Manuscript Number: ACR-17-0621.R1

Manuscript Type: Brief Report

Running title: **Minimal disease activity with secukinumab in PsA**

Title: Minimal Disease Activity among Active Psoriatic Arthritis Patients Treated with Secukinumab: 2-year Results from the FUTURE 2 Study

Laura C Coates, MBChB, MRCP, PhD[1]*; Philip J Mease, MD[2]; Laure Gossec, MD, PhD[3]; Bruce Kirkham, MD, FRCP[4]; Bintu Sherif, MS[5]; Corine Gaillez, MD[6], Shephard Mpofu, MD[6]; Steffen M Jugl, MD[6]; Chetan Karyekar, MD, PhD[7]; Kunal K Gandhi, MD, MPH[7]

[1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

[2]Swedish Medical Centre and University of Washington, Seattle, WA, United States of America

[3]Sorbonne Universités, UPMC Université Paris 06, GRC-UPMC 08 (EEMOIS); Department of Rheumatology, Pitié Salpêtrière Hospital, AP-HP, Paris, France

[4]Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

[5]RTI Health Solutions, Research Triangle Park, NC, United States of America

[6]Novartis Pharma AG, Basel, Switzerland

[7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States of America

***Corresponding author:** Dr. Laura C Coates, MBChB, MRCP, PhD, NIHR Clinician Scientist, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Botnar Research Centre, Windmill Road, Oxford, OX3 7LD, United Kingdom. Tel: +44-(0)-1865 227 374. E-mail: laura.coates@ndorms.ox.ac.uk

Abstract

Objective: To evaluate minimal disease activity (MDA) among psoriatic arthritis (PsA) patients receiving secukinumab through 2 years in the FUTURE 2 study (NCT01752634).

Methods: Patients with active PsA were randomized to receive subcutaneous secukinumab 300, 150, or 75 mg or placebo. MDA was assessed in the overall population (anti-tumor necrosis factor [TNF]-naïve and inadequate responders [anti-TNF-IR]) and in patients stratified by prior anti-TNF exposure and by time since diagnosis at Weeks 16, 24, 52, and 104. Function, patient-reported outcomes (PROs) including health-related quality of life (QoL), and work productivity were assessed in MDA responders versus non-responders.

Results: Overall, 28% (27/98) and 23% (23/100) of patients achieved MDA at Week 16 with secukinumab 300 and 150 mg, respectively, versus 10% (9/94) with placebo. In the anti–TNF-naïve cohort, a higher proportion of patients achieved MDA at Week 16 with secukinumab 300 and 150 mg (34% and 32%, respectively) versus placebo (13%). The corresponding value in the anti-TNF-IR cohort was 15% and 8% with secukinumab 300 and 150 mg, respectively, versus placebo (3%). At Week 16, 27.1% (16/59) of MDA responders achieved a very low disease activity (VLDA) response, with the percentage being numerically greater with secukinumab 300 and 150 mg (30% [8/27] and 26% [6/23], respectively) versus placebo (22% [2/9]). The MDA and VLDA responses with secukinumab 300 and 150 mg were sustained through 2 years. MDA responders showed greater improvements in QoL outcomes compared to non-responders through 2 years.

Conclusion: A greater proportion of patients achieved MDA with secukinumab versus placebo at Week 16, with response rates sustained through 2 years. MDA was associated with improved PROs, including QoL, through 2 years.

Keywords: Anti-TNF, Disease Activity, Inflammation, Psoriatic Arthritis, Spondyloarthritis, Remission

Significance and Innovations

- As yet, no published studies have assessed MDA in PsA patients with an inadequate response or intolerance to anti-TNF therapies (anti–TNF-IR). FUTURE 2 is the first study to report MDA in anti–TNF-IR patients with up to three previous anti-TNF failures.
- Secukinumab-treated patients had significantly higher MDA response rates compared to those receiving placebo in the short-term period (Week 16), with sustained responses over 2 years. The analysis also covered individual components of MDA as well as VLDA.
- Patients achieving MDA with secukinumab also experienced greater improvements in highly relevant PROs, including health-related QoL, fatigue, and social functioning.

INTRODUCTION

Psoriatic arthritis (PsA) is an irreversible, progressive, heterogeneous inflammatory chronic condition associated with structural bone damage, joint pain, stiffness and swelling, and prominent extra-articular manifestations, such as psoriasis, enthesitis, and dactylitis.(1) Uncontrolled PsA has a significant impact on the health-related quality of life (QoL) of patients.(2) Studies show that it is important to assess the disease activity in multiple domains of this complex disease when considering treatment targets or measures of remission in PsA.(3) Minimal disease activity (MDA) is a validated composite comprehensive clinical outcome that encompasses concepts of remission with low or very low disease activity (VLDA) and includes patient-reported outcomes (PROs), peripheral arthritis, enthesitis, and skin measures. A patient is classified as having achieved MDA upon meeting at least five of the seven pre-defined criteria determining MDA response.(3, 4) MDA is a key composite index that is used to tightly monitor PsA patients across multiple facets of the disease.(3, 5) It is gaining acceptance as a clinically important and patient-relevant outcome.(6, 7) Secukinumab, a fully human monoclonal antibody that selectively neutralizes interleukin (IL)-17A, significantly improved the signs and symptoms of PsA sustained through 104 weeks in the Phase III, randomized, placebo-controlled FUTURE 2 study (NCT01752634).(8, 9) Herein, we explored the MDA response rates in PsA patients treated with secukinumab, the impact of secukinumab on individual components of MDA, and the relationship of MDA with PROs and QoL through 104 weeks in the FUTURE 2 study.

