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Laura C Coates, Peter Nash, Tore K Kvien, Laure Gossec, Philip J Mease, et al.. Comparison of remission and low disease activity states with DAPSA, MDA and VLDA in a clinical trial setting in psoriatic arthritis patients: 2-year results from the FUTURE 2 study. *Seminars in Arthritis and Rheumatism*, 2020, 50 (4), pp.709 - 718. 10.1016/j.semarthrit.2020.03.015 . hal-03286904

HAL Id: hal-03286904

<https://hal.sorbonne-universite.fr/hal-03286904>

Submitted on 15 Jul 2021

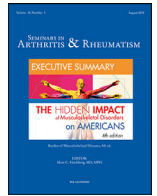
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Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Comparison of remission and low disease activity states with DAPSA, MDA and VLDA in a clinical trial setting in psoriatic arthritis patients: 2-year results from the FUTURE 2 study

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ARTICLE INFO

Keywords:

Remission
DAPSA
MDA
Psoriatic arthritis
Disease activity
Spondyloarthritis

ABSTRACT

Objectives: Remission (REM) or low disease activity (LDA) states were compared in a clinical trial setting of the FUTURE 2 study (NCT01752634) using Disease Activity Index for Psoriatic Arthritis (DAPSA) and Minimal Disease Activity (MDA) composite indices in secukinumab treated PsA patients.

Methods: The proportion of patients reaching DAPSA-REM (cut-off ≤ 4) or REM+LDA (≤ 14), and very low disease activity (VLDA; achieving 7/7 criteria) or MDA ($\geq 5/7$), were compared in the overall population, by prior use of anti-TNF therapy, and by time since diagnosis using as observed data. The proportion of patients who met individual core component and other variables of interest were also computed to assess residual disease activity in DAPSA-REM/REM+LDA states and VLDA/MDA responses. The relationship between DAPSA/MDA and patient reported outcomes (PROs), including health-related quality of life, physical function, and fatigue were assessed using mixed model for repeated measures.

Results: More patients could achieve DAPSA-REM or DAPSA-REM+LDA status than VLDA or MDA responses, respectively, at all the time points in the overall population, irrespective of anti-TNF status and time since diagnosis. Higher proportion of patients reaching DAPSA-REM or VLDA achieved more thresholds of core components (joints, pain, patient and physician global assessments, and function) than DAPSA-REM+LDA or MDA over Week 104. There were differences with numerically higher proportion of patients achieving patient global assessment ≤ 10 mm and ≤ 20 mm, and physician global assessment ≤ 10 mm with MDA than with DAPSA-REM+LDA, and patient pain VAS ≤ 15 mm, PASI ≤ 1 , HAQ ≤ 0.5 with VLDA or MDA than with DAPSA-REM or DAPSA-REM+LDA, respectively, through 104 weeks. Improvements in PROs were significantly better for patients in DAPSA-REM+LDA versus DAPSA-moderate+high disease activity status, and for MDA responders versus non-responders.

Conclusion: These analysis add to the evidence that both DAPSA and MDA composite index measures can be used for evaluation of the status and treatment response utilizing a treat to target approach in PsA patients in a clinical trial setting and improve patient health related outcomes.

Funding: The study and analysis was funded by Novartis Pharma AG, Basel, Switzerland.

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Introduction

Psoriatic arthritis (PsA) is an immune-mediated, chronic inflammatory disorder that affects ~30% of psoriasis (PsO) patients, and is associated with pain, impaired physical and social function and health-related quality of life (HRQoL) [1,2]. PsA shows musculoskeletal manifestations such as peripheral and axial arthritis, enthesitis, dactylitis, and inflammation of the distal interphalangeal (DIP) joints along with characteristic skin and nail involvement [2–5]. Tools such as American College of Rheumatology (ACR) improvement criteria, Disease Activity Status related to Disease Activity Score using 28 joint counts and C-reactive protein (DAS28-CRP), or DAS28-erythrocyte sedimentation rate (DAS28-ESR) originally developed for rheumatoid arthritis perform well for measuring joint response and disease activity status in PsA clinical trials with polyarticular manifestations [4,6–7]. These tools only focus on joints and do not take into account enthesitis, dactylitis and skin manifestations. The 28-joint count as used in DAS28 does not include DIP joints of the hands and foot/ankle joints which are frequently involved in PsA patients [6–9].

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-Outcome Measures in Rheumatology (OMER-ACT), the European League Against Rheumatism (EULAR), and the recent update of Treat-to-Target (T2T) recommendations for spondyloarthritis by international task force have recommended that the treatment target should be clinical remission (REM), with low or minimal disease activity (LDA/MDA) as the alternative treatment target of PsA [4,10–11]. Several composite measures, which partly assess multiple clinical domains, have been developed and validated in PsA clinical trials including psoriatic arthritis response criteria (PsARC), psoriatic arthritis joint activity index (PsAJAI), disease activity for psoriatic arthritis (DAPSA), psoriatic arthritis disease activity score (PASDAS), group for research and assessment of psoriasis and psoriatic arthritis composite exercise (GRACE), minimal disease activity (MDA), and composite psoriatic disease activity index (CPDAI) [12].

The selection of the optimal composite index to reflect REM or LDA is still debated as none targets all the clinical manifestations of PsA. Based on the T2T, EULAR and GRAPPA recommendations, DAPSA or MDA are considered for defining REM or LDA, the treatment targets of PsA [10,13]. The DAPSA is a simple, disease-specific unidimensional measure, focused on joint involvement with validated cut-off points for measuring disease activity states in PsA (Supplementary Table S1) [8,9,14]. Aside from defining disease activity states including REM and LDA, it is a continuous measure that allows to follow patients from treatment start to the time of reaching or not reaching the therapeutic target, including the extent of assessment at 3 months to determine whether treatment should be continued or not in accordance with the T2T strategy [14]. DAPSA-REM/DAPSA-LDA states with separate skin and enthesitis assessment are recommended as treatment targets of PsA and are associated with less functional disability and structural damage compared with high disease activity (HDA) states [15]. MDA is another validated multidimensional composite index, which combines joint involvement with enthesitis, skin, and function domain, but does not include CRP [16–20]. MDA is a categorical index defined as a response fulfilling five out of seven criteria whereas very low disease activity (VLDA) response fulfills all seven criteria (Supplementary Table S1), and therefore do not provide information on the actual level of disease activity [14]. MDA/VLDA have been associated with low radiographic progression, and with a positive impact on HRQoL, and work productivity [16,20].

Secukinumab is a fully human monoclonal IgG1 antibody that selectively neutralizes interleukin (IL)-17A [21]. In the placebo-controlled, double-blind, Phase III FUTURE 2 study (NCT01752634), secukinumab provided rapid, improved and sustained efficacy in patients with active PsA who were either naïve to anti-tumor necrosis factor therapy (anti-TNF-naïve) or had an inadequate response or intolerance with

prior use of up to 3 anti-TNF agents (anti-TNF-IR) irrespective of time since diagnosis over 104 weeks [22,23].

