37.9%, and -10.8%, for secukinumab 300 mg, 150 mg and PBO, respectively (P < 0.0001). Responses improved further by Wk 32 with a NAPSI change of -63.2% and -52.6%, for secukinumab 300 mg and 150 mg, respectively. At Wk 32, PASI 90 responses were achieved in 72.1% and 61.4% of subjects, and PASI 100 responses in 36.9% and 28.1% for secukinumab 300 mg and 150 mg, respectively. At Wk 16, subjects on secukinumab showed significant improvements in NAPPA-QOL with a median decrease in total score of 60.9%, 49.9% and 15.8% for secukinumab 300 mg, 150 mg and PBO, respectively. The percentage of subjects achieving a weighted NAPPA-PBI global score of 2 and above (i.e. at least moderate benefits) was 75.4%, 61.3% and 8.6% for secukinumab 300 mg, 150 mg and PBO, respectively. The most common adverse events were nasopharyngitis, headache and upper respiratory tract infections, similar to previous studies.
- ▶ **Conclusions:** In the prospective, placebo-controlled TRANSFIGURE trial, secukinumab demonstrated significant and clinically meaningful efficacy, quality of life improvement and patient-reported benefit in nail psoriasis.

Figure 2. NAPS I Improvement up to Week 32



* $P \leq 0.01$ vs. placebo; ** $P \leq 0.001$ vs. placebo; *** $P < 0.0001$ vs. placebo.
 NAPS I, Nail Psoriasis Severity Index

Conclusions: In the prospective, placebo-controlled TRANSFIGURE trial, secukinumab demonstrated significant and clinically meaningful efficacy, quality of life improvement and patient-reported benefit in nail psoriasis

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Tildrakizumab



TILDRAKIZUMAB TREATMENT IMPROVED MEASURES OF PSORIATIC ARTHRITIS IN ADULTS WITH CHRONIC PLAQUE PSORIASIS.

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- ▶ **Background:** Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. Recent evidence with biologic medications that target IL-17 and IL-12/23 (i.e., secukinumab and ustekinumab) have demonstrated efficacy in the treatment of PsA leading to their inclusion in the 2015 EULAR recommendations for the management of psoriatic arthritis (1). Tildrakizumab is an investigational high-affinity, humanized, IgG1/κ, anti-IL-23p19 monoclonal antibody.
- ▶ **Objectives:** This analysis was done to evaluate the effect of tildrakizumab on PsA endpoints in a small population of patients with PsA participating in a Phase 2 chronic plaque psoriasis study.
- ▶ **Methods:** A randomized, double-blind study (NCT01225731) was conducted in 355 adults with moderate to severe plaque psoriasis. Patients were randomized to receive tildrakizumab 5 mg, 25 mg, 100 mg, 200 mg or placebo subcutaneously at Weeks 0 and 4, then every 12 weeks for 52 weeks. The primary efficacy endpoint was the proportion of patients achieving a PASI 75 at Week 16. Patients with PsA (defined by subject history) were examined. PsA endpoints included: mean change in Psoriatic Arthritis Screening and Evaluation (PASE), Health Assessment Questionnaire (HAQ), pain assessed with Visual Analog Scale (VAS), and high-sensitivity C-Reactive Protein (hsCRP), measured from baseline through Week 16.
- ▶ **Results:** 339 patients completed 16 weeks of treatment, PASI 75 responses were 33.3%, 64.4%, 66.3%, 74.4% and 4.4%, in the 5 mg, 25 mg, 100 mg, 200 mg tildrakizumab and placebo groups, respectively ($p \leq 0.001$) (2). Overall, 65 patients (18%) had PsA (5 mg n=8, 25 mg n=15, 100 mg n=17, 200 mg n=17, placebo n=26). Mean changes from baseline are listed below. Results show numerically greater improvements for all doses of tildrakizumab vs. placebo for PASE, and pain parameters. Additionally, tildrakizumab 25 mg and 200 mg demonstrated numerically greater improvement vs. placebo for HAQ (Table). In the overall study population, mean (SD) changes from baseline at Week 16 in observed hsCRP (mg/L) was -0.8 (5.7), -2.3 (6.1), -2.7 (9.2), -3.0 (13.4), and -1.3 (3.6) for the 5 mg, 25 mg, 100 mg, 200 mg, and placebo groups, respectively; hsCRP results for PsA patients only are shown (Table).