METHODS

Study design and patients

FUTURE 2 is an ongoing, multicenter, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the efficacy and safety of subcutaneous (s.c.) secukinumab treatment in active PsA patients. Details of the study design, inclusion and exclusion criteria, and 104-week results are reported elsewhere.(8, 9) Briefly, patients were randomized (1:1:1:1) to receive s.c. secukinumab 300, 150, or 75 mg or placebo at baseline; Weeks 1, 2, 3 and 4; and every 4 weeks thereafter. Placebo-treated patients were re-randomized, based on clinical response at Week 16, to receive s.c. secukinumab 300 or 150 mg either at Week 16 (non-responders) or at Week 24 (responders). Results for placebo are only shown up to Week 16 to preclude bias from placebo non-responders switching to active treatment. MDA was assessed in the overall study population and in patients stratified by prior use of anti-tumor necrosis factor (TNF) therapy (i.e., anti–TNF-naïve or with previous inadequate response or inability to tolerate up to three different anti-TNF therapies [anti–TNF-IR]) and/or by time since diagnosis (≤2 years [early disease] vs. >2 years [established disease]). Herein, only data for the approved doses of secukinumab (i.e. 300 and 150 mg) are reported.

The study was conducted in accordance with the principles of the Declaration of Helsinki, International Conference of Harmonization Good Clinical Practice, and all applicable laws and regulations.

Outcomes

Patients were considered to have achieved MDA response upon meeting at least five of the seven following criteria: tender joint count (TJC) ≤1, swollen joint count (SJC) ≤1, Psoriasis Area and Severity Index (PASI) score ≤1, patient pain visual analog scale (VAS) score ≤15, patient global disease activity VAS score ≤20, Health Assessment Questionnaire-Disability Index (HAQ-DI) score ≤0.5, and tender entheseal points ≤1.(3) Patients with partial missing criteria not meeting five of the seven MDA criteria were considered MDA non-responders. A patient meeting all seven MDA criteria was classified as having achieved VLDA.(5) Patients with less than 3% of their body surface area affected by psoriatic skin involvement at baseline were assigned a constant absolute PASI score of 1. All seven criteria for evaluating MDA were assessed at baseline and at multiple time points through Week 104. The proportion of patients achieving MDA and VLDA were calculated at Weeks 16, 24, 52, and 104. The shift in MDA response status for secukinumab was evaluated to assess sustained response up to Week 104, starting with the proportion of MDA responders at Week 16. The shift analysis of MDA response status at Week 16 was repeated for Weeks 24 and 52 as well. The proportion of MDA responders at Week 16 who sustained the MDA response up to Weeks 52 and 104 was evaluated. The proportion of patients achieving each individual core component was calculated among MDA responders and non-responders at Weeks 16, 24, 52, and 104.

In addition, the relationship between PROs and MDA response was assessed through Week 104. Health-related QoL and social functioning were assessed in MDA responders and non-responders using the 36-item Short-Form Health Survey physical

(SF-36 PCS) and mental (SF-36 MCS) component summary, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Psoriatic Arthritis Quality of Life questionnaire (PsAQoL), Dermatology Life Quality Index (DLQI), and Work Productivity and Activity Impairment-General Health (WPAI-GH). MDA responders and non-responders were compared at Weeks 16, 24, 52, and 104.

Statistical analysis

The proportion and 95% confidence intervals were computed for MDA response and each MDA criterion up to Week 104. These results were summarized for each randomized treatment group (secukinumab 150 and 300 mg and placebo) in the overall population and in patients stratified by prior anti-TNF therapy use and/or by time since diagnosis. Fisher's exact test was used to compare each secukinumab group to placebo. The change in PRO and MDA response was assessed using mixed-effects model for repeated measures (MMRM) with MDA response, analysis visit, and anti-TNF inhibitor status as factors and weight and baseline PRO score as continuous covariates. MDA response by analysis visit and PRO baseline score by analysis visit were included as interaction terms in the model. An unstructured covariance was assumed for the MMRM model with treatment groups pooled for the analysis.

Shift in response was assessed in a subset of patients (i.e., MDA responders at selected time points), with no comparison performed between secukinumab treatment arms. The numerator was based on patients who sustained the MDA response. The denominator was based on the total number of MDA responders with evaluation. All analyses were based on observed data using the full analysis set, which comprised all patients from the randomized set to whom study treatment had been assigned following

the intent-to-treat principle according to the treatment assigned at randomization. Statistical analyses were performed using SAS version 9.4 (SAS Institute; Cary, NC; 2011).

RESULTS

Demographic and baseline characteristics were comparable across treatment groups in FUTURE 2.(8) High retention rates were observed among patients treated with secukinumab. At Week 104, 87% (87/100) and 80% (80/100) of patients randomized to secukinumab 300 and 150 mg, respectively, had evaluable data for the MDA analysis.

In the overall population, a higher proportion of patients achieved MDA at Week 16 with secukinumab 300 and 150 mg (28% [27/98] and 23% [23/100], respectively) versus placebo (10% [9/94]). At Week 24, 32% (31/97) and 25% (24/96) of patients achieved MDA with secukinumab 300 and 150 mg, respectively.