The objective of this post-hoc analysis was to specifically compare DAPSA-REM, VLDA and DAPSA-REM+LDA and MDA composite scores proposed as a target for remission or low disease activity in PsA using the overall population and the subgroups stratified by anti-TNF status and time since diagnosis from the FUTURE 2 two year study. This analysis also determined the level of residual disease activity as assessed by the individual core components of interest with DAPSA, MDA and VLDA over Week 104 and investigated the relationship of DAPSA states with PROs related to HRQoL, social and physical function, and work productivity.

Methods

Study design and patients

FUTURE 2 is an ongoing 5-year, randomized, multi-center, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of subcutaneous (s.c.) secukinumab treatment in patients with active PsA. Details of the study design, inclusion and exclusion criteria, and 104-week results have been reported previously [22,23]. Briefly, patients were randomized (1:1:1:1) to receive s.c. secukinumab 300, 150, 75 mg or placebo at baseline, Weeks 1, 2, 3 and 4, and every 4 weeks thereafter. Placebo treated patients were re-randomized to receive secukinumab 300 or 150 mg at either Week 16 or Week 24, based on clinical responses. The study consisted of a screening period of up to 10 weeks followed by randomization and treatment of patients for 52 weeks, and extended treatment for 4 years, which is currently ongoing. The primary endpoint of the study was the proportion of patients achieving ACR20 response at Week 24.

Only the data for the approved doses of secukinumab (300 and 150 mg) and placebo are reported here. Analysis was also stratified by: (1) prior use of anti-TNF therapy (anti-TNF-naïve or -IR) and (2) time since first PsA diagnosis (≤ 2 years [early disease] or > 2 years [established disease]). The study was conducted in compliance with the Declaration of Helsinki, International Council for Harmonization Guidelines for Good Clinical Practice and local country regulations.

Efficacy outcomes

For each patient with evaluable data at the visit of interest, DAPSA was calculated as the sum of: (1) swollen joint count (SJC; range: 0–66), (2) tender joint count (TJC; range: 0–68), (3) patient pain assessment visual analog scale (VAS) measurement in centimeters (range: 0–10), (4) patient global assessment VAS measurement in centimeters (range: 0–10), and (5) serum acute-phase response, represented by CRP level in mg/dL (range: 0–10 mg/dL) [9]. DAPSA REM, REM+LDA, moderate disease activity (MoDA), and HDA were defined as disease activity states having a cut-off score of ≤ 4 , ≤ 14 , > 14 to ≤ 28 and > 28 , respectively (Supplementary Table S1).

MDA response was defined as achievement of at least five of the following seven criteria: TJC ≤ 1 (of 68), SJC ≤ 1 (of 66), psoriasis activity and severity index (PASI) ≤ 1 or PsO affecting $< 3\%$ body surface area (BSA), patient pain VAS ≤ 15 mm, patient global disease activity VAS ≤ 20 mm, Health Assessment Questionnaire-Disability Index (HAQ-DI) ≤ 0.5 , and tender enthesal points ≤ 1 . In addition, patients who met all seven MDA criteria were classified as achieving VLDA (Supplementary Table S1). Patients without a history of PsO at baseline were assigned a PASI score of 1 post-baseline. Patients with partial missing criteria not meeting five out of the seven MDA criteria were classified as MDA non-responders.

The proportion of patients achieving DAPSA-REM/REM+LDA and VLDA/MDA, along with individual core components of these states and responses were evaluated at Weeks 16, 24, 52, and 104 using observed data. Shift analysis in patients in each DAPSA state at Week 16 was evaluated for secukinumab 300 and 150 mg to assess

sustainability of status at Weeks 24, 52 and 104. In addition, PROs related to HRQoL, physical and social function, and work productivity were compared between patients in the DAPSA-REM+LDA versus DAPSA-MoDA+HDA states and MDA responders versus non-responders up to Week 104. PROs were also compared between ACR70 responders and non-responders.

Statistical analysis

All analyses were performed on observed data using the full analysis set (FAS) of patients in the FUTURE 2 trial. All statistical analyses were performed in SAS version 9.4 or higher (SAS Institute; Cary, NC; 2011). This post-hoc analysis was not powered to test any specific hypothesis.

The proportion of patients (with 95% confidence interval), in the secukinumab 300, 150 mg, or placebo group categorized as achieving DAPSA-REM, DAPSA-REM+LDA disease activity states, VLDA and MDA responses were assessed in the overall population up to Week 104. Remission was indicated by DAPSA-REM and VLDA, and low disease activity by DAPSA-REM+LDA and MDA.

The proportion of patients in each treatment group who met each individual core component and other variables of interest under each category of DAPSA-REM, VLDA, DAPSA-REM+LDA and MDA were computed up to Week 104 in order to assess residual disease activity in these respective states/responses. The variables that were dichotomized included: SJC66 ≤1, TJC68 ≤1, resolution of enthesitis sites (enthesitis site count = 0), resolution of dactylitic digits (dactylitis count = 0), patient pain VAS ≤15 mm (1–100 mm scale) [20], patient global assessment ≤10 mm (on a 1–100 mm scale), patient global assessment ≤20 mm (on a 1–100 mm scale), physician global assessment ≤10 mm (1–100 mm scale), PASI ≤1, and HAQ-DI ≤0.5, and CRP <0.5 mg/dL [24]. SJC66 ≤1, TJC68 ≤1, PASI ≤1, HAQ-DI ≤0.5 variables were core components of MDA whereas DAPSA is a continuous composite measure not including these cut-offs of individual components.

The PROs were assessed using the mixed model for repeated measures (MMRM) with data pooled across treatment arms. Change from baseline in each outcome (continuous PRO score) was modeled as a function of analysis visit, DAPSA disease state at the analysis visit, and randomization stratum (anti-TNF status, naïve or IR) as categorical variables and weight and baseline clinical characteristics as continuous variables with DAPSA disease state by analysis visit and baseline clinical characteristics and demographics by analysis visit as interaction terms. An unstructured covariance structure was used for MMRM analyses. Although data from all available scheduled analysis visits and from patients in all DAPSA disease states were used, least-square (LS) mean change from baseline and standard errors (SE) along with P-value were provided for DAPSA-REM+LDA versus -MoDA+HDA over Week 104. Only subjects with assessments at baseline and at the visits of interest were included. These MMRM analyses were repeated for MDA response (response versus no response) in place of DAPSA disease state.

Results

Patients

At baseline, demographic and core components related to DAPSA and MDA were balanced across secukinumab 300 and 150 mg, and placebo groups (Supplementary Table S2). The mean time since first diagnosis of PsA in the cohort was >6 years. Around two-thirds of patients were anti-TNF- naïve in all groups. The mean DAPSA score at baseline in the secukinumab 300 mg, 150 mg, and placebo groups was 42.0, 46.8, and 44.9, respectively.

