Secukinumab Improves GRAPPA-OMERACT Core Domains of Psoriatic Arthritis

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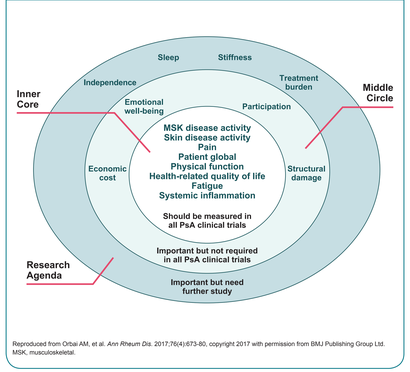
BACKGROUND

- Psoriatic arthritis (PsA) is a chronic inflammatory and heterogeneous disease that may affect peripheral and axial joints, entheses, nails, and/or skin, and is associated with pain, impaired physical function, and poor quality of life[1]
- Most clinical studies use the ACR responder criteria for primarily assessing treatment efficacy in PsA, which do not cover all disease domains observed in PsA[2]
- The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), in conjunction with Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT), has been working on improving and standardizing assessments more specific to PsA outcomes; these assessments include disease manifestations in addition to those included in ACR responder criteria[2]
  - The PsA core domain set, initially implemented in 2006,[3] has been updated by GRAPPA and was endorsed by OMERACT[4] in 2016 to better reflect the benefit of the drugs and to include the perspectives of both patients and physicians (**Figure 1**)

Figure 1. Updated 2016 PsA Core Domain Set



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- Secukinumab is a fully human monoclonal antibody that selectively neutralizes IL-17A and has been shown to have efficacy in the treatment of PsA and ankylosing spondylitis (AS), demonstrating rapid onset of action and sustained responses, with a consistent safety profile[5–10]
- Here, we present an *ad hoc* analysis of the efficacy of secukinumab compared with placebo through the prism of GRAPPA-OMERACT recommendations across all individual PsA core domains, using pooled data from 4 on-label Phase III FUTURE studies[5–8] and spine symptoms among patients with AS in the Phase III MEASURE 2 study[9,10]

METHODS

- This analysis included patients with active PsA who participated in the Phase III clinical trials FUTURE 2 (N = 397), FUTURE 3 (N = 414), FUTURE 4 (N = 341), and FUTURE 5 (N = 996)[5–8]
- Data were pooled from these studies using secukinumab dosed subcutaneously at:
  - 300 mg with loading dose
  - 150 mg with loading dose
  - 150 mg without loading dose (no load)
  - Placebo at the end of the 16-week double-blind period
- Because information about axial disease in PsA was not assessed in the FUTURE studies, data from the MEASURE 2 study, a Phase III clinical trial in patients with AS in which 72 patients received secukinumab 150 mg and 74 patients received placebo, was used to assess spine symptoms[9,10]
- Efficacy at Week 16 was evaluated according to the updated GRAPPA-OMERACT PsA core domains using non-responder imputation for missing data for musculoskeletal disease activity and PASI scores or as-observed data for other outcomes, and was assessed via multiple instruments (**Table 1**)

Table 1. PsA Outcome Measures and Prespecified End Points for Resolution and Improvement[a]