The MDA response rates at Weeks 16 and 24 with secukinumab were maintained and continued to improve through Week 104 (Figure 1A). In the anti–TNF-naïve cohort, a higher proportion of patients achieved MDA at Week 16 with secukinumab 300 mg (34% [22/65]) or 150 mg (32% [20/63]) vs placebo (13% [8/60]), with response rates in anti–TNF-IR patients being 15% (5/33) for secukinumab 300 mg and 8% (3/37) for 150 mg vs 3% (1/34) for placebo. These response rates were sustained through Week 104 (Figure 1B and 1C).

The shift analysis showed that a higher proportion of secukinumab-treated patients achieved MDA at Weeks 52 (78% with 300 mg and 74% with 150 mg) and 104 (85% with 300 mg and 62% with 150 mg; Supplementary Figure S1).

A majority (70% [19/27]) of MDA responders at Week 16 sustained their MDA response through Week 52 with secukinumab 300 mg, and about half (48% [11/23]) sustained their response with secukinumab 150 mg. At Week 104, 58% (15/26) of patients in the secukinumab 300 mg group and 33% (7/21) in the secukinumab 150 mg group sustained their MDA response (Supplementary Table S1).

A higher proportion of patients with early PsA disease (≤2 years since first PsA diagnosis) as compared to those with a later onset (>2 years since first PsA diagnosis) achieved MDA at Weeks 24 and 52 with both secukinumab 300 and 150 mg (in %, Week 24: 43 vs. 29 [300 mg] and 29 vs. 23 [150 mg], Week 52: 38 vs. 34 [300 mg] and 33 vs. 32 [150 mg]). At Week 16, MDA response rates with secukinumab (300 and 150 mg combined) were highest among anti–TNF-naïve patients with a shorter time since diagnosis. The MDA response rates through Week 104 in the overall population and in the anti–TNF-naïve and anti–TNF-IR populations stratified by time since diagnosis are shown in Supplementary Figure S2.

At Week 16, the percentage of patients achieving each MDA criterion in descending order was as follows: tender entheseal points ≤1, PASI ≤1, HAQ-DI ≤0.5, SJC ≤1, patient global VAS ≤20, patient pain VAS ≤15, and TJC ≤1. A similar trend was noted in the percentage of patients achieving each MDA criterion at Weeks 52 and 104 (Table 1).

At Week 16, 27.1% (16/59) of patients met the criteria for VLDA among the MDA responders in the overall population, with the percentage being numerically greater among those receiving secukinumab 300 and 150 mg (30% [8/27] and 26%[6/23], respectively) compared with the placebo arm (22% [2/9]) (Table 1). A higher proportion

of secukinumab-treated patients in MDA achieved VLDA at Week 104 (49% [19/39] with 300 mg and 40% [10/25] with 150 mg). At Week 16, the absolute percentage of patients who met the criteria for VLDA in the overall population was 8% (8/98) and 6% (6/100) in the secukinumab 300 and 150 mg arms, respectively vs. 2% (2/94) in the placebo arm. This proportion improved to 22% (19/87) and 13% (10/80) in the secukinumab 300 and 150 mg arms, respectively, at Week 104.

The least square mean change from baseline was higher among MDA responders than non-responders at Week 16 for SF-36 PCS (8.8 vs. 4.0; *P* <0.0001), SF-36 MCS (6.7 vs. 3.9: *P* <0.01), FACIT Fatigue (8.7 vs. 4.2; *P* <0.0001), PsAQoL (–4.7 vs. –3.0; *P* <0.0001), and DLQI total score (–9.3 vs. –7.0; *P* <0.001).

A similar trend was observed for work productivity and social functioning (WPAI-GH) outcome measures at Week 16 with the least square mean change from baseline being higher among MDA responders than non-responders for all the domains: % activity impairment due to health (–23.7 vs. –10.2; *P* <0.0001), % overall work impairment due to health (–19.1 vs. –9.1; *P* <0.01), % work time missed due to health (–9.6 vs. –5.5) and % impairment while working due to health (–19.0 vs. –8.0; *P* <0.01).

Overall, MDA responders reported significantly greater and sustained improvement in QoL and work productivity than non-responders over 104 weeks (Table 2).

DISCUSSION

Secukinumab-treated patients had significantly higher MDA response rates at the individual level compared to those receiving placebo in the short-term period (Week 16), with responses sustained over the long term (Week 104). Compared to patients

receiving placebo, the proportion of secukinumab-treated patients achieving MDA was higher in both anti–TNF-naïve and the more difficult to treat anti–TNF-IR sub-populations.

It is notable that patients with high disease activity at baseline also reached the MDA state in the current study. The relevance of these results in clinical practice is promising and needs to be further explored in prospective studies.(10)

MDA response rates in this study were comparable with those previously reported with anti-TNF therapies among biologic-naïve patients enrolled in clinical trials with responses ranging from 39% to 42% at 1 year,(4, 11-14) even though the population in FUTURE 2 included difficult to treat patients as well. The commonly used definition for early PsA is disease/symptom duration less than 2 years. The proportion of patients in the overall population achieving MDA with secukinumab was greater among those with ≤2 years since first PsA diagnosis versus those with >2 years since diagnosis at Weeks 16 and 52.

As yet, no published studies have assessed MDA in PsA patients with at least one inadequate response or inability to tolerate anti-TNF therapies. FUTURE 2 is the first study to report MDA in anti–TNF-IR patients with up to three previous anti-TNF failures. The finding that greater MDA can be achieved in anti–TNF-naïve PsA patients with early disease is notable and supports the rationale for early and aggressive treatment; however, the small sample size and the potential impact of the study exclusion criteria like certain comorbidities that got excluded from enrolment, warrants further research.