The retention rate of patients in FUTURE 2 was high; of patients originally randomized, 86% in 300 mg arm and 76% in 150 mg arm completed 104 weeks of treatment and only 3 patients in 300 mg and 7 patients in 150 mg dropped out of the study due to lack of efficacy [23].

DAPSA states and MDA responses using as observed data

In the overall population, more patients treated with secukinumab 300 mg or 150 mg versus placebo could reach remission or low disease activity as early as Week 16 (DAPSA-REM: 14% and 10% vs 5%; VLDA: 8% and 6% vs 2%; DAPSA-REM+LDA: 42% and 44% vs 18%; MDA: 28% and 23% vs 10%, respectively). The proportion of patients achieving DAPSA-REM+LDA states and MDA response further increased until Week 104 with usually higher state/response rates observed with secukinumab 300 versus 150 mg group (Fig. 1). More patients could achieve DAPSA-REM or DAPSA-REM+LDA status than VLDA or MDA responses, respectively, at all the time points.

More patients in the anti-TNF-naïve than the -IR subgroup achieved DAPSA-REM+LDA ([anti-TNF-naïve]: 75% and 62%; [anti-TNF-IR]: 46% and 33% with secukinumab 300 and 150 mg respectively) and MDA responses ([anti-TNF-naïve]: 49% and 37%; anti-TNF-IR: 25% and 10%) over Week 104 (Fig. 2A-B). Similar to the overall population, more patients achieved DAPSA-REM status compared with VLDA response, and DAPSA-REM+LDA status compared with MDA response, over 104 weeks, irrespective of anti-TNF status and time since diagnosis (Fig. 2A-B and 3A-B).

Shift analysis of DAPSA state or MDA response from Week 16 to Weeks 24, 52 and 104

The MDA shift analysis showed that a high proportion of secukinumab-treated patients who were MDA responders at Week 16 maintained the response at Week 104 (85% and 62%, respectively, with secukinumab 300 mg and 150 mg) [20]. Similarly, a high proportion of secukinumab-treated patients with DAPSA-LDA state at Week 16 maintained their status or improved to -REM at Week 104 (80% with 300 mg and 69% with 150 mg) and a high proportion of secukinumab-treated patients with DAPSA REM state at Week 16

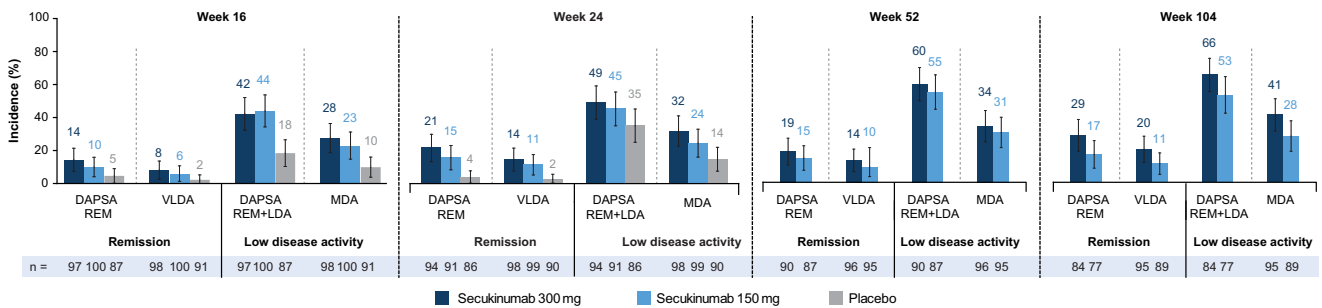


Fig. 1. Proportion of patients achieving DAPSA states and VLDA/MDA responses over Week 104 in the overall population. Data shown as observed in full analysis set, n is number of evaluable patients, N is total number of randomized patients in each treatment arm (secukinumab 300 mg [N = 100], secukinumab 150 mg [N = 100], placebo [N = 98]). DAPSA, disease activity index for psoriatic arthritis; LDA, low disease activity; MDA, minimal disease activity; REM, remission; VLDA, very low disease activity.

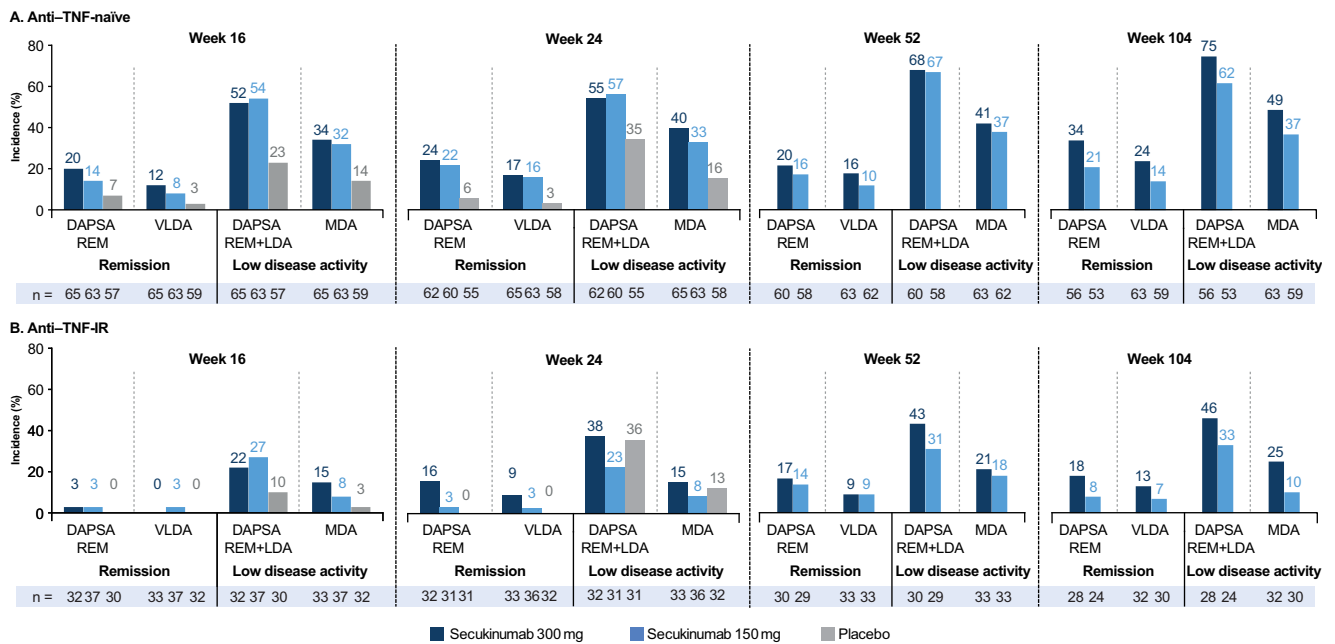


Fig. 2. Proportion of patients achieving DAPSA states and VLDA/MDA responses over Week 104 by anti-TNF status at baseline. Data shown as observed in full analysis set, n is number of evaluable patients, N is total number of randomized patients in each treatment arm (TNF-naïve: secukinumab 300 mg [N = 67], secukinumab 150 mg [N = 63], placebo [N = 63]; TNF-IR: secukinumab 300 mg [N = 33], secukinumab 150 mg [N = 37], placebo [N = 35]) DAPSA, disease activity index for psoriatic arthritis; LDA, low disease activity; MDA, minimal disease activity; REM, remission; VLDA, very low disease activity.