Table: Mean Changes from Baseline in PsA Parameters*

	5 mg (n=6)	25 mg (n=12)	100 mg (n=14)	200 mg (n=13)	Placebo (n=10)
PASE	2.2 (-10.3, 14.7)	-7.9 (-17.1, 1.3)	-6.1 (-14.7, 2.5)	-6.1 (-16.1, 4.0)	-0.3 (-10.9, 10.4)
HAQ	0.0 (-0.3, 0.3)	-0.3 (-0.5, -0.1)	0.0 (-0.2, 0.2)	-0.2 (-0.4, 0.0)	0.1 (-0.1, 0.3)
VAS Pain	-13.8 (-38.9, 11.3)	-17.2 (-34.7, 0.3)	-12.3 (-28.7, 4.0)	-16.9 (-33.9, 0.1)	10.2 (-8.9, 29.2)
hsCRP	-1.9 (2.3)	-3.1 (5.5)	-2.4 (4.3)	-6.0 (21.7)	-1.6 (1.9)

**Mean changes (95% CI) for PASE, HAQ, and VAS Pain are based on constrained longitudinal data analysis; mean changes (SD) for hsCRP are based on observed data*

Conclusions: Numerical improvements in measures of PsA were observed with tildrakizumab in a small sample of patients with chronic plaque psoriasis who had concomitant PsA. Tildrakizumab 25 mg, 100 mg, and 200 mg were associated with numerically lower hsCRP levels compared with 5 mg and placebo. Further research is needed to better evaluate tildrakizumab in the treatment of PsA.

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Bimekizumab



BIMEKIZUMAB, A MONOCLONAL ANTIBODY THAT INHIBITS BOTH IL-17A AND IL-17F, PRODUCES A PROFOUND RESPONSE IN BOTH SKIN AND JOINTS: RESULTS OF AN EARLY-PHASE, PROOF-OF-CONCEPT STUDY IN PSORIATIC ARTHRITIS

S. Glatt¹, F. Strimenopoulou¹, P. Vajjah¹, S. Shaw¹, L. Ionescu², S. Popa³, D. Baeten^{4,*}

- ▶ **Background:** Bimekizumab (UCB4940) is a potent and selective monoclonal antibody inhibiting the activity of both IL-17A and IL-17F, which are key pro-inflammatory cytokines overexpressed in skin lesions of patients with psoriasis.¹ Blocking both IL-17A and IL-17F may provide a therapeutic advantage.
- ▶ **Objectives:** To study the safety/tolerability and efficacy of multiple-dose bimekizumab in patients with PsA with inadequate responses to at least 1 DMARD and/or 1 biologic DMARD (NCT02141763).
- ▶ **Methods:** 52 patients were randomized to receive either bimekizumab (N=38) or PBO (N=14). Four active dose-level groups were studied using a single loading dose (80–560 mg bimekizumab) administered at wk 0; further doses (40–320 mg bimekizumab) were administered at wks 3 and 6. ACR and PASI scores were examined; safety and PK variables were also investigated.
- ▶ **Results:** At baseline, patients had a mean SJC(66) of 12.6 and TJC(68) of 29.6, and mean baseline CRP of 12.5 mg/mL. For patients with skin involvement of >3% (N=23) a mean baseline PASI of 15.9 (SD=14.6) was observed. Onset of response was rapid for both skin and joints: by wk 8, an ACR20 RR of 80% was observed for the top 3 doses (N=32) compared with 17% in the PBO group (N=12). Clinically relevant responses in disease activity measures were observed to wk 20. A summary of results in skin and joints is presented in the table.