The individual components most frequently reached among MDA responders in this cohort were related to enthesitis, skin, and functional status. Several studies on the IL-

23/IL-17 axis have shown that innate immunity is intrinsically involved in the pathogenesis of psoriasis and PsA. Psoriatic skin lesions have an increased expression of IL-23 and IL-17, and the notable responses in enthesitis and PASI scores in this study may suggest a possible relationship of the IL-23/IL-17 pathway with the skin-entheseal axis.(15) The arthritis-related components of MDA were also achieved by many patients who were MDA responders.

In this study, 40%–49% of patients achieving MDA were able to meet the VLDA criteria at 2 year. This is notable in the context of a recent study suggesting that the VLDA criteria are more stringent than other composite markers with lesser residual disease activity in patients achieving VLDA.(5) Additionally, the exclusion of laboratory markers in VLDA makes target assessment easier in clinical practice.

A potential limitation in the case of MDA is that PsA patients could achieve MDA even if they had active disease in some domains, particularly skin, but in this cohort, levels of residual skin disease were very low. This reflects the marked efficacy of secukinumab in skin disease since a majority of the MDA responders performed well on the PASI score. Patients with less than 3% of their body surface area affected by psoriatic skin involvement at baseline could potentially have developed worsening of their psoriasis later in the study and may limit them to be evaluated on the PASI score. Although, this number is unlikely to be considerable to impact the overall MDA analyses, given the strong positive and long-lasting results reported with secukinumab in psoriasis in multiple clinical studies.

MDA criteria have been shown to have construct validity and correlate well with a patient-acceptable disease state. They are a composite measure including multiple

domains of psoriatic disease. However, unlike other composites, individual criteria are not added up in MDA but considered separately to assess each individual item cut point. This ensures that activity in one domain is not “hidden” within a composite score that sums components into one final number.

In the current study, the HAQ-DI was not a common reason to prevent people from being in MDA. If the disease was quiescent but the HAQ-DI criterion was not met (e.g. due to disability from previous joint damage), a patient would still achieve an MDA response if all the other parameters were met (by meeting 6 of 7 criteria), thus achieving MDA rather than remission which is a recommended alternative target.

Patients achieving MDA with secukinumab also experienced greater improvements in PROs, health-related QoL, fatigue, and social functioning. Thus, achieving MDA directly translates to benefits for patients in the most relevant aspects. Furthermore, the improvements in social functioning (WPAI-GH) among MDA responders suggest that achieving MDA could limit burden on health systems, society, and economy on a large scale through the linked improved work productivity and ability to contribute to the society.

In conclusion, PsA patients treated with secukinumab achieved early and sustained MDA over 2 years in both anti–TNF-naïve and anti–TNF-IR sub-populations. The more stringent VLDA criterion was achieved in 40%–49% of MDA responders in the overall population. Patients achieving MDA with secukinumab experienced greater improvements in highly relevant PROs.

Acknowledgments: The authors thank the patients who participated in the study, the study investigators, RTI Health Solutions for support with the *post-hoc* data analyses,

and John Gallagher, medical consultant for Novartis Pharma AG. Medical writing support for the development of this manuscript was provided by MK Vivek Sanker and Neeta Pillai (Novartis, India) and was funded by Novartis Pharma AG, Basel, Switzerland.

REFERENCES

1. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(suppl 2):ii14-ii7.
2. Boehncke WH, Menter A. Burden of disease: psoriasis and psoriatic arthritis. Am J Clin Dermatol. 2013;14(5):377-88.
3. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis. 2010;69(1):48-53.
4. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res (Hoboken). 2010;62(7):965-9.
5. Coates LC, Emery P, Conaghan PG, Helliwell PS. What should be the primary target of ‘treat to target’ in PsA? [abstract]. Arthritis Rheumatol. 2016;68(suppl 10).
6. Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis. 2014;73(1):6-16.

7. Coates LC, Cook R, Lee KA, Chandran V, Gladman DD. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. Arthritis Care Res (Hoboken). 2010;62(7):970-6.
8. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386(9999):1137-46.
9. McInnes IB, Ritchlin CT, Rahman P, Gottlieb AB, Kirkham B, Kajekar R, et al. Secukinumab provides sustained improvements in the signs and symptoms of active psoriatic arthritis: 104 weeks results from a phase 3 trial. Arthritis Rheumatol. 2016.
10. Queiro R, Cañete JD, Montilla C, Abad M, Montoro M, Gómez S, et al. Minimal disease activity and impact of disease in psoriatic arthritis: a Spanish cross-sectional multicenter study. Arthritis Research & Therapy. 2017;19(1):72.
11. Mease PJ, Heckaman M, Kary S, Kupper H. Application and modifications of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: subanalyses of ADEPT. J Rheumatol. 2013;40(5):647-52.
12. Haddad A, Thavaneswaran A, Ruiz-Arruza I, Pellett F, Chandran V, Cook RJ, et al. Minimal disease activity and anti-tumor necrosis factor therapy in psoriatic arthritis. Arthritis Care Res (Hoboken). 2015;67(6):842-7.
13. Kavanaugh A, van der Heijde D, Beutler A, Gladman D, Mease P, Krueger GG, et al. Radiographic progression of patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy: results through 5

years of a randomized, placebo-controlled study. Arthritis Care Res (Hoboken). 2016;68(2):267-74.

