Subcutaneous Secukinumab Inhibits Radiographic Progression in Psoriatic Arthritis: Primary Results from a Large Randomized, Controlled, Double-Blind Phase 3 Study

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INTRODUCTION

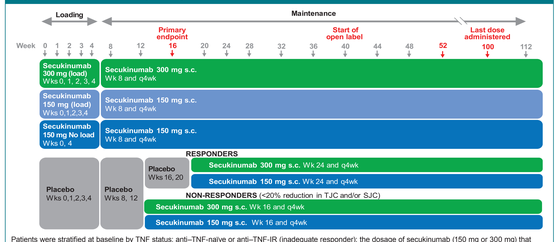
- Secukinumab, a fully human monoclonal antibody that selectively neutralizes IL-17A, has shown significant and rapid efficacy in psoriatic arthritis (PsA)[1,2]
- This poster presents primary results of the ongoing study FUTURE 5 (NCT02404350), the largest randomized controlled trial (RCT) conducted to date of a biologic treatment for PsA, assessing efficacy, including radiographic inhibition of structural damage, and safety of subcutaneous (s.c.) secukinumab 300 mg and 150 mg

METHODS

Study Design

- FUTURE 5 is a randomized, double-blind, placebo-controlled, parallel-group phase III trial
- Adults (N = 996) with active PsA, stratified by previous anti-tumor necrosis factor (TNF) use, were randomized 2:2:2:3 to s.c. secukinumab 300 mg with loading dose (LD), 150 mg with LD, 150 mg without LD, or placebo (**Figure 1**)
- All groups received secukinumab or placebo at Baseline (BL), Weeks (Wks) 1, 2, 3, and 4, and then every 4 wks. At Wk 16, placebo non-responders (patients with < 20% improvement from BL in tender or swollen joint counts) were switched to secukinumab 300 mg or 150 mg; remaining placebo patients were switched at Wk 24

Figure 1. FUTURE 5 Study Design



Patients were stratified at baseline by TNF status: anti–TNF-naïve or anti–TNF-IR (inadequate responder); the dosage of secukinumab (150 mg or 300 mg) that placebo patients were randomized to receive at Wk 16 (non-responders) or 24 (responders) was predetermined at baseline.
q4wk, every 4 wks; s.c. subcutaneous; SJC, swollen joint count; TJC, tender joint count

Major inclusion/exclusion criteria

- Patients ≥18 years of age who met the Classification Criteria for Psoriatic Arthritis (CASPAR)
- Symptoms of moderate to severe PsA for ≥ 6 months
- Use of concomitant corticosteroids (≤ 10 mg/day prednisone or equivalent), NSAIDs, and methotrexate (≤ 25 mg/wk) at stable doses, or ≤ 3 anti–TNF agents with either inadequate response or safety or intolerance issue (anti–TNF-IR) was allowed
- No active or history of ongoing infection (patients with latent tuberculosis were allowed if treatment had been initiated), prior use of biologics other than anti–TNF agents; active inflammatory disease other than PsA

Study endpoints

- **Primary endpoint:** ACR20 response (≥ 20% improvement from BL in American College of Rheumatology response criteria) at Wk 16
- **Key (1st hierarchical) secondary endpoint:** radiographic structural progression at Wk 24, as measured by change from baseline in van der Heijde-modified Total Sharp Score (vdH-mTSS), assessed centrally by two (three if adjudication required) blinded-readers, based on hand/wrist/foot X-rays obtained at BL, Wk 16 (non-responders), and Wk 24
- **Other hierarchical secondary endpoints at Wk 16:** PASI 75 (≥75% improvement from BL in Psoriasis Area and Severity Index); PASI 90, ACR50 response; change from baseline in HAQ-DI score (Health Assessment Questionnaire – Disability Index); change from baseline in DAS28-CRP score (28-joint Disease Activity Score using C-Reactive Protein); resolution of enthesitis; and resolution of dactylitis

Statistics

- Statistical analyses used non-responder imputation for binary efficacy variables (e.g. ACR20/50/70, HAQ-DI, etc.), linear extrapolation for radiographic data, and mixed-effects repeated measures model (MMRM) for continuous variables (e.g. DAS28-CRP)
- For each binary endpoint, missing values were imputed as non-responders; the rescue penalty was used for Placebo patients rescued
- Testing results used a pre-defined hierarchical hypothesis testing strategy to adjust for multiplicity