	PBO	Bimekizumab top 3 doses	PBO	Bimekizumab top 3 doses
Joints: ACR20 RR [95% CI]	N/A	N/A	17% [5%, 45%], N=12	80% [63%, 91%], N=30
Joints: ACR50 RR [95% CI]	N/A	N/A	8% [2%, 35%], N=12	40% [25%, 58%], N=30
Joints: Mean DAS(CRP) [95% CI]	5.1 [4.6, 5.6], N=11	5.0 [4.6, 5.4], N=30	3.9 [3.2, 4.6], N=11	3.1 [2.7, 3.6], N=29
Skin: PASI 90 RR [95% CI]	N/A	N/A	0% [0%, 43%], N=5	87% [62%, 96%], N=15
Skin: Mean PASI [SD]	17.6 [18.0], N=5	11.1 [9.2], N=15	14.1 [17.9], N=5	0.2 [0.6], N=15

Conclusions: In patients with PsA, bimekizumab demonstrated rapid onset, sustained and deep efficacy on disease activity in skin and joints, and within this limited patient and exposure set, was safe and well tolerated. Bayesian analysis indicated that bimekizumab ACR20 RR is greater than that reported for current therapies including anti-IL-17A. Results support that inhibition of both IL-17A and IL-17F could provide additional clinical benefit in IL-17-mediated diseases.

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Ixekizumab



EFFICACY AND SAFETY OF IXEKIZUMAB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS: 52 WEEK RESULTS FROM A PHASE 3 STUDY (SPIRIT-P1)

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- ▶ **Background:** Ixekizumab (IXE) is an IgG4 monoclonal antibody that binds with high affinity and specificity to the proinflammatory cytokine IL-17A. In this phase 3 study (SPIRIT-P1), IXE was superior to placebo (PBO) in achieving American College of Rheumatology 20 (ACR20) response at Week 24 in biologic disease-modifying antirheumatic drug-naïve (bDMARD-naïve) patients with active psoriatic arthritis (PsA)¹.
- ▶ **Objectives:** To evaluate efficacy and safety of IXE over 52 weeks in patients with active PsA.
- ▶ **Methods:** A total of 417 bDMARD-naïve patients with active PsA were randomized 1:1:1:1 to IXE 80 mg once every 4 weeks (Q4W) or once every 2 weeks (Q2W) including a 160 mg starting dose, to 40 mg adalimumab (ADA), or to PBO (all subcutaneous dosing) during the Double-Blind Treatment Period (DBTP: Weeks 0 to 24). Of these, 381 patients completed the DBTP and entered the Extension Period (EP: Weeks 24 to 52) where they were assigned to 80 mg IXE Q4W or Q2W. Patients randomized to IXE at Week 0 continued the same dose regimen in the EP. Patients randomized to PBO or ADA at Week 0 were re-randomized (1:1) to 80 mg IXE Q4W or Q2W at Week 16 (inadequate responders) or 24. Those patients who initially received PBO started IXE at Week 16 or 24; patients who initially received ADA started IXE at Week 24 or 32 after an 8 week wash out period. Efficacy measures included ACR20/50/70 response, Health Assessment Questionnaire-Disability Index (HAQ-DI) Score, Disease Activity Score 28 diarthrodial joint count based on C-reactive protein (DAS 28-CRP), Psoriasis Area and Severity Index 75, 90, 100 (PASI 75/90/100), Leeds Enthesitis Index (LEI), and Leeds Dactylitis Index-Basic (LDI-B). Efficacy and safety were analyzed using the EP population defined as all patients who received at least 1 dose of study drug in the EP. Missing values were imputed by nonresponder imputation for categorical data and modified baseline observation carried forward for continuous data.
- ▶ **Results:** A total of 304 patients completed the EP. Efficacy and safety results in the EP population are summarized in Table 1. Improvements from baseline in ACR20/50/70, HAQ-DI, DAS 28-CRP, PASI 75/90/100, LEI and LDI-B were observed at Week 52. The frequency of treatment-emergent adverse events (AEs) in the EP was similar to that observed in the DBTP; the majority were mild or moderate in severity. Serious AEs occurred in 12 patients and no deaths occurred in the EP population.