14. Zummer M, Rahman P, Arendse R, Starr M, Kelsall J, Avina-Zubieta JA, et al. Predictors of early minimal disease activity in psa patients treated with anti-tnf in a real-world registry [abstract]. Arthritis Rheumatol. 2015;67(suppl 10).

15. Sakkas LI, Bogdanos DP. Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data. Autoimmunity Reviews. 2017;16(1):10-5.

TABLES

Table 1: a) Core components of MDA and b) VLDA among MDA responders

Table 2: PROs and MDA

Table 1: Core Components of MDA and VLDA

	Week	MDA Responders			MDA Non-responders		
		Secukinumab			Secukinumab		
		300 mg s.c. (N=100)	150 mg s.c. (N=100)	Placebo (N=98)	300 mg s.c. (N=100)	150 mg s.c. (N=100)	Placebo (N=98)
a) MDA core components[a], n/m (%)							
Tender entheseal points ≤1	16	27/27 (100)	23/23 (100)	8/9 (89)	49/70 (70)	52/77 (68)	42/79 (53)
	52	32/33 (97)	27/29 (93)	-	44/60 (73)	44/59 (75)	-
	104	39/ 39 (100)	24/ 25 (96)	-	35/ 48 (73)	38/ 52 (73)	-
PASI score ≤1	16	25/27 (93)	17/23 (74)	8/9 (89)	54/71 (76)	47/77 (61)	49/81 (61)
	52	33/33 (100)	24/29 (83)	-	47/62 (76)	31/59 (53)	-
	104	36/ 39 (92)	20/ 25 (80)	-	39/ 48 (81)	33/ 53 (62)	-
HAQ-DI score ≤0.5	16	24/27 (89)	19/23 (83)	8/9 (89)	21/70 (30)	26/77 (34)	24/78 (31)
	52	31/33 (94)	27/29 (93)	-	17/57 (30)	19/59 (32)	-
	104	36/ 39	23/ 25	-	14/ 48	22/ 52	-

		(92)	(92)		(29)	(42)	
SJC ≤1	16	17/27 (63)	18/23 (78)	7/9 (78)	16/70 (23)	16/77 (21)	12/78 (15)
	52	28/33 (85)	23/29 (79)	-	24/57 (42)	22/59 (37)	-
	104	35/ 39 (90)	23/ 25 (92)	-	27/ 47 (57)	21/ 52 (40)	-
Patient global VAS ≤20	16	22/27 (82)	20/23 (87)	8/9 (89)	9/70 (13)	9/77 (12)	3/78 (4)
	52	30/33 (91)	22/29 (76)	-	4/57 (7)	8/59 (14)	-
	104	34/ 39 (87)	19/ 25 (76)	-	5/ 48 (10)	7/ 52 (14)	-
Patient pain VAS score ≤15	16	24/27 (89)	19/23 (83)	8/9 (89)	6/70 (9)	8/77 (10)	4/78 (5)
	52	28/33 (85)	23/29 (79)	-	3/57 (5)	3/59 (5)	-
	104	30/ 39 (77)	20/ 25 (80)	-	4/ 48 (8)	3/ 52 (6)	-
TJC ≤1	16	22/27 (82)	18/23 (78)	5/9 (56)	2/70 (3)	11/77 (14)	6/78 (8)
	52	21/33 (64)	21/29 (72)	-	9/57 (16)	6/59 (10)	-
	104	34/ 39 (87)	21/ 25 (84)	-	9/ 47 (19)	4/ 52 (8)	-

b) VLDA among MDA responders in the overall population, n/M (%)				
VLDA	16	8/27 (30)	6/23 (26)	2/9 (22)
	52	13/33 (39)	9/29 (31)	-
	104	19/39 (49)	10/25 (40)	-

[a]Listed in the descending order of percentage of patients overall achieving each criterion at Week 16. Data presented as observed in the full analysis set. N, number of patients randomized to the treatment group; n, number of patients who achieved each criterion; m, number of patients with evaluation; M, number of MDA responders with evaluation.

HAQ-DI, Health Assessment Questionnaire Disability Index; MDA, minimal disease activity; NA, not applicable; PASI, Psoriasis Area and Severity Index; s.c., subcutaneous; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale; VLDA, very low disease activity.

Table 2: PROs and MDA

PROs, LS mean change from baseline ± SE[a]						
	Week	**MDA Responders**	**MDA Non-responders**	**Difference (Responders - Nonresponders)**	**95% CI**	***P* value**
SF-36 PCS	16	8.8 ± 0.6	4.0 ± 0.4	4.70	3.57, 5.84	<0.0001
	52	9.5 ± 0.6	4.8 ± 0.5	4.72	3.50, 5.94	<0.0001
	104	9.5 ± 0.6	3.6 ± 0.5	5.89	4.51, 7.26	<0.0001
SF-36 MCS	16	6.7 ± 0.9	3.9 ± 0.5	2.86	1.16, 4.56	=0.0011
	52	6.8 ± 0.8	4.2 ± 0.6	2.60	0.94, 4.26	=0.0022
	104	7.8 ± 0.8	4.2 ± 0.7	3.56	1.66, 5.45	=0.0003
FACIT-Fatigue	16	8.7 ± 0.9	4.2 ± 0.6	4.51	2.89, 6.13	<0.0001
	52	9.0 ± 0.7	5.5 ± 0.6	3.50	2.05, 4.95	<0.0001
	104	9.3 ± 0.9	5.4 ± 0.7	3.90	2.05, 5.76	<0.0001
PsAQoL	16	–4.7 ± 0.4	–3.0 ± 0.3	–1.67	–2.40,	<0.0001