Inner circle (core) domains *(should be measured in all PsA clinical trials)*	
Domain	**Measure**
Musculoskeletal disease activity (arthritis, enthesitis, dactylitis)	No. (%) of patients achieving ≥ 50% improvement in SJC76, TJC78, LEI, and LDI No. (%) of patients achieving complete resolution in SJC76, TJC78, LEI, and LDI
Skin disease activity	No. (%) of patients achieving PASI100 or PASI75 No. (%) of patients achieving mNAPSI75 No. (%) of patients achieving IGA 0/1 (clear/almost clear)
Pain	LSM change from baseline in pain VAS (scale, 0-100) No. (%) of patients with ≥ 3-point improvement in pain VAS
Patient global assessment	LSM change from baseline in patient global assessment (scale, 0-100) No. (%) of patients with ≥ 3-point improvement in patient global assessment VAS
Physical function	LSM change from baseline in HAQ-DI (scale, 0-3) No. (%) of patients achieving MCID of ≥ 0.35 in the HAQ-DI
HRQOL	No. (%) of patients achieving MCID of ≥ 2.5 in the SF-36 PCS and SF-36 MCS LSM change from baseline in PsAQOL (scale, 0-20) LSM change from baseline in DLQI (scale, 0-30)
Fatigue	LSM change from baseline in FACIT-Fatigue score (scale, 0-52) No. (%) of patients with ≥ 3.5-point improvement in FACIT-Fatigue score
Systemic inflammation	No. (%) of patients achieving resolution of elevated CRP (> 10 mg/L)
Middle circle domains *(important but not required in all PsA clinical trials)*	
Domain	**Measure**
Participation	LSM change from baseline in WPAI:GH (% impairment)
Structural damage	No. (%) of patients without structural progression (change from baseline vdH-mTSS of ≤ 0.5)
Spine symptoms (MEASURE 2)	Mean change from baseline in BASDAI No. (%) of patients achieving 20% improvement in BASDAI No. (%) of patients achieving inactive disease (BASDAI < 4) No. (%) of patients achieving ASAS40 response

ASAS40, 40% improvement in Assessment in SpondyloArthritis international Society response criteria; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; HRQOL, health-related quality of life; IGA, Investigator's Global Assessment; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; LSM, least squares mean; MCID, minimal clinically important difference; MCS, mental component summary; mNAPSI75, 75% improvement in the modified Nail Psoriasis Severity Index; PASI75/100, 75%/100% improvement in the Psoriasis Area and Severity Index; PCS, physical component summary; PsAQOL, psoriatic arthritis–specific quality of life; SF-36, 36-Item Short Form Health Survey; SJC76, swollen joint count based on 76 joints; TJC78, tender joint count based on 78 joints; VAS, 100-mm visual analog scale; vdH-mTSS, van der Heijde-modified Total Sharp Score; WPAI:GH, Work Productivity and Activity Impairment Questionnaire: General Health.

[a] Where meaningful improvement has been defined for an outcome measure, this threshold was used; where meaningful improvement was unknown, a threshold was selected that was judged to be significant based on current measures in use (eg, 50%-75% improvement) or LSM change; for musculoskeletal disease activity elements and skin disease activity, complete resolution (100% improvement) was also assessed.

RESULTS

Baseline Characteristics

- This pooled analysis included 2049 patients from the FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5 studies, of whom 461 received secukinumab 300 mg, 572 received secukinumab 150 mg, 335 received secukinumab 150 mg no load, and 681 received placebo
- Baseline demographics and disease characteristics were broadly similar in all treatment groups (**Table 2**)
  - The study enrolled a mixed population of biologic-naive patients and TNF inadequate responders (up to 32%)

Table 2. Pooled Baseline Patient Characteristics of Patients Across FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5 Studies