Table 1. Efficacy and Safety Outcome Measures at Week 52^a (Extension Period Population)

	IXEQ4W/ IXEQ4W (N=97)	IXEQ2W/ IXEQ2W (N=96)	ADA/ IXEQ4W (N=49)	ADA/ IXEQ2W (N=48)	PBO/ IXEQ4W (N=45)	PBO/ IXEQ2W (N=46)	Total IXEQ4W (N=191)	Total IXEQ2W (N=190)
ACR20, n (%)	67 (69.1)	66 (68.8)	34 (69.4)	28 (58.3)	26 (57.8)	33 (71.7)	127 (66.5)	127 (66.8)
ACR50, n (%)	53 (54.6)	51 (53.1)	29 (59.2)	21 (43.8)	19 (42.2)	21 (45.7)	101 (52.9)	93 (48.9)
ACR70, n (%)	38 (39.2)	38 (39.6)	17 (34.7)	14 (29.2)	9 (20.0)	14 (30.4)	64 (33.5)	66 (34.7)
HAQ-DI, Mean (SD) CFB	-0.53 (0.56)	-0.55 (0.52)	-0.47 (0.48)	-0.42 (0.47)	-0.38 (0.53)	-0.42 (0.60)	-0.48 (0.53)	-0.48 (0.53)
DAS 28-CRP, Mean (SD) CFB	-2.16 (1.21)	-2.37 (1.35)	-2.15 (1.21)	-2.00 (0.95)	-1.85 (1.10)	-2.05 (1.06)	-2.09 (1.19)	-2.20 (1.19)
PASI 75, N ^b , n (%)	66 52 (78.8)	55 45 (81.8)	34 22 (64.7)	33 22 (66.7)	31 19 (61.3)	29 19 (65.5)	131 93 (71.0)	117 86 (73.5)
PASI 90, N ^b , n (%)	66 44 (66.7)	55 43 (78.2)	34 17 (50.0)	33 17 (51.5)	31 16 (51.6)	29 18 (62.1)	131 77 (58.8)	117 78 (66.7)
PASI 100, N ^b , n (%)	66 37 (56.1)	55 37 (67.3)	34 12 (35.3)	33 15 (45.5)	31 15 (48.4)	29 13 (44.8)	131 64 (48.9)	117 65 (55.6)
LEI, N ^c , Mean (SD) CFB	67 -1.9 (1.65)	54 -1.8 (1.56)	28 -2.0 (1.91)	25 -1.1 (2.29)	22 -1.1 (2.18)	26 -1.7 (2.00)	117 -1.8 (1.84)	105 -1.6 (1.87)
LEI (0), N ^d , n (%)	65 36 (55.4)	52 26 (50.0)	28 14 (50.0)	23 6 (26.1)	22 9 (40.9)	26 11 (42.3)	115 59 (51.3)	101 43 (42.6)
LDI-B, N ^e , Mean (SD) CFB	48 -3.7 (3.99)	35 -3.8 (2.87)	11 -5.4 (5.02)	11 -4.8 (3.41)	16 -3.1 (2.59)	19 -2.2 (1.84)	75 -3.8 (3.93)	65 -3.5 (2.83)
LDI-B (0), N ^f , n (%)	40 32 (80.0)	33 27 (81.8)	9 7 (77.8)	11 8 (72.7)	13 9 (69.2)	19 11 (57.9)	62 48 (77.4)	63 46 (73.0)
TEAE, n (%)	54 (55.7)	54 (56.3)	20 (40.8)	21 (43.8)	28 (62.2)	27 (58.7)	102 (53.4)	102 (53.7)
SAE, n (%)	4 (4.1)	0	5 (10.2)	1 (2.1)	1 (2.2)	1 (2.2)	10 (5.2)	2 (1.1)
Discontinued due to AE, n (%)	1 (1.0)	0	0	0	1 (2.2)	1 (2.2)	2 (1.0)	1 (0.5)