RESULTS

Baseline Demographics and Disease Characteristics

- Of 996 patients who were randomized, 66 (6.9%) had discontinued by Wk 24, with the greatest number (*n* = 37) coming from the placebo group. The most common reason for discontinuation was patient/guardian decision, followed by adverse events (AEs)
- The treatment arms were well balanced for demographics/disease history/background characteristics, with no meaningful differences between the treatment groups (**Table 1**). Approximately 30% were anti–TNF-IR and approximately 50% used concomitant methotrexate

Table 1. Demographics and Baseline Disease Characteristics

Characteristic	Secukinumab 300 mg with LD (n = 222)	Secukinumab 150 mg with LD (n = 220)	Secukinumab 150 mg without LD (n = 222)	Placebo (n = 332)	Total (n = 996)
Age (years), mean (SD)	48.9 (12.8)	48.4 (12.9)	48.8 (11.8)	49.0 (12.1)	48.8 (12.4)
Female, n (%)	114 (51.4)	109 (49.5)	102 (45.9)	171 (51.5)	496 (49.8)
Weight (kg)	81.9 (16.9)	83.3 (19.6)	84.1 (20.5)	84.1 (19.6)	83.4 (19.2)
White race, n (%)	184 (82.9)	178 (80.9)	180 (81.1)	274 (82.5)	816 (81.9)
Time since first diagnosis of psoriatic disease (years), mean (SD)	6.7 (8.3)	6.7 (7.1)	6.2 (6.1)	6.6 (7.6)	6.6 (7.3)
Anti–TNF-naïve, n (%)	154 (69.4)	155 (70.5)	158 (71.2)	234 (70.5)	701 (70.4)
Methotrexate use at randomization, n (%)	112 (50.5)	108 (49.1)	120 (54.1)	159 (47.9)	499 (50.1)
Systemic glucocorticoid at randomization, n (%)	34 (15.3)	44 (20.0)	37 (16.7)	53 (16.0)	168 (16.9)
Patients with specific disease characteristics, n (%)					
Psoriasis affecting ≥3% of BSA	110 (49.5)	125 (56.8)	117 (52.7)	162 (48.8)	514 (51.6)
Presence of enthesitis	140 (63.1)	141 (64.1)	129 (58.1)	192 (57.8)	602 (60.4)
Presence of dactylitis	82 (36.9)	80 (36.4)	103 (46.4)	124 (37.3)	389 (39.1)
Disease and quality of life scores, mean (SD)					
Tender joint count (78 joints)	19.8 (15.1)	21.2 (15.9)	21.8 (16.0)	21.2 (16.2)	21.0 (15.8)
Swollen joint count (76 joints)	10.0 (8.0)	12.1 (10.5)	11.9 (10.3)	11.7 (10.8)	11.5 (10.1)
DAS28-CRP score	4.5 (1.0)	4.7 (1.0)	4.6 (1.1)	4.6 (1.1)	4.6 (1.1)
HAQ-DI score	1.2 (0.6)	1.3 (0.6)	1.3 (0.7)	1.3 (0.6)	1.3 (0.6)
vdH-mTSS	7.4 (13.8)	7.7 (13.9)	8.7 (21.3)	8.9 (22.0)	XX (XX)

Efficacy

- The primary and all hierarchical secondary endpoints, except for enthesitis and dactylitis resolution for 150 mg without LD, were met (**Table 2**)

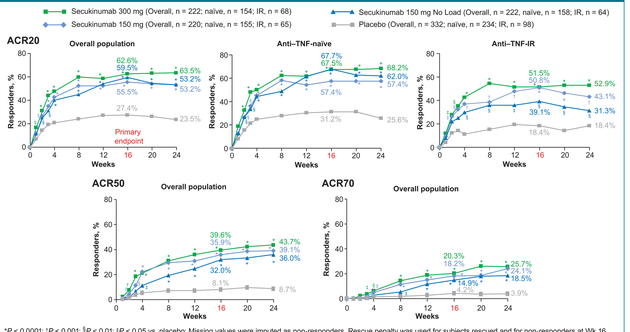
Table 2. Comparison of secukinumab vs. placebo at Wk 16 for pre-specified hierarchical endpoints