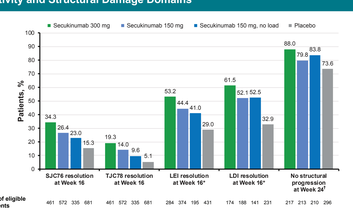
Characteristic	Secukinumab 300 mg (n = 461)	Secukinumab 150 mg (n = 572)	Secukinumab 150 mg, No Load (n = 335)	Placebo (n = 681)
Age, mean (SD), years	48.6 (12.78)	48.4 (12.28)	49.3 (11.81)	49.3 (12.27)
Female, n (%)	235 (51.0)	298 (52.1)	164 (49.0)	377 (55.4)
Race, n (%)				
White	412 (89.4)	512 (89.5)	293 (87.5)	615 (90.3)
Asian	29 (6.3)	38 (6.6)	27 (8.1)	38 (5.6)
Black or African American	2 (0.4)	0	0	5 (0.7)
American Indian or Alaska Native	1 (0.2)	5 (0.9)	6 (1.8)	2 (0.3)
Native Hawaiian or other Pacific Islander	0	1 (0.2)	0	0
Unknown	0	0	2 (0.6)	2 (0.3)
Other	17 (3.7)	16 (2.8)	7 (2.1)	19 (2.8)
TNF-IR, n (%)	145 (31.5)	173 (30.2)	91 (27.2)	204 (30.0)
TJC78, mean (SD)	19.9 (14.59)	22.0 (17.04)	20.8 (16.15)	21.7 (16.51)
SJC76, mean (SD)	9.9 (7.51)	11.4 (9.76)	11.3 (9.92)	11.1 (9.86)
Presence of enthesitis, n (%)	284 (61.6)	374 (65.4)	195 (58.2)	431 (63.3)
Presence of dactylitis, n (%)	174 (37.7)	188 (32.9)	141 (42.1)	231 (33.9)
DAS28-CRP score, mean (SD)	4.56 (1.03)	4.69 (1.07)	4.56 (1.07)	4.62 (1.07)
DAS28-ESR score, mean (SD)	5.00 (1.20)	5.11 (1.23)	4.95 (1.18)	5.07 (1.22)
HAQ-DI score, mean (SD)	1.19 (0.64)	1.21 (0.63)	1.20 (0.67)	1.23 (0.63)
Patient global assessment, mean (SD)	57.7 (21.51)	58.2 (21.82)	56.3 (22.75)	56.6 (21.22)
Physician global assessment, mean (SD)	54.2 (18.07)	56.5 (17.59)	56.2 (18.57)	54.5 (18.71)
Time since PsA diagnosis, mean (SD), years	7.33 (8.44)	6.70 (7.71)	6.05 (6.70)	6.78 (7.45)

DAS28, disease activity score using 28 joints; ESR, erythrocyte sedimentation rate; TNF-IR, tumor necrosis factor inadequate responder.

Pooled Efficacy

- Secukinumab 300 mg demonstrated significant improvement in all core domains compared with placebo (**Table 3**)
- Improvement was also seen in all secukinumab dose groups in the musculoskeletal disease activity and structural damage domains, with the secukinumab 300-mg dose group generally demonstrating the greatest improvement (**Table 3; Figure 2**)

Figure 2. Patient Improvement Across the Musculoskeletal Disease Activity and Structural Damage Domains



All *P* values vs placebo are *P* < 0.008, except secukinumab 150 vs placebo for no structural progression at Week 24 (*P* = 0.1027).
* Among patients with enthesitis or dactylitis at baseline only.
† Data shown are from the FUTURE 5 study only. No structural progression was defined as a change from baseline vdH-mTSS of ≤ 0.5.

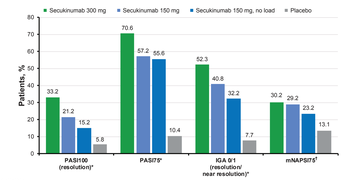
Table 3. Pooled Efficacy Results Across GRAPPA-OMERACT PsA Core Domains