Abbreviations: ACR20/50/70=American College of Rheumatology 20/50/70 index; ADA=adalimumab 40 mg; AE=adverse event; CFB=change from baseline; DAS 28-CRP=Disease Activity Score 28 diarthrodial joint count based on C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; IXE=ixekizumab; IXEQ2W=ixekizumab 80 mg once every 2 weeks; IXEQ4W=ixekizumab 80 mg once every 4 weeks; LDI-B=Leeds Dactylitis Index-Basic; LEI=Leeds Enthesitis Index; N=number of patients in the analysis population; n=number of responders; PASI 75/90/100=Psoriasis Area and Severity Index 75/90/100; PBO=placebo; SAE=serious adverse event; SD=standard deviation; TEAE=treatment-emergent adverse event.

^a For efficacy analyses, baseline was defined as the last non-missing assessment recorded on or prior to the date of first injection of study treatment at Week 0. For analyses of TEAEs, baseline was defined as AEs which started prior to the study drug injection at Week 24 with an exception of patients who were randomized to ADA during the entire Double-Blind Treatment Period and started IXE at Week 32 where baseline was defined as AEs which started prior to the study drug injection at Week 32.

^b Only patients with psoriatic lesions $\geq 3\%$ of BSA at baseline were included in the analysis.

^c Only patients with enthesitis at baseline were included in the analysis.

^d Only patients with enthesitis and LEI > 0 at baseline were included in the analysis.

^e Only patients with dactylitis at baseline were included in the analysis.

^f Only patients with dactylitis and LDI-B > 0 at baseline were included in the analysis.

Conclusions: IXE demonstrated clinically significant improvement in signs and symptoms of PsA including arthritis, dactylitis and enthesitis as well as skin manifestations across treatment groups in the EP. The safety profile of IXE observed in the EP was similar to that observed in the DBTP and other phase 3 studies of IXE in patients with plaque psoriasis (UNCOVER studies).

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CLINICAL AND PRECLINICAL ASSESSMENT OF THE ANTI-MCAM MONOCLONAL ANTIBODY PRX003, A POTENTIAL NOVEL TREATMENT FOR TH17-MEDIATED INFLAMMATORY DISEASES

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- ▶ **Background:** Melanoma cell adhesion molecule (MCAM; CD146) is expressed on the surfaces of a small population of T cells that have the capacity to produce a multitude of cytokines; further, expression of MCAM is a defining characteristic of TH17 cells. As such, MCAM is hypothesized to be central to the pathogenesis of numerous autoimmune disorders, including psoriasis and psoriatic arthritis. Laminin α 4 (LAMA4), the primary MCAM ligand, promotes T-cell transmigration into sites of inflammation. Thus, inhibition of MCAM/LAMA4 binding may limit cell infiltration and subsequent pathogenic inflammation. PRX003, a monoclonal antibody designed to bind an MCAM epitope critical for LAMA4 interactions, blocks adhesion of MCAM-expressing cells to LAMA4 rather than targeting an individual cytokine, thus preventing the infiltration of cells responsible for disease pathogenesis.
- ▶ **Objectives:** Study objectives were twofold: (1) to demonstrate preclinical proof of concept for anti-MCAM antibodies in mice overexpressing RAC1, an aggressive transgenic model of psoriasis and (2) to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of PRX003 in healthy human subjects.
- ▶ **Methods:** The effects of anti-MCAM antibodies (murine homolog of PRX003) on the MCAM expression of circulating immune cells and on disease progression were assessed in RAC1 mice treated 3 \times /week with anti-MCAM antibodies (0.1 or 10 mg/kg) or isotype control from postnatal day 7 (when disease progression is evident) through postnatal day 34. In a first-in-human, randomized, double-blind, placebo-controlled, phase 1, single ascending dose-escalation study (NCT02458677), PRX003 was administered by intravenous infusion over approximately 60 minutes. Five escalating dose cohorts received 0.3, 1.0, 3.0, 10, or 30 mg/kg of PRX003 or placebo (6 subjects randomized to PRX003 and 2 to placebo per cohort) and were subsequently monitored in an inpatient unit for 24 hours and by periodic follow-up for 12 weeks. PD measurements in humans included MCAM expression on circulating T-lymphocytes and serum soluble MCAM.
- ▶ **Results:** Anti-MCAM antibodies demonstrated target-mediated binding to circulating immune cells after administration to RAC1 transgenic mice. Furthermore, anti-MCAM antibody-treated mice experienced marked reductions in MCAM expression levels on circulating cells, resulting in diminished (by 40% to 60%) psoriatic disease progression, as evidenced by less erythema, scaling, and skin thickness than were observed in RAC1 transgenic mice treated with an isotype control antibody. PRX003 may thus have a beneficial impact on inflammatory diseases in humans. Data on the safety, tolerability, serum PRX003 PK, and immunogenicity of PRX003 in healthy human subjects, including PK/PD modeling of markers of target engagement, will be presented for the first time.
- ▶ **Conclusions:** The results of these studies and of previously published reports support further examination of PRX003 in patients with inflammatory disease. A phase 1 multiple ascending dose trial of PRX003 in patients with plaque psoriasis (NCT02630901) is planned.