	52	–5.6 ± 0.4	–3.4 ± 0.3	–2.25	–0.95 –3.00, –1.51	<0.0001
	104	–6.3 ± 0.4	–3.6 ± 0.3	–2.73	–3.68, –1.79	<0.0001
DLQI	16	N = 24 –9.3 ± 0.7	N = 113 –7.0 ± 0.5	–2.21	–3.44, –0.98	=0.0005
	52	N = 39 –10.2 ± 0.7	N = 85 –8.8 ± 0.5	–1.40	–2.86, 0.06	=0.0595
	104	N = 42 –10.8 ± 0.6	N = 74 –8.3 ± 0.4	–2.50	–3.67, –1.32	<0.0001
WPAI-GH						
% Activity impairment due to health	16	–23.7 ± 2.7	–10.2 ± 1.5	–13.55	–19.21, –7.88	<0.0001
	52	–25.6 ± 2.1	–13.9 ± 1.6	–11.72	–16.24, –7.19	<0.0001
	104	–26.1± 2.2	–11.3 ± 1.7	–14.78	–19.82, –9.73	<0.0001
% Overall work impairment due to health[b]	16	–19.1 ± 3.3	–9.1 ± 2.0	–9.99	–17.28, –2.70	=0.0076
	52	–21.4 ± 2.8	–11.8 ± 2.3	–9.59	–16.26, –2.92	=0.0051
	104	–17.9± 2.7	–11.8 ± 2.3	–6.12	–12.89, 0.65	=0.0760
% Work	16	–9.6 ± 2.5	–5.5 ± 1.4	–4.03	–9.55,	=0.1511

time missed due to health [b]	52	–8.3 ± 2.3	–3.8 ± 1.8	–4.54	–10.00, 1.49 0.92	=0.1029
	104	–2.4 ± 2.9	–1.8 ± 2.5	–0.68	–7.78, 6.41	=0.8500
% Impairment while working due to health [b]	16	–19.0 ± 3.0	–8.0 ± 1.8	–11.06	–17.68, –4.44	=0.0012
	52	–20.1 ± 2.6	–10.6 ± 2.1	–9.47	–15.37, –3.58	=0.0018
	104	–19.4 ± 2.2	–11.6 ± 1.9	–7.88	–13.09, –2.68	=0.0032

[a]Data are from MMRM analysis; at Week 16: MDA responders (N = 59) and MDA non-responders (N = 233); at Week 52: MDA responders (N = 93) and MDA non-responders (N = 174); at Week 104: MDA responders (N = 89) and MDA non-responders (N = 157); N, number of patients in each group of the specified analysis set.

[b]Outcome measure applies only to patients who were employed.

CI, confidence interval; DLQI, Dermatology Life Quality Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; LS, least squares; MDA, minimal disease activity; MMRM, mixed model repeated measures; PRO, patient-reported outcome; PsA QoL, Psoriatic Arthritis Quality of Life questionnaire; SE, standard error; SF-36 MCS, 36-item Short Form Health Survey Mental Component Summary; SF-36 PCS, 36-item Short Form Health Survey Physical Component Summary; WPAI-GH, Work Productivity and Activity Impairment-General Health.