Improvement in Patients With PsA at Week 16 in FUTURE Trials[a]					
PsA Core Domains	**Measures and Improvement Definitions**	**Secukinumab 300 mg (n = 461)**	**Secukinumab 150 mg (n = 572)**	**Secukinumab 150 mg, No Load (n = 335)**	**Placebo (n = 681)**
Inner circle (core) domains (should be measured in all PsA clinical trials)					
Musculoskeletal disease activity - Arthritis - Enthesitis - Dactylitis	SJC76, ≥ 50% improvement	314/461 (68.1)	353/572 (61.7)	201/335 (60.0)	258/681 (37.9)
	SJC76 resolution	158/461 (34.3)	151/572 (26.4)	77/335 (23.0)[b]	104/681 (15.3)
	TJC78, ≥ 50% improvement	289/461 (62.7)	316/572 (55.2)	183/335 (54.6)	204/681 (30.0)
	TJC78 resolution	89/461 (19.3)	80/572 (14.0)	32/335 (9.6)[b]	35/681 (5.1)
	LEI, ≥ 50% improvement[c]	197/284 (69.4)	219/374 (58.6)	115/195 (59.0)	178/431 (41.3)
	LEI resolution[c]	151/284 (53.2)	166/374 (44.4)	80/195 (41.0)[b]	125/431 (29.0)
	LDI, ≥ 50% improvement[c]	107/174 (61.5)	107/188 (56.9)[b]	75/141 (53.2)[b]	92/231 (39.8)
	LDI resolution[c]	107/174 (61.5)	98/188 (52.1)	74/141 (52.5)[b]	76/231 (32.9)
Skin disease activity	PASI100 (resolution)[d]	71/214 (33.2)	65/306 (21.2)	26/171 (15.2)	19/326 (5.8)
	PASI75[d]	151/214 (70.6)	175/306 (57.2)	95/171 (55.6)	34/326 (10.4)
	mNAPSI75[d]	85/281 (30.2)	106/363 (29.2)	51/220 (23.2)	59/449 (13.1)
	IGA 0/1	112/214 (52.3)	125/306 (40.8)	55/171 (32.2)	25/326 (7.7)
Pain	PsA pain, mean change from BL[e]	−19.75 (n = 440)	−15.94 (n = 545)	−15.44 (n = 320)	−4.46 (n = 616)
	PsA pain VAS, ≥ 3-point improvement[e]	313/440 (71.1)	403/545 (73.9)	229/319 (71.8)	331/617 (53.6)
Patient global assessment	Patient global, mean change from BL[e]	−20.04 (n = 440)	−15.92 (n = 545)	−14.60 (n = 320)	−5.31 (n = 616)
	Patient global, ≥ 3-point improvement	335/440 (76.1)	398/542 (73.4)	215/319 (67.4)[b]	354/617 (57.4)
Physical function	HAQ-DI, mean change from BL[e]	−0.48 (n = 438)	−0.36 (n = 544)	−0.40 (n = 320)	−0.16 (n = 615)
	HAQ-DI, MCID ≥ 0.35	262/459 (57.1)	281/571 (49.2)	172/335 (51.3)	226/680 (33.2)
HRQOL	SF-36 PCS, MCID ≥ 2.5, %	65.9	59.4	61.8	42.0
	SF-36 MCS, MCID ≥ 2.5, %	48.4[b]	50.0[b]	49.9[b]	40.4
	PsAQOL, mean change from BL[e]	−3.65 (n = 443)	−3.26 (n = 548)	−3.16 (n = 319)	−1.20 (n = 622)
	DLQI, mean change from BL[f]	−7.11 (n = 273)	−6.57 (n = 166)	−6.29 (n = 339)	−2.14 (n = 356)
Fatigue	FACIT-Fatigue, mean change from BL[e]	6.21 (n = 442)	5.26 (n = 546)	5.42 (n = 319)	1.79 (n = 621)
	FACIT-Fatigue responder (change from BL ≥ 3.5)	247/442 (55.9)	319/546 (58.4)	181/319 (56.7)	239/621 (38.5)
Systemic inflammation	Elevated CRP (> 10 mg/L) resolution	83/111 (74.8)	86/134 (64.2)	52/75 (69.3)	55/154 (35.7)
Middle circle domains (important but not required in all PsA clinical trials)					
Participation	WPAI:GH, mean change from BL[e]	−13.98 (n = 283)	−10.85 (n = 392)	−13.39 (n = 186)	−4.62 (n = 417)
Structural damage	No structural progression at Week 24[c]	191/217 (88.0)	170/213 (79.8)[b]	176/210 (83.8)[b]	218/296 (73.6)
Improvement in Patients With Ankylosing Spondylitis at Week 16 in MEASURE 2[g]					
		Secukinumab 150 mg (n = 72)		**Placebo (n = 74)**	
Spine symptoms	BASDAI, mean change from BL	−2.19[h]		−0.85	
	BASDAI, 20% improvement	48/67 (71.6)		24/64 (37.5)	
	BASDAI inactive (< 4)	31/67 (46.3)[h]		12/64 (18.8)	
	ASAS40 responder	26/72 (36.1)[i]		8/74 (10.8)	

BL, baseline.
[a] All *P* values vs placebo are *P* < 0.0001 except where indicated. All *P* values are for hypothesis generation. No adjustment was made for multiple comparisons. [b] *P* = 0.0025. [c] *P* = 0.0077. [d] Calculated only among patients who had enthesitis, dactylitis, skin involvement (affected body surface area ≥ 3%), or nail psoriasis at BL. [e] *P* = 0.0096. [f] *P* = 0.0005. [g] *P* = 0.0119. [h] *P* < 0.0003. [i] *P* = 0.0005. [j] *P* = 0.001. [k] Least squares mean change from BL; *n* is the number of patients with measures at both BL and Week 16 visit. [l] No MCID has been defined in PsA. [m] *P* = 0.0029. [n] *P* < 0.01. [o] Defined as a change from BL vdH-mTSS of ≤ 0.5. Data shown are from the FUTURE 5 study only. [p] *P* = 0.1027. [q] *P* = 0.0053. [r] *P* < 0.001. [s] *P* = 0.0008. [t] *P* = 0.0003.

- Similar results were also seen in the skin disease activity domain, with patients receiving secukinumab 300 mg demonstrating the greatest improvement in all measurements (**Table 3; Figure 3**)

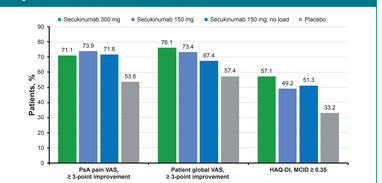
Figure 3. Patient Improvement Across the Skin Disease Activity Domain at Week 16



All *P* values vs placebo are *P* ≤ 0.001.
* Among patients with BSA ≥ 3% at baseline.
† Among patients with nail involvement at baseline.

- Significant improvement was seen in all secukinumab dose groups across the pain, patient global assessment visual analog scale, and physical function domains (**Table 3; Figure 4**)

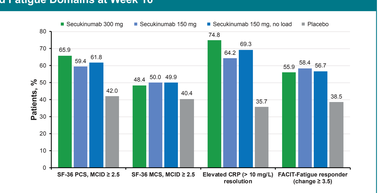
Figure 4. Patient Improvement Across Pain, Patient Global Assessment, and Physical Function Domains at Week 16



All *P* values vs placebo are *P* < 0.003.

- The percentages of patients who achieved minimal clinically important differences in the 36-Item Short Form Health Survey (SF-36) physical component summary and SF-36 mental component summary (≥ 2.5-point improvement) were similar among all 3 secukinumab groups (range, 48.4%–65.9%) and were significantly greater than in the placebo group (range, 40.4%–42.0%) (**Table 3; Figure 5**)
- Improvement was also seen in all secukinumab dose groups across the systemic inflammation and fatigue domains

Figure 5. Patient Improvement Across HRQOL, Systemic Inflammation, and Fatigue Domains at Week 16



All *P* values vs placebo are *P* < 0.005.

- Secukinumab 300 mg and 150 mg no-load doses had the greatest mean change from baseline (−13.98 and −13.39, respectively) in the Work Productivity and Activity Impairment Questionnaire: General Health measure, followed by secukinumab 150 mg load (−10.85), compared with placebo (−4.62) for the participation domain (**Table 3**)
- Secukinumab 150 mg demonstrated greater improvements in the spine symptom domain in patients with AS than did placebo in all 3 BASDAI measures and in achievement of 40% improvement in Assessment in SpondyloArthritis international Society response criteria (**Table 3**)

CONCLUSIONS

- Secukinumab demonstrated robust and consistent efficacy across all GRAPPA-OMERACT PsA core domains using pooled data from 4 on-label Phase III studies (FUTURE 2 through FUTURE 5)
- Secukinumab 300 mg had the greatest efficacy across most of the PsA core domains compared with placebo at Week 16
- Using data from MEASURE 2, secukinumab 150 mg improved spine symptoms in patients with AS
- This analysis demonstrates that secukinumab is an option for patients with PsA, regardless of their symptom manifestation

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