	Secukinumab 300 mg with LD (n = 222)	Secukinumab 150 mg with LD (n = 220)	Secukinumab 150 mg without LD (n = 222)	Placebo (n = 332)
ACR20 response: primary endpoint (%)	62.6*	55.5*	59.5*	27.4
Pre-specified secondary endpoints				
mTSS structural progression (mean change from BL)[a]	0.08[a]	0.17[ns]	-0.09[a]	0.50
PASI 75 response (%)[b]	70.0*	60.0*	58.1*	12.3
PASI 90 response (%)[b]	53.6*	36.8*	31.6*	9.3
ACR50 response (%)	39.6*	35.9*	32.0*	8.1
HAQ-DI score (LS mean change from BL)	-0.55*	-0.44*	-0.45*	-0.21
DAS28-CRP score (LS mean change from BL)	-1.49*	-1.29*	-1.29*	-0.63
Enthesitis resolution (%)[c]	55.7†	54.6†	41.9	35.4
Dactylitis resolution (%)[d]	65.9*	57.5†	56.3	32.3

*$P < 0.0001$; †$P < 0.001$; *< 0.01; **$P < 0.05$ un-adjusted p-values vs. placebo.
[a]Wk 24 data; [b]Data from patients with BL psoriasis affecting ≥ 3 BSA; [c]Data from patients with enthesitis at BL; [d]Data from patients with dactylitis at BL
BSA, body surface area; LS, least squares

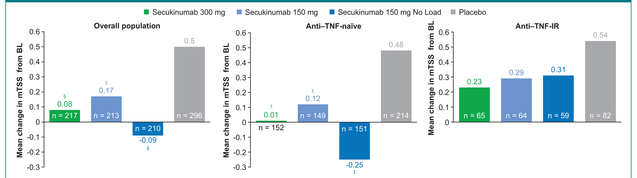
- All secukinumab doses were significantly superior to placebo (Wk 16) for all ACR response levels (**Figure 2**)
  - Secukinumab 150 mg with LD group had a faster onset of response than the 150 mg without LD group, particularly for the more stringent endpoints of ACR50 and ACR70
  - Secukinumab 300 mg had higher response rates than both 150 mg doses, and the 150 mg with LD group had better responses than the 150 mg without LD groups; differences were more pronounced in the anti–TNF-IR subgroup
  - Anti–TNF-naïve patients had better responses than anti–TNF-IR patients
- Radiographic structural progression (mean change from baseline vdH-mTSS score) was significantly inhibited at Wk 24 in all secukinumab dose groups vs. placebo (**Figure 3**)
  - Lower mean change from baseline vdH-mTSS at Wk 24 for secukinumab vs. placebo in anti–TNF-naïve and anti–TNF-IR subgroups was consistent with changes for the Overall population
  - A greater proportion of patients had no radiographic progression (change from BL vdH-mTSS ≤ 0.5) with secukinumab vs. placebo: 88% (300 mg), 80% (150 mg), 84% (150 mg without LD), and 74% (placebo)

Figure 2. ACR20/50/70 response rates from BL up to Wk 24 (primary endpoint at Wk 16)



*$P < 0.0001$; †$P < 0.001$; §$P < 0.01$; ‡$P < 0.05$ vs. placebo; Missing values were imputed as non-responders. Rescue penalty was used for subjects rescued and for non-responders at Wk 16.

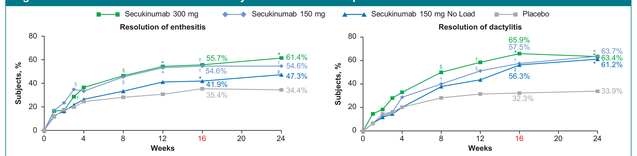
Figure 3. Mean change from baseline vdH-mTSS at Wk 24 (A) in the Overall population and (B) by anti-TNF status



‡$P < 0.001$; §$P < 0.01$; †$P < 0.05$ vs. placebo (Non-parametric ANCOVA-linear extrapolation); Only subjects with an available change from BL data are included.