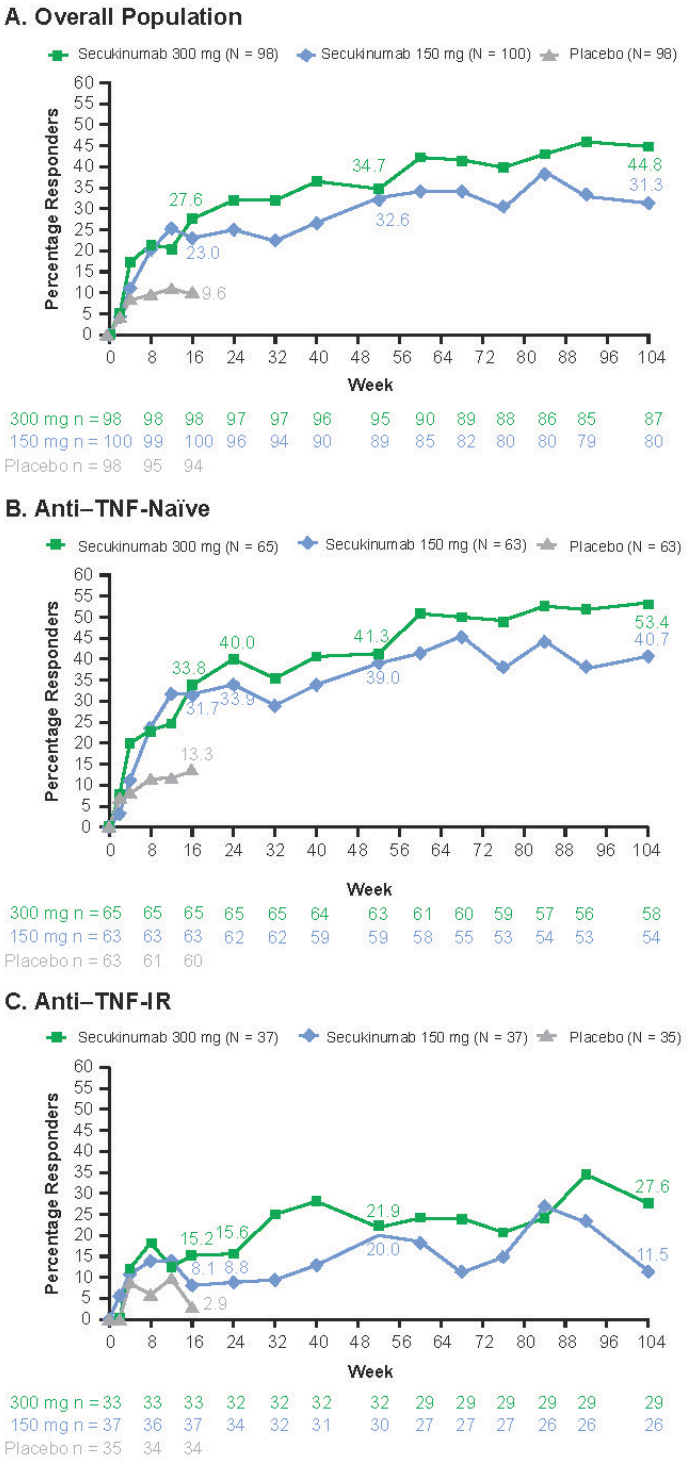
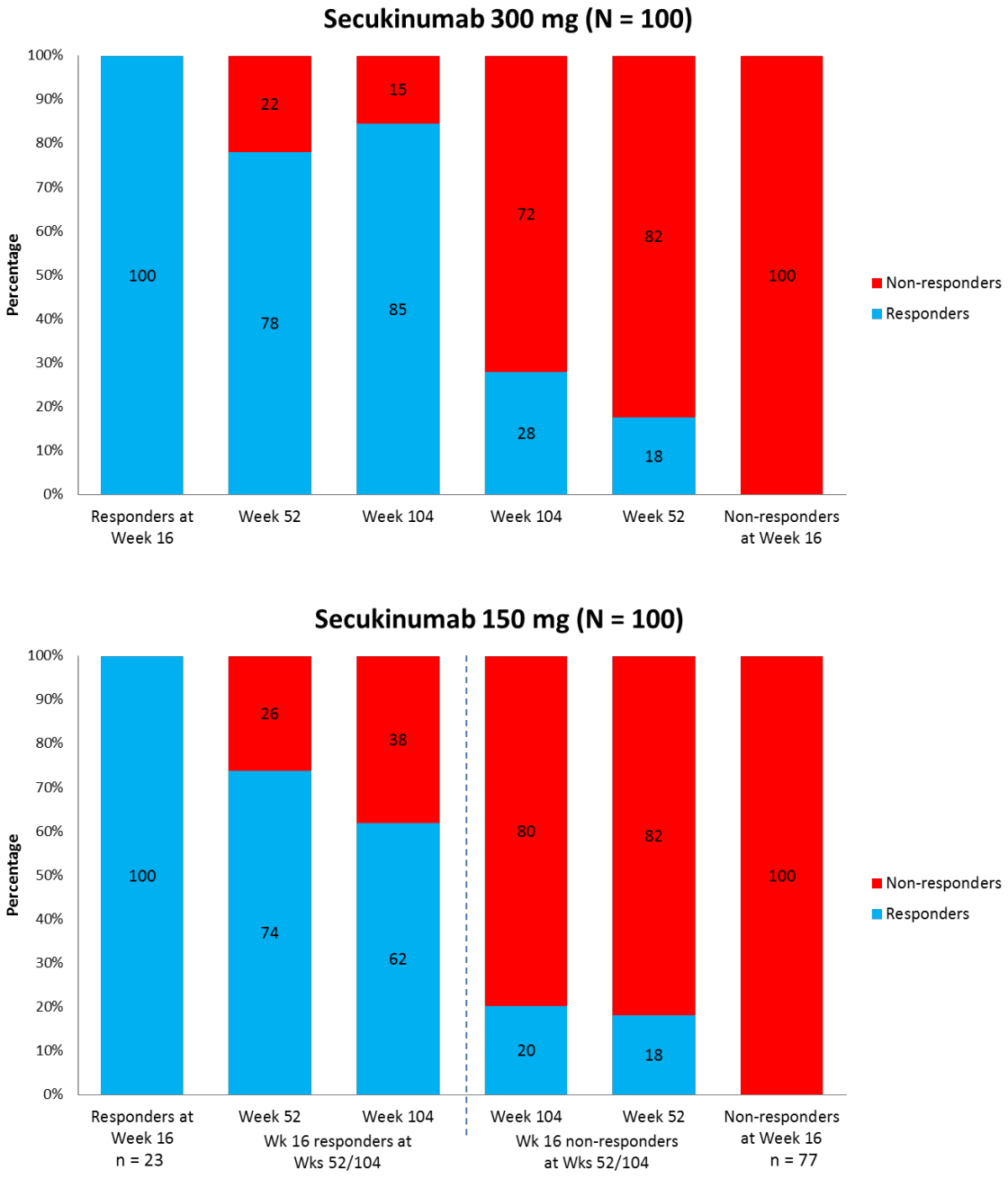


Figure 1. MDA response through 104 weeks. Data presented as observed in full analysis set; N, total number of randomized patients; n, number of patients with evaluable measurements. IR, inadequate response; MDA, minimal disease activity; TNF, tumor necrosis factor.