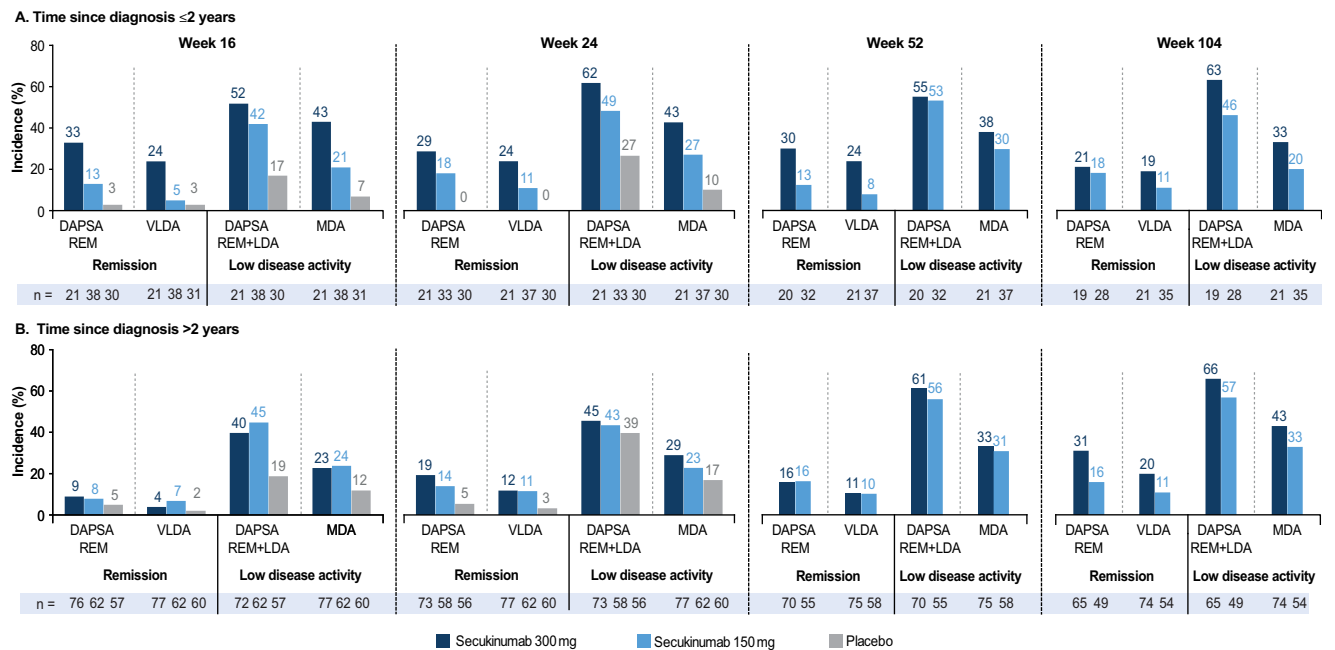


Fig. 3. Proportion of patients achieving DAPSA states and VLDA/MDA responses over Week 104 by time since diagnosis. Data shown as observed in full analysis set, n is number of evaluable patients, N is total number of randomized patients in each treatment arm (Time since diagnosis <= 2 years: secukinumab 300 mg [N = 22], secukinumab 150 mg [N = 38], placebo [N = 34]; Time since first PsA diagnosis > 2 years: secukinumab 300 mg [N = 78], secukinumab 150 mg [N = 62], placebo [N = 64]) DAPSA, disease activity index for psoriatic arthritis; LDA, low disease activity; MDA, minimal disease activity; REM, remission; VLDA, very low disease activity.

maintained this status at Week 104 with secukinumab 300 mg (71.4%) (Supplementary Figure S1).

DAPSA and MDA individual core components

Overall, a higher proportion of patients reaching DAPSA-REM or VLDA achieved more thresholds of core components than DAPSA-REM +LDA or MDA notably for joints (secukinumab 300/150 mg [SJC66<=1]:

DAPSA-REM 100%/100%, VLDA 100%/100%, DAPSA-REM+LDA 89%/85%, MDA 90%/92%; [TJC68<=1]: DAPSA-REM 100%/100%, VLDA 100%/100%, DAPSA-REM+LDA 73%/59%, MDA 87%/84%, Fig. 4A-D), pain, patient and physician global assessments (secukinumab 300/150 mg [Patient pain VAS<=15 mm]: DAPSA-REM 92%/100%, VLDA 100%/100%, DAPSA-REM +LDA 60%/51%, MDA 77%/80%; [Patient global assessment<=10 mm]: DAPSA-REM 63%/54%, VLDA 68%/50%, DAPSA-REM+LDA 36%/22%, MDA 49%/36%; [Patient global assessment<=20 mm]: DAPSA-REM 100%/92%,

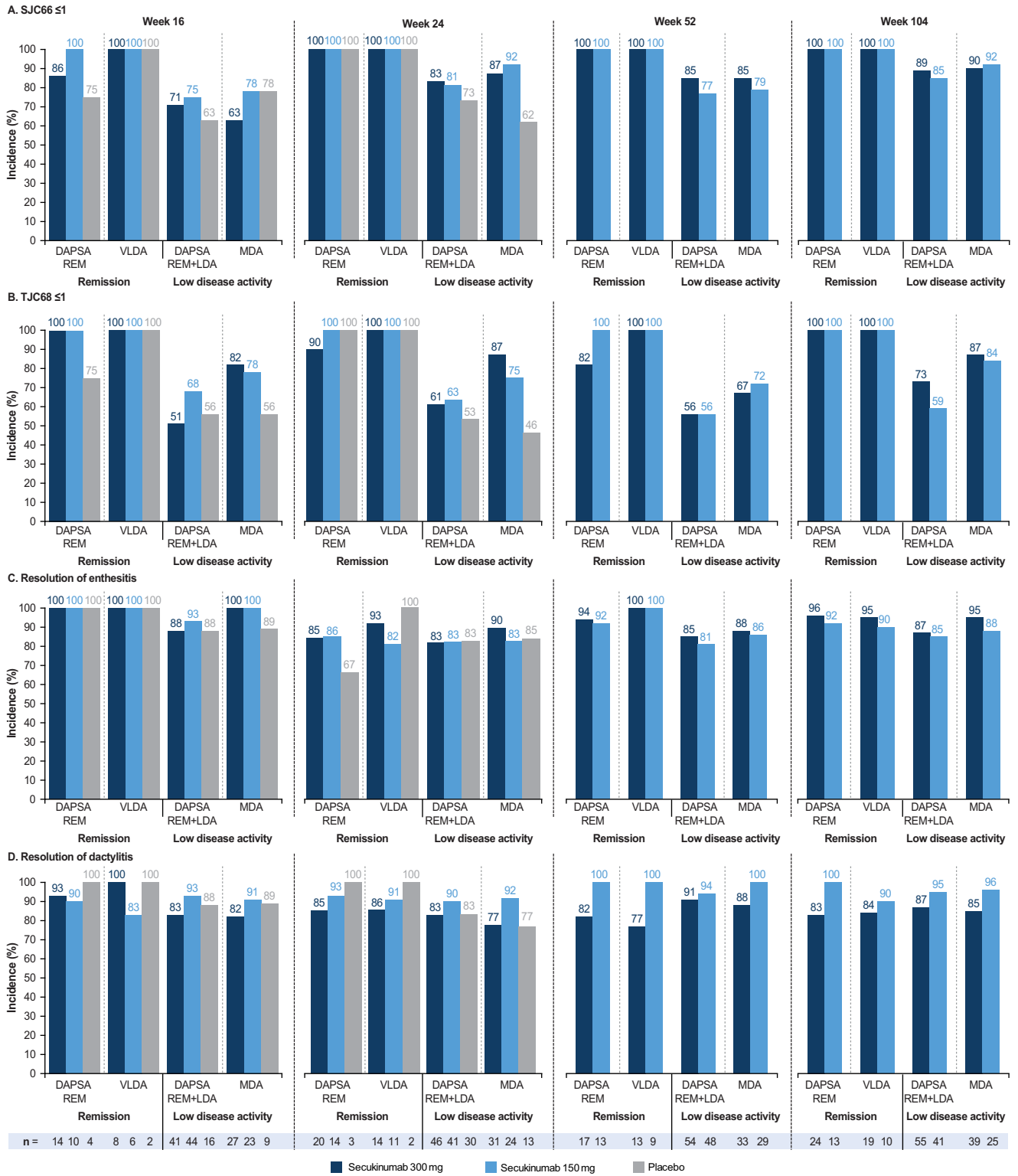


Fig. 4. Proportion of patients achieving absolute thresholds* of articular and non-articular musculoskeletal components in patients achieving remission or low disease activity over Week 104

Data shown as observed in full analysis set, n is number of evaluable patients. Residual disease activity of patients achieving remission/low disease activity with both DAPSA and MDA was assessed using these individual components. SJC66 ≤1 and TJC68 ≤1 were core components of MDA whereas DAPSA is a continuous composite measure not including these cut-offs of individual components.

*Data represent absolute thresholds and not thresholds by change from baseline

DAPSA, disease activity index for psoriatic arthritis; LDA, low disease activity; MDA, minimal disease activity; REM, remission; SJC, swollen joint count, TJC, tender joint count, VLDA, very low disease activity.

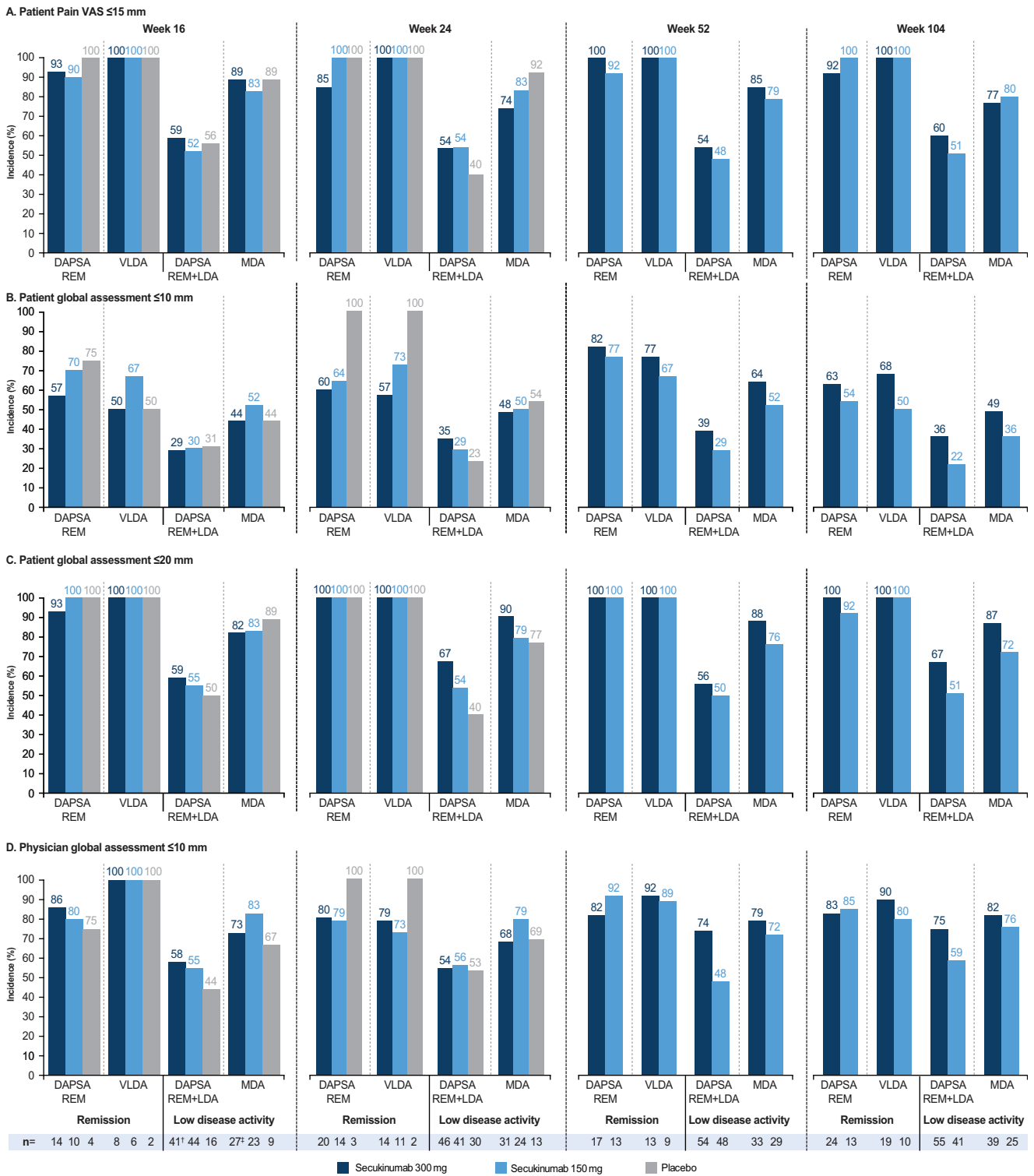


Fig. 5. Proportion of patients achieving absolute thresholds* of pain, patient and physician global assessment in patients reaching remission or low disease activity over Week 104. Data shown as observed in full analysis set, n is number of evaluable patients. Residual disease activity of patients achieving remission/low disease activity with both DAPSA and MDA was assessed using these individual components.

*Data shown represent absolute thresholds and not thresholds by change from baseline;

[†]n = 40 for physician global assessment ≤10 mm; [‡]n = 26 for physician global assessment ≤10 mm

The ranges for individual components were: patient pain VAS ≤15 mm (1–100 mm scale), patient global assessment ≤10/ 20 mm (1–100 mm scale), and physician global assessment ≤10 mm (1–100 mm scale)

DAPSA, disease activity index for psoriatic arthritis; LDA, low disease activity; MDA, minimal disease activity; REM, remission; VAS, visual analog scale, VLDA, very low disease activity.

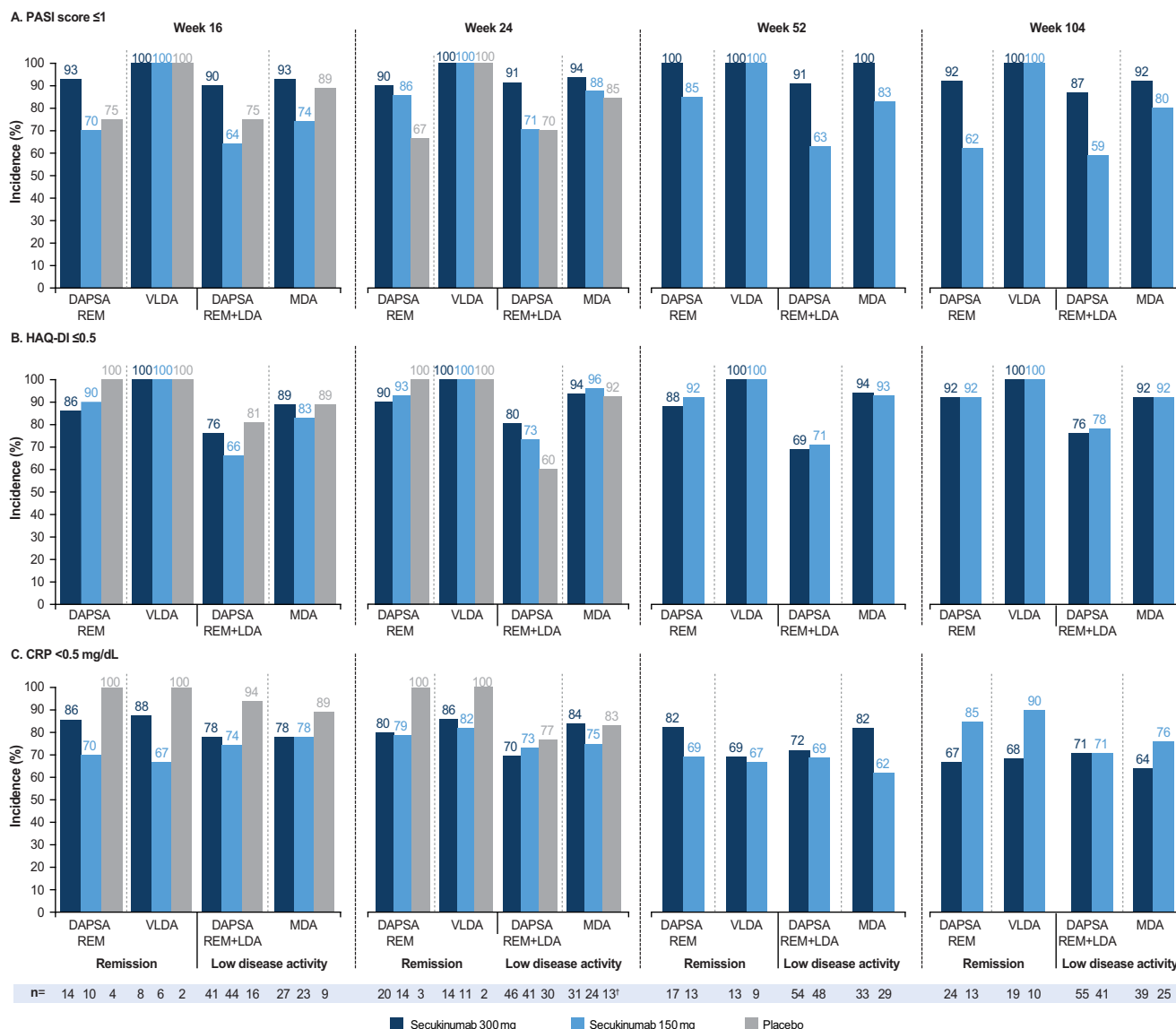


Fig. 6. Proportion of patients achieving absolute thresholds* of skin, physical function, and inflammatory components in patients reaching remission or low disease activity over Week 104

Data shown as observed in full analysis set, n is number of evaluable patients. Residual disease activity of patients achieving remission/low disease activity with both DAPSA and MDA was assessed using these individual components. PASI ≤1 and HAQ-DI ≤0.5 were core components of MDA whereas DAPSA is a continuous composite measure not including these cut-offs of individual components.

*Data shown represent absolute thresholds and not thresholds by change from baseline;

†n = 12 for CRP <0.5 mg/dL

CRP, C-reactive protein; DAPSA, disease activity index for psoriatic arthritis; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; MDA, minimal disease activity; PASI, Psoriasis Activity and Severity Index; REM, remission; VLDA, very low disease activity.

VLDA 100%/100%, DAPSA-REM+LDA 67%/51%, MDA 87%/72%; [Physician global assessment ≤10 mm]: DAPSA-REM 83%/85%, VLDA 90%/80%, DAPSA-REM+LDA 75%/59%, MDA 82%/76%; Fig. 5A-D), and function ([HAQ-DI ≤0.5]: DAPSA-REM 92%/92%, VLDA 100%/100%, DAPSA-REM+LDA 76%/78%, MDA 92%/92%; Fig. 6A-C) over Week 104. A high proportion of patients achieved SJC66 ≤1, resolution of enthesitis and dactylitis, CRP <0.5 mg/dL, with no differences between DAPSA-REM and VLDA and between DAPSA-REM+LDA and MDA through 104 weeks (Figs. 4 and 6). Nearly all secukinumab-treated patients achieved TJC68 ≤1 with both DAPSA-REM and VLDA, while the proportion was higher for MDA than DAPSA-REM+LDA through 104 weeks (Fig. 4). There were differences with numerically higher proportion of patients achieving patient global assessment ≤10 mm and ≤20 mm, and physician global assessment ≤10 mm with MDA than with DAPSA-REM+LDA, and patient pain VAS ≤15 mm, PASI ≤1, HAQ ≤0.5 with VLDA or

MDA than with DAPSA-REM or DAPSA-REM+LDA, respectively, through 104 weeks (Fig. 5 and 6).

PROs with DAPSA and MDA

At Week 16, LS mean change from baseline for PROs were higher among patients reaching DAPSA-REM+LDA versus DAPSA-MoDA+HDA and among patients with a MDA response versus those without MDA for SF-36 MCS, SF-36 PCS, FACIT Fatigue, PsA QoL, DLQI total score, and HAQ-DI (only for DAPSA), with improvements sustained over Week 104 (Supplementary Figure S2A-B). For WPAI-GH, the scores for impairment while working, overall work impairment, and activity impairment caused by health were improved in patients in the DAPSA-REM+LDA versus DAPSA-MoDA+HDA state and in MDA responders versus non-responders) over Week 104 (Supplementary

Figure S3A–B). All assessed PROs except three scores related to work impairment were improved in ACR70 responders versus non-responders at Weeks 16 and 104 (Supplementary Table S3).

Discussion

In this post-hoc analysis, we focused on a side-by-side comparison of DAPSA and MDA targets to assess their applicability and suitability as a REM/LDA composite index measure through 2 years of secukinumab treatment because these 2 instruments have been mentioned by EULAR, GRAPPA and T2T recommendations as appropriate composite measures to monitor treatment efficacy in patients with PsA [10,13].

In the past few years, different research groups have developed specific composite indices across multiple manifestations of PsA. The PsARC was historically the first instrument to be developed and validated for PsA including 4 items - patient and physician global assessment, TJC and SJC on 68 and 66 joints, respectively. Despite its sensitivity to change between active treatment and placebo in clinical trials, it did not perform as well compared to ACR response or EULAR criteria [12]. The PASDAS and the GRACE Index are specific PsA instruments developed for clinical trials by GRAPPA and OMERACT. PASDAS is a weighted composite score (range:0–10) of measures of patient and physician global assessment on 0 to 100 mm VAS, the physical component summary of the Study Short Form-36 (SF-36), SJC, TJC, Leeds Enthesitis Count, tender dactylitis count and CRP [12]. Secukinumab-treated patients has demonstrated higher rates of PASDAS remission/LDA at Week 16 versus placebo, with sustained states/responses over 2 years in FUTURE 2 study [25]. The GRACE Index measures 8 variables, including TJC, SJC, HAQ, patient VAS for global assessment, skin, and joints, PASI and Psoriatic Arthritis Quality of Life (PsAQoL). These variables are transformed and combined using the arithmetic mean and their complexity makes it more time consuming to calculate [12]. DAPSA and MDA are the two outcome measures that have been validated in several PsA studies, showing significantly lower SJC, TJC, PASI, dactylitis and enthesitis scores with better body function and activity scores [26–30]. DAPSA is a continuous composite score which can show change over time and focuses primarily on peripheral joints, while MDA is a categorical multifactorial measure of articular and extra-articular manifestations.

More patients achieved DAPSA-REM and DAPSA-REM+LDA status than VLDA or MDA responses, respectively, in the overall population and subpopulations over 104 weeks. The difference in design and components of the two measures presents some dichotomies that need to be considered in the interpretation of these results. DAPSA-REM looks at the total sum of 5 items, thus allowing one item to be higher as long as the sum is within the set margin. This occasionally allows higher residual disease activity for one of the components than would be possible in VLDA, as patients fail to achieve VLDA if they miss any one of the defined individual categorical cut points. In many of these circumstances, patients were in MDA but not VLDA if one or two cut points were not met.

The present analysis complement the results of the FUTURE 2 study reported earlier wherein secukinumab provided rapid and sustained improvements in signs and symptoms in patients with active PsA over 104 weeks, and PROs [23]. Secukinumab-treated patients who reached remission had better disease status as reflected by more frequent achievement of the threshold of components for joints, pain, patient and physician global assessments, and physical function than low disease activity state. Enthesitis and dactylitis were resolved in high proportion of patients at 104 weeks, irrespective of remission or low disease state. Indeed, one of the interesting findings of this study was that the majority of patients met all individual components with both DAPSA and MDA, though DAPSA does not include enthesitis, dactylitis or extra-articular variables, and MDA does not include laboratory measure of inflammation. TJC68 \leq 1, patient pain VAS \leq 15 mm, patient global assessment \leq 10 mm and \leq 20 mm, PASI \leq 1, and HAQ \leq 0.5,

were numerically slightly more frequently achieved by MDA than DAPSA, which is not surprising as MDA comprises these components (including skin and HAQ) in a categorical way. Most patients who achieved DAPSA cut-off points but not MDA/VLDA cut points still had low levels of residual disease but were numerically slightly less likely to achieve stringent cut points for individual variables including PASI, patient pain and global and physician global assessments. Thus, MDA and VLDA are harder to achieve than the DAPSA equivalents with secukinumab and other agents but may represent a somewhat lower disease activity state. Nevertheless, similar results regarding the various musculoskeletal components of PsA were seen with DAPSA-REM/LDA and MDA upon TNF-inhibition [31]. Further research comparing outcomes looking at patient opinion, physician opinion and long term impact such as quality of life, functional ability, progression of damage and disease impact are necessary to decide which is optimal. The only direct evidence to date for T2T in PsA is the tight control of inflammation in early psoriatic arthritis (TICOPA) trial which used MDA as the target and still saw an increase in drug-related adverse events, so the benefits and potential risks of adverse events will need careful consideration in the future [32].

These analysis of different remission and low disease activity targets in clinical trial setting are consistent with those recently reported in a real life clinical cohort showing that VLDA and MDA measures are more stringent than DAPSA-REM and DAPSA-REM+LDA, respectively, and highlight a slightly higher level of residual disease activity with DAPSA targets [29]. Linked to this, VLDA/MDA show higher specificity to identify the patient perspective of disease control, whilst DAPSA shows a high sensitivity to identify patient-perceived low disease activity [33].

In this study, both DAPSA-REM+LDA versus -MoDA+HDA state and MDA responders versus non-responders were associated with a significant improvement of highly relevant PROs, including HRQoL, physical and social function, fatigue, and work productivity over 104 weeks, enabling patients to regain an almost normal life.

Measuring the early treatment response for these targets can be predictive of the long-term outcomes and would help to guide better treatment decisions in line with T2T strategy in PsA patients [34]. Previously published shift analysis on MDA showed that a majority of MDA responders with secukinumab 300 mg at Week 16 sustained their MDA response over Week 104 [20]. Similarly, we found that patients treated with secukinumab 300 mg in DAPSA-REM and -REM+LDA at Week 16 mostly sustained the status over Week 104.

Data from the literature on the efficacy of other biologics to achieve DAPSA-REM/LDA targets or MDA response in PsA are very limited and mainly post hoc analysis, though few placebo-controlled, double-blind, randomized controlled trials have evaluated these targets in response to PsA therapy. The RAPID-PsA study in patients who had failed previous treatment with \geq 1 disease modifying anti-rheumatic drug (DMARD) and were treated with TNF inhibitor, certolizumab, also reported higher proportion of patients achieving DAPSA-REM/REM+LDA rates than VLDA/MDA [35]. In the ADalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), the patients with moderately to severely active PsA and a history of inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs), the MDA response rate was significantly higher with adalimumab versus placebo at Week 24 [36]. In the GO-REVEAL trial, a higher proportion of inadequate responder patients to DMARDs or NSAIDs, showed significantly higher MDA response rate or DAPSA-REM/REM+LDA states with golimumab versus placebo up to Week 52 [34, 37]. Another IL-17A inhibitor, ixekizumab, showed significantly higher MDA response compared with placebo when administered every four weeks (q4w) or every two weeks (q2w) at Week 24 (29% and 38% for q4w and q2w respectively vs 15% for placebo) with sustained response to Week 52 in biologic-naïve patients with PsA [38]. Both MDA (47.7% vs 35.3%) and DAPSA-REM rates (26.5% vs 18%) were

noted to be high in patients treated with ixekizumab versus adalimumab in biologic-naïve patients with PsA at Week 24 [39].

A potential limitation of the current analysis was that FUTURE 2 was not primarily designed to be a T2T study and the targets were analyzed retrospectively using *post-hoc* analysis. In addition, the analysis used as observed data and the small sample size of subgroups may limit the scope of interpretation of results and warrant future analysis. Another limitation is that correlation with structural damage was not possible in this study as structural outcomes were not assessed in FUTURE 2. We did not analyze data with or without concomitant DMARD treatment as no differential data were reported between both groups for ACR response in FUTURE 2 study [23]. The study population predominantly included patients with polyarticular arthritis and therefore additional studies in other subtypes of disease (e.g. oligoarthritis, patients with predominant enthesitis) are needed to judge the targets in these other subtypes. There is also the need for a research agenda to further assess the superiority of one composite index over the other in clinical trial and clinical practice, strengths or situations when one or other measure is preferred, and determine whether we continue to need both measures in clinical trials or move forward with a single recommended measure.

In conclusion, the results suggest that although VLDA and MDA are more stringent composite indices than DAPSA-REM and DAPSA-REM+LDA, respectively, with a slightly higher level of residual disease activity observed with DAPSA targets, they all improved health related quality of life, functional ability and work productivity in contrast with patients who did not achieve these targets. Additionally, almost twice as many patients achieved DAPSA-REM than VLDA and patients in DAPSA-REM had not only very good articular responses, but also extraarticular responses, such as enthesitis and dactylitis scores and skin improvement. Thus, the study also provides further evidence on the applicability of DAPSA and MDA measures for evaluation of disease activity in clinical trial setting. Further prospective T2T studies should be designed to confirm these findings.

Key messages

1. In this post-hoc analysis, we compared DAPSA and MDA targets to assess their applicability and suitability as a REM/LDA composite index measure through 2 years of secukinumab treatment.
2. The results suggest that VLDA and MDA are more stringent composite indices than DAPSA-REM and DAPSA-REM+LDA, respectively, with a slightly higher level of residual disease activity observed with DAPSA targets. The study also adds to the available evidence on the applicability of DAPSA and MDA measures for evaluation of disease activity and treatment response in clinical trial setting.
3. Improvements in PROs were significantly better for patients in DAPSA-REM/LDA versus DAPSA-MoDA/HDA status, and for MDA responders versus non-responders.

Role of the funding source

The study was sponsored by Novartis Pharma AG, Basel, Switzerland, and designed by the scientific steering committee and Novartis personnel. Novartis personnel collated and did the analysis of the data. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the analysis. Medical writing support was funded by Novartis.

Data sharing

The datasets generated and/or analyzed during the current study are not publicly available. Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting

clinical documents from eligible studies. These requests are reviewed and approved based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data may be requested from the corresponding author of the manuscript.

Declaration of Competing Interests

LCC: Consultant and honoraria: AbbVie, Amgen, Celgene, Galapagos, Lilly, Janssen, Pfizer, Novartis, and UCB **PN:** Research grants and honoraria: Novartis, AbbVie, Roche, Pfizer, BMS, Janssen, Sanofi, Janssen, UCB, Lilly, and Celgene **TKK:** Consultant: AbbVie, Biogen, Celltrion, Janssen, MSD, Novartis, Oktal, Hospira/Pfizer, Sandoz, Eli Lilly and UCB; Speakers bureau: Biogen, Celltrion, Oktal, Hospira/Pfizer, Sandoz, and Eli Lilly **LG:** Grant/research support: BMS, UCB, Eli Lilly and Pfizer; Consultant: AbbVie, BMS, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Roche and UCB **PJM:** Grant/research support, Consultant and Speakers bureau: AbbVie, Amgen, BMS, Celgene, Eli Lilly, Galapagos, Genentech, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, SUN Pharma, and UCB **LR:** Consultant for: Novartis through employment at RTI, Employee of: RTI Health Solutions **LP:** Shareholder and employee of Novartis **SJ:** Shareholder and employee of Novartis **KG:** Shareholder and employee of Novartis **CG:** Shareholder and employee of Novartis and Shareholder of BMS **JS:** Grant/research support: AbbVie, Janssen, Eli Lilly, MSD, Pfizer, Roche, Amgen, AstraZeneca, Astro, Celgene, Celltrion, Gilead, ILTOO, Novartis-Sandoz, Pfizer, Samsung, Sanofi, and UCB. Consultant: AbbVie, Janssen, Eli Lilly, MSD, Pfizer, Roche, Amgen, AstraZeneca, Astro, Celgene, Celltrion, Gilead, ILTOO, Novartis-Sandoz, Pfizer, Samsung, Sanofi, and UCB.

Acknowledgement

The authors thank the patients who participated in the study, the study investigators and John Gallagher, Novartis Pharmaceuticals UK Limited for valuable review. Medical writing and editorial support for this manuscript were provided by Sarabjeet Kaur and M K Vivek Sanker, Novartis Healthcare Private Limited, India, which was funded by Novartis Pharma in accordance with Good Publication Practice (GPP3) guidelines (<http://www.ismpp.org/gpp3>). The first draft of the manuscript was prepared by Sarabjeet Kaur with inputs from all authors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.semarthrit.2020.03.015>.

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