NO REACTIVATION OF DORMANT MYCOBACTERIUM TUBERCULOSIS IN HUMAN IN VITRO GRANULOMA MODEL AFTER ANTI-IL-17A TREATMENT, IN CONTRAST TO ANTI-TNFA TREATMENT

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- ▶ **Background:** IL-17A inhibition has shown significant efficacy in the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis. Blocking critical mediators of innate and adaptive immunity may carry the risk of an increased susceptibility to infections. While Mycobacterium tuberculosis infections can be an important complication of anti-TNF α therapies, the role of the Th17/IL-17 pathway in host resistance to this intracellular pathogen is less clear. A comparison of tool antibodies neutralizing TNF α or IL-17A in an acute murine M. tuberculosis infection model, confirmed the importance of TNF α in host resistance to M. tuberculosis, and highlighted that anti-IL-17A treatment for four weeks in vivo does not impair immunity to this intracellular pathogen¹.
- ▶ **Objectives:** To investigate the effect of adalimumab (anti-TNF α antibody) and secukinumab (anti-IL-17A antibody) on M. tuberculosis dormancy and reactivation, we utilized a novel in vitro human 3D microgranuloma model².
- ▶ **Methods:** Human peripheral blood mononuclear cells were infected with M. tuberculosis. Dormant mycobacteria exhibited the following characteristics: (1) loss of acid-fastness, (2) accumulation of lipid bodies, (3) development of rifampicin-tolerance, and (4) gene expression changes². We measured Auramine-O and Nile red staining indicative of M. tuberculosis membrane acid fastness and accumulating lipid bodies, respectively, and also investigated rifampicin resistance. In this in vitro human 3D microgranuloma model we studied the anti-TNF α antibody adalimumab at 10 ng/ml, and the IL-17A antibody secukinumab at 10, 100, and 1000 ng/ml.
- ▶ **Results:** M. tuberculosis from granulomas treated with anti-TNF α antibody (adalimumab) showed increased staining for Auramine-O, decreased Nile red staining, and decreased rifampicin resistance, indicating M. tuberculosis reactivation. In contrast, anti-IL-17A antibody (secukinumab) treatment was comparable to control treatment indicating that the drug did not trigger M. tuberculosis reactivation in human microgranuloma in vitro.
- ▶ **Conclusions:** Overall, these results confirm the importance of TNF α in host resistance to M. tuberculosis infection, and highlight that anti-IL-17A treatment in vitro does not reverse M. tuberculosis dormancy in this human granuloma model, in accordance with available clinical data^{3,4}