- Secukinumab significantly improved the percentage of patients achieving complete resolution of enthesitis and dactylitis vs. placebo (**Figure 4**)

Figure 4. Resolution of enthesitis and dactylitis from baseline up to Week 24[a]



*$P < 0.0001$; †$P < 0.001$; ‡$P < 0.01$; §$P < 0.05$ vs. placebo; [a]Resolution of dactylitis and enthesitis were not significant for secukinumab 150 mg without load in hierarchical testing; Missing values were imputed as non-responders. Rescue penalty was used for subjects rescued and for non-responders at Week 16.

Safety

- Wk 24 data presented for the safety analysis (**Table 3**); the 'Any Secukinumab' arm includes placebo patients who switched to secukinumab at Wk 16 due to non-response
- Adverse event exposure-adjusted incidence rates (per 100 patient-years) at Wk 24 were similar across treatment groups: 250 (300 mg with LD), 245 (150 mg with LD), 247 (150 mg without LD) and 313 (placebo)
- The most commonly reported AEs were consistent with previous trials and mostly represented an upper respiratory tract infection
- No deaths, systemic fungal infections, tuberculosis infections or major adverse cardiac events were reported

Table 3. Exposure, Discontinuations, AEs and SAEs up to Wk 24[a]

Variable	Secukinumab 300 mg with LD (n = 222)	Secukinumab 150 mg with LD (n = 220)	Secukinumab 150 mg without LD (n = 222)	Any Secukinumab (n = 822)[b]	Placebo (n = 332)
Exposure					
Patient-years	102.0	101.8	101.2	329.7	122.7
Days (mean)	167.8	169.0	166.5	146.5	135.0
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to AE, n (%)	3 (1.4)	4 (1.8)	3 (1.4)	11 (1.3)	7 (2.1)
Non-fatal SAE, n (%)	7 (3.2)	9 (4.1)	6 (2.7)	25 (3.0)	12 (3.6)
Number of subjects with any AE, n (%)	140 (63.1)	138 (62.7)	136 (61.3)	463 (56.3)	206 (62.0)
Selected AEs of interest, n (%)					
Candida infection	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Oral candidiasis	2.0 (0.9)	1 (0.5)	0 (0.0)	3 (0.4)	1 (0.3)
Vulvovaginal candidiasis	1 (0.5)	2.0 (0.9)	0 (0.0)	3 (0.4)	1 (0.3)
Injections site reactions	6 (2.7)	5 (2.3)	3 (1.4)	15 (1.8)	4 (1.2)
Selected SAEs of interest, n (%)					
Crohn's disease	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)	0 (0.0)
Ulcerative colitis	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)	0 (0.0)
Anaphylactic reaction	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified	0 (0.0)	0 (0.0)	1 (0.5)[c]	2 (0.2)[d]	0 (0.0)

[a]Up to the Week 24 data cutoff point for interim analysis; [b]Any secukinumab group represents each originally randomized secukinumab patient plus placebo patients who switched to active treatment at Wk 16 due to non-response; [c]Bladder neoplasm reported as a non-serious AE (Day 34); [d]Includes melanoma (Day 139) in one placebo patient switched to secukinumab (Day 113).
AE, adverse event; CI, confidence interval; IR, incidence rate expressed as per 100 patient-years; SAE, serious adverse event

CONCLUSION

- FUTURE 5 is the largest randomized, controlled study to date of a biologic in PsA
- This is the first study to demonstrate that s.c. secukinumab 300 mg and 150 mg dosing regimens inhibit radiographic progression
- Both doses provided improvements in the signs and symptoms of PsA; secukinumab 300 mg consistently provided numerically better responses than the 150 mg dose (with or without LD)
- The loading regimen generally provided an earlier onset of response, which was more prominently seen in higher efficacy endpoints, and enthesitis and dactylitis resolution
- Efficacy across all endpoints was greater in patients who were anti–TNF-naïve than those who were anti–TNF-IR
- The safety profile was consistent with that previously reported[3] with no new safety signals identified

REFERENCES

1. Mease PJ, et al. *N Engl J Med*. 2015;373:1329–39.
2. McInnes IB, et al. *Lancet* 2015;386:1137–46.
3. Mease PJ, et al. *Ann Rheum Dis*. 2017;76(Suppl. 2):952.

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