Supplementary Files

1. **Supplementary Figure S1: Shift analysis of Week 16 MDA response at Weeks 52 and 104**
2. **Supplementary Figure S2: MDA response through 104 weeks by disease duration**
3. **Supplementary Table S1: Sustainability of MDA response through 104 weeks**

Supplementary Figure S1: Shift analysis of Wk 16 MDA response at Wks 52 and 104

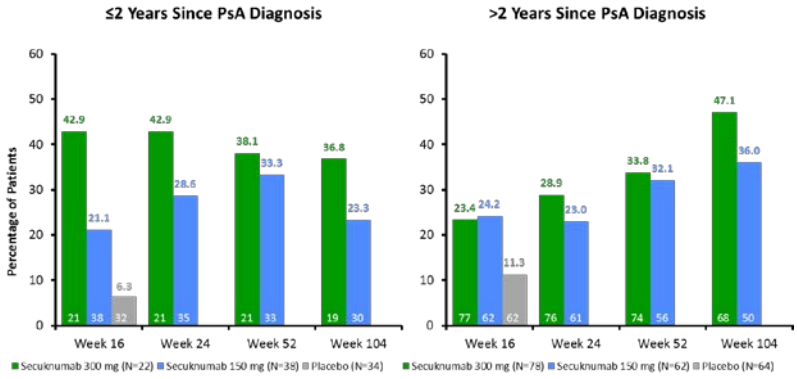


Data presented as observed in the full analysis set; N, total number of randomized patients; n, number of patients with evaluable measurements.

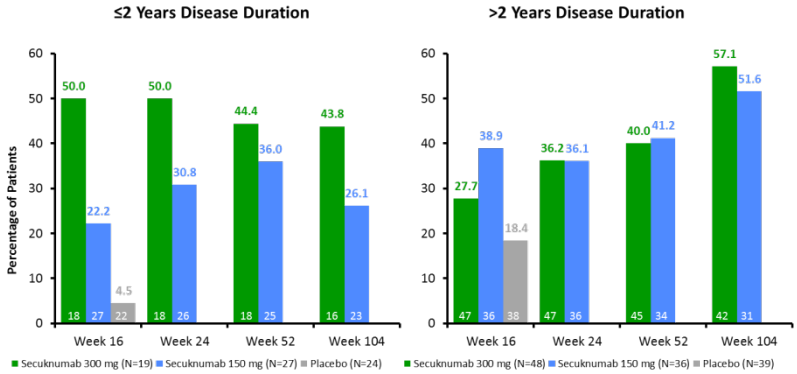
MDA, minimal disease activity; Wk, week.

Supplementary Figure S2: MDA response through 104 weeks by disease duration

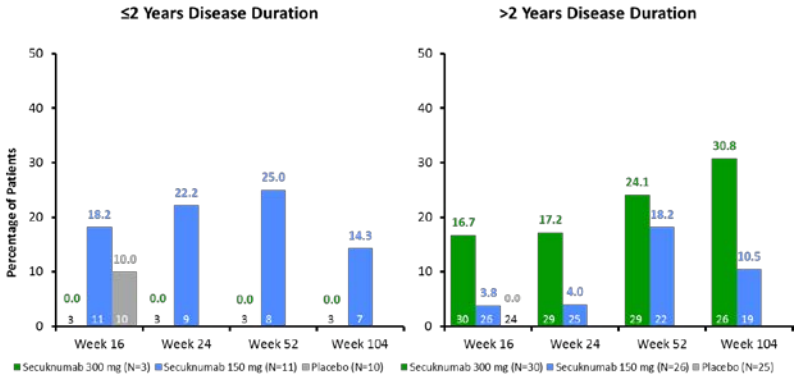
A. Overall Population



B. Anti-TNF-naïve



C. Anti-TNF-IR



Values presented at the base of each coloumn indicate number of patients with evaluable measurements. Data presented as observed in full analysis set.

IR, inadequate response; MDA, minimal disease activity; PsA, psoriatic arthritis; TNF, tumor necrosis factor.

Supplementary Table S1: Sustainability of MDA response through 104 weeks

MDA Response	Secukinumab 300 mg s.c. N = 100 n/M (%)	Secukinumab 150 mg s.c. N = 100 n/M (%)
MDA Response at Week 16	27	23
MDA Response at Week 16 and sustained through Week 24	23/27 (85.2)	19/23 (82.6)
MDA Response at Week 16 and sustained through Week 52	19/27 (70.4)	11/23 (47.8)
MDA Response at Week 16 and sustained through Week 104	15/26 (57.7)	7/21 (33.3)

MDA defined as achieving 5 of the following 7 factors: Tender joint count ≤ 1; Swollen joint count ≤ 1; PASI ≤ 1; Patient pain VAS ≤ 15; Patient global VAS ≤ 20; HAQ-DI ≤ 0.5; Tender entheseal points ≤ 1. Patients with partial missing criteria who did not meet the 5 out of 7 MDA criteria were considered MDA non response. Data presented as observed in the full analysis set.

M, total number of responders with evaluation; n: number of patients who sustained their MDA response; N, total number of randomized patients.

HAQ-DI, Health Assessment Questionnaire Disability Index; MDA, minimal disease activity; PASI, Psoriasis Area and Severity Index; s.c., subcutaneous; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale