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CLINICAL SCIENCE

Effectiveness of IL-12/23 inhibition (ustekinumab) versus tumour necrosis factor inhibition in psoriatic arthritis: observational PsABio study results

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ABSTRACT

Objectives To evaluate 6-month effectiveness of ustekinumab versus tumour necrosis factor inhibitor (TNFi), analysing predictors of low disease activity (LDA)/remission.

Methods PsABio is a prospective, observational cohort study of patients with psoriatic arthritis (PsA) at 92 sites in eight European countries, who received first-line to third-line ustekinumab or a TNFi. Comparative achievement at 6 months of clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) LDA/remission, and minimal disease activity (MDA)/very LDA using propensity score (PS)-adjusted multivariate logistic regression was assessed.

Results In the final analysis set of 868 participants with 6-month follow-up data (ustekinumab, n=426; TNFi, n=442), with long-standing disease and a high mean cDAPSA score (31.0 vs 29.8, respectively), proportions of patients in ustekinumab/TNFi treatment groups achieving cDAPSA LDA at 6 months were 45.7%/50.7%. cDAPSA remission was achieved in 14.9%/19.2%, and MDA in 26.4%/30.8% of patients. PS-adjusted odds ratios (OR; 95% confidence interval (CI)) of reaching cDAPSA LDA and MDA were 0.73 (0.46 to 1.15) and 0.87 (0.61 to 1.25) with ustekinumab versus TNFi, indicating no significant difference. High baseline body mass index or high cDAPSA were associated with a lower chance (OR (95% CI)) of reaching cDAPSA LDA with TNFi (0.94 (0.89 to 0.99) and 0.64 (0.52 to 0.79), respectively). Predictive factors were similar to previously published evidence, with cDAPSA and 12-item Psoriatic Arthritis Impact of Disease scores and chronic widespread pain at baseline appearing as new risk factors for unfavourable outcome. Safety data were similar between groups.

Conclusion Treatment targets were reached similarly after 6 months of treatment with ustekinumab and TNFi.

Key messages

What is already known about this subject?

- ► Psoriatic arthritis (PsA) is a heterogeneous disease, and randomised controlled trials (RCTs) may not adequately represent patients receiving a biologic in clinical practice.
- ► Treatment decisions can be challenging in PsA because of the variety of available drugs, and although efficacy and safety have been demonstrated in RCTs, real-world data comparing biologics are limited.

What does this study add?

- ► The PsABio study provides real-world observational data on outcomes of patients starting treatment with either ustekinumab or tumour necrosis factor inhibitors.

How might this impact on clinical practice or future developments?

- ► The PsABio study provides comparative data to help inform treatment decisions in clinical practice.
- ► Information on previously known and potential new negative predictors of treatment response in patients with PsA may help inform patient prognosis.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated disease that affects approximately 20%–30% of patients with psoriasis.[1 2] PsA has a variable disease course, and may present with a combination of peripheral and axial disease signs, including arthritis, enthesitis, dactylitis and skin and nail manifestations. Current treatment options include non-steroidal anti-inflammatory drugs (NSAIDs); conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); targeted synthetic DMARDs (tsDMARDs) and biological DMARDS (bDMARDs).[3 4]

The interleukin (IL)-12 and IL-23/IL-17 axes are implicated as significant pathways in disease pathogenesis.[5–7] A number of bDMARDs directed against IL-12/IL-23, IL-17 or IL-23 are now available to treat PsA, alongside tumour necrosis factor inhibitors (TNFi).[8] The IL-12/23 axis can be inhibited with ustekinumab, a fully human immunoglobulin G1 monoclonal antibody that blocks the p40 subunit shared by these two cytokines.[5 9] Two phase 3, placebo-controlled trials—PSUMMIT 1[10] and PSUMMIT 2[11]—demonstrated ustekinumab efficacy on joints and skin, and safety in patients with PsA.

Treatment decisions are challenging in PsA, given the wide array of available drugs, and the scarcity

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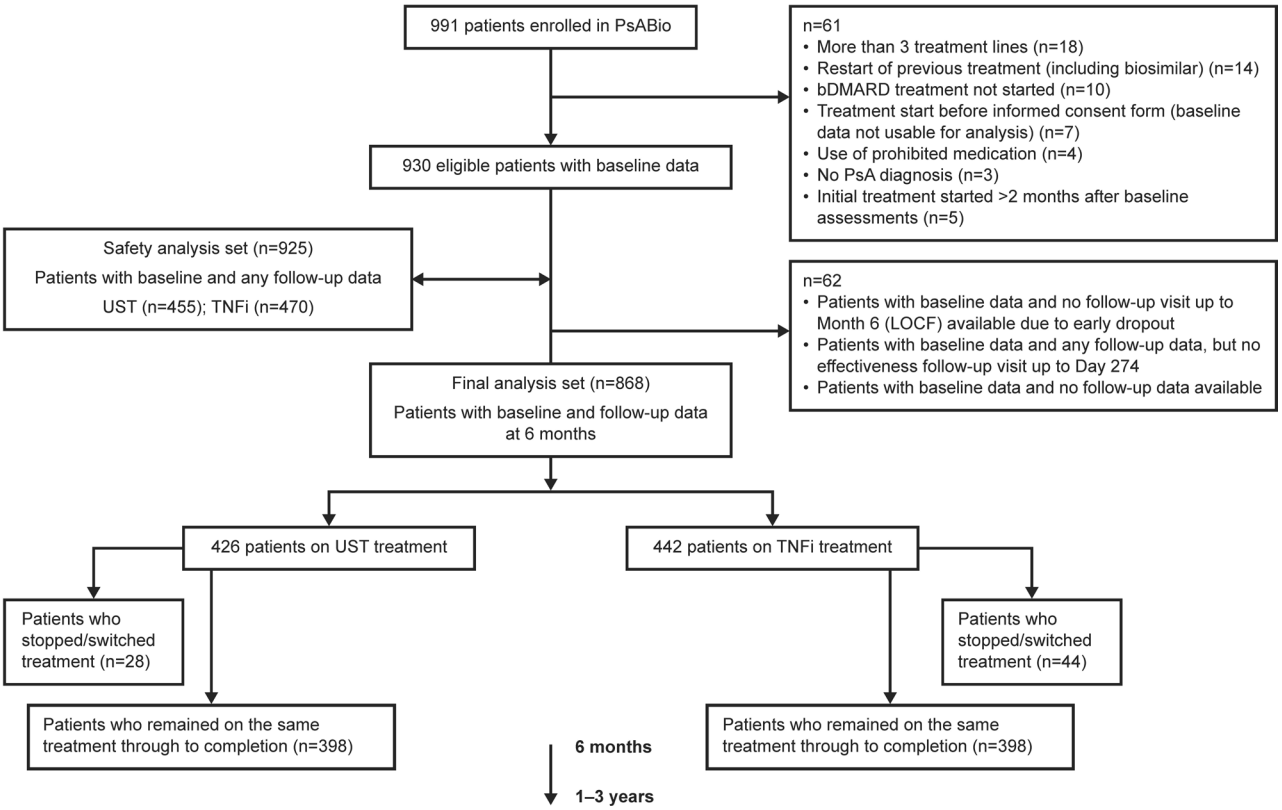

Figure 1 Patient population flow diagram. The FAS included patients who completed the 6-month initial treatment, as well as those who switched/stopped their original treatment during the 6-month follow-up period. Patients who switched/stopped their biological disease-modifying antirheumatic drug were imputed as non-responders. bDMARD, biological disease-modifying antirheumatic drug; FAS, final analysis set; LOCF, last observation carried forward; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

of head-to-head trials of biologics.[12–14] Although clinical trials provide important information on drug efficacy and safety, real-world patient populations may not fully represent those in clinical practice.[15] There are currently no published studies in PsA comparing ustekinumab and TNFi effectiveness in a large-cohort, real-world setting. Such data are important for making evidence-based treatment decisions in clinical practice.

The ultimate goal of PsA treatment is to achieve the lowest disease activity possible, defined by several composite measures, the most widely used being the clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) and minimal disease activity/very low disease activity (MDA/VLDA).[3 16–18] Here, we present the first real-world comparative 6-month effectiveness study for ustekinumab versus TNFi.

METHODS

Study design

PsABio (NCT02627768) is an international, prospective, observational, cohort study designed to evaluate the persistence, effectiveness and tolerability of ustekinumab versus TNFi as a first-line, second-line or third-line bDMARD in PsA. Each patient is followed biannually for up to 3 years, with a first analysis performed once all patients have reached the 6-month time point (figure 1). Outcomes are focused on achievement of cDAPSA low disease activity (LDA)/remission and MDA/VLDA and analysing predictors of reaching cDAPSA LDA or MDA.

Patients

Participants were enrolled between December 2015 and June 2018, at 92 sites in Belgium, France, Greece, Italy, the Netherlands, the Russian Federation, Spain and the UK, and treated according to standard clinical practice. The choice of bDMARD was made independently by each patient's rheumatologist; TNFi choice was at the investigator's discretion.

Adult patients with PsA, according to the ClASsification for Psoriatic ARthritis (CASPAR) criteria,[19] starting ustekinumab or any approved TNFi (including biosimilars; online supplemental table S1) as a first-line, second-line or third-line bDMARD therapy for PsA (online supplemental table S2), were included. All participants with baseline and effectiveness data, available between baseline and the 6-month (±3 months) follow-up (including patients who switched/stopped treatment due to adverse events (AEs), inefficacy or other reasons), were included in this analysis.

Patients were excluded if they were treated beyond third line, had received an investigational drug, vaccine or invasive medical device within 30 days before study start, or were currently enrolled in an interventional study.

Data were collected at baseline, then every 6 months with a window of ±3 months for flexibility with standard clinical practice. Data came from patients' medical records, including available patient-reported outcomes data, and were collected and entered into an electronic case report form, except for physician-reported and investigator-reported scales/assessments, which were recorded on paper forms. Patients who stopped/switched ustekinumab or TNFi were retained and followed up on their new treatment (another TNFi or bDMARD, or a csDMARD or tsDMARD, or no additional therapy). In total, 991 patients entered the study; 477 started ustekinumab, 501 started TNFi, 10 did not start either treatment, and three were not diagnosed

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with PsA. Another 48 patients were excluded from the analysis owing to protocol violations (figure 1).

Evaluations

Treatment effectiveness

The following data were recorded for both ustekinumab and TNFi to allow comparison of effectiveness at 6 months. PsABio focused on the composite disease activity measures cDAPSA LDA and remission,[17 20] and achievement of MDA and VLDA.[21] cDAPSA is based on the summation of four variables: tender joint count of 68 joints (TJC68), swollen joint count of 66 joints (SJC66), Patient Global Assessment (PtGA) visual analogue scale (VAS, in cm) and patient pain (PtP) VAS. cDAPSA LDA is defined as a score of ≤13, and cDAPSA remission as a score of ≤4.[17] The MDA/VLDA criteria assess seven domains (cut-offs): TJC68 (≤1); SJC66 (≤1); enthesitis (Leeds Enthesitis Index[22]; ≤1); skin involvement (Psoriasis Area and Severity Index [≤1] or psoriasis body surface area [BSA; ≤3%]); Health Assessment Questionnaire (HAQ) score (≤0.5); PtGA VAS (≤20, VAS in mm); and PtP VAS (≤15). If five of seven domain cut-offs are met, MDA has been achieved; VLDA if all seven are met.

Data were also collected for the following variables: Physician Global Assessment (PGA) VAS for disease activity; the presence of dactylitis; and psoriasis skin involvement (BSA according to four categories (clear/almost clear skin, <3% but not clear/almost clear skin, 3%–10% and >10%)).

Patient-reported outcomes and assessments

Aside from those needed for the MDA/VLDA and cDAPSA, additional patient-reported outcomes were collected (see online supplemental methods).

Safety

Safety data included collection of reported AEs and serious AEs from the first use of ustekinumab or a TNFi in the study.

Statistical analyses

Data validation, development of a detailed analysis plan and all statistical analyses were performed by or under the authority of the sponsor (Janssen Pharmaceutica NV, Beerse). In this analysis, the full analysis set (FAS) included patients who completed the 6-month initial treatment period, plus those who switched/stopped their original treatment during the 6-month follow-up. The safety set included all patients with baseline and any available follow-up data. Partially missing data were imputed where required for analysis. For validated scales, missing items were imputed according to recommendations of the scale developers. Percentages were calculated over non-missing data. In addition to observed case analysis, endpoint analysis used the last observation carried forward (LOCF). Actual values and changes from baseline were summarised, including the 95% CI, at each assessment time point and at LOCF.

As the analysis was exploratory, no predefined hypotheses were tested and no adjustment for multiplicity was applied. Hence, between-group differences and changes over time were described using the 95% confidence interval (CI) rather than by p values, as the latter provide no information about the variability of an estimated association.[23]

Comparative effectiveness and predictor analyses were performed to investigate LOCF month 6 outcomes between and within treatment cohorts. Comparative effectiveness was also described by bDMARD treatment line. Patients who switched/stopped their original treatment during the 6-month follow-up period were imputed as non-responders (binary endpoints), or no improvement from baseline (continuous endpoints). Patients with cDAPSA LDA included those in cDAPSA remission; patients in MDA included those in VLDA.

Comparative effectiveness between treatment cohorts included propensity score (PS) adjustment for imbalanced baseline covariates. For all potential confounders, the balance between the treatment cohorts and the prognostic effect on the outcome of interest were investigated. The PS was estimated using a logistic regression model, with treatment as the dependent variable and a set of potential confounders as independent variables. After optimisation to achieve a good balance of all confounders, the PS, stratified on the quintiles, was used to estimate the adjusted treatment effects for the selected outcomes. Weighting on the PS (inverse probability of treatment weighting) was used as a sensitivity analysis. Primarily based on clinical judgement and published evidence, the following potential baseline confounders were investigated: age, sex, country, smoking, number of comorbidities, BSA, PsA subtype according to Moll and Wright criteria,[24] disease duration, cDAPSA score, 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) score, presence of enthesitis or dactylitis, Fibromyalgia Rapid Screening Tool (FiRST) score, line of bDMARD treatment, csDMARD cotreatment and concomitant NSAID or oral corticosteroid use.

The predictor analyses investigated possible predictors for achieving cDAPSA, LDA and MDA outcomes. The effect of all variables was first investigated using univariate analysis. Variables with $p \leq 0.5$ were then included in multiple logistic regression analysis, using a forward selection method with the probability for variable entry set to $p=0.20$, including the examination of interaction terms. Six different models were generated: total group, and ustekinumab and TNFi cohorts, respectively, for cDAPSA LDA/remission and MDA/VLDA. The final multivariate model with odds ratios (ORs; 95% CI) is presented for factors with significant ($p<0.05$) effect on the respective outcome separately for the total, ustekinumab and TNFi cohorts.

In addition to the analysis on the FAS discussed in this paper, a completer analysis was performed, including only patients who stayed on ustekinumab or a TNFi for the entire 6-month follow-up period. The completer analysis, which arrived at similar results, is presented in online supplemental table S3.

RESULTS

Patient disposition

Of 991 enrolled participants, 930 were eligible and had baseline data (figure 1); 62 were not included in the FAS owing to unavailability of effectiveness data.

The FAS comprised 868 patients for whom both baseline and follow-up data to month 6 were available (426 ustekinumab, 442 TNFi), including 28 (6.6%) patients who switched/stopped ustekinumab and 44 (10.0%) who switched/stopped TNFi during the first 6-month period. The completer analysis set comprised 796 patients (online supplemental table S3). The safety analysis set comprised 455 patients in the ustekinumab group and 470 in the TNFi group (n=925 with follow-up data; figure 1).

Baseline demographics and clinical characteristics

At baseline, participants in the ustekinumab group were significantly older compared with the TNFi group (mean age, 51.2 vs 48.5 years, respectively; based on 95% CI), had significantly longer disease duration (mean, 7.5 vs 6.2 years) and more extensive use of third-line bDMARDs (20.4% vs 12.0%), but less frequent ongoing csDMARD exposure (39.2 vs 54.5%),

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Table 1 Demographics at baseline

	UST (n=426)	TNFi (n=442)
Age, years (95% CI)	51.2 (12.47) (**50.0 to 52.3**)	48.5 (12.59) (**47.3 to 49.7**)
Sex—male, n (%) (95% CI)	183 (43.0) (38.2 to 47.8)	202 (45.7) (41.0 to 50.5)
Disease duration since initial diagnosis, years (95% CI)	7.5 (8.1) (**6.8 to 8.3**)	6.2 (6.6) (**5.6 to 6.8**)
BMI, kg/m^2 (95% CI)	28.6 (6.3) (27.9 to 29.3)	27.7 (5.0) (27.2 to 28.3)
csDMARD exposure, n (%) (95% CI)		
Previous exposure	376 (88.3) (84.8 to 91.2)	411 (93.0) (84.8 to 91.2)
Ongoing exposure at baseline	167 (39.2) (**34.5 to 44.0**)	241 (54.5) (**49.8 to 59.2**)
Methotrexate exposure ongoing at baseline, n (%) (95% CI)	127 (29.8) (**25.5 to 34.4**)	187 (42.3) (**37.7 to 47.1**)
Other treatments exposure ongoing at baseline, n (%) (95% CI)		
NSAIDs	232 (54.5) (**49.6 to 59.3**)	307 (69.5) (**64.9 to 73.7**)
Glucocorticosteroids	138 (32.4) (28.0 to 37.1)	152 (34.4) (30.0 to 39.0)
Line of bDMARD treatment, n (%) (95% CI)		
First line	193 (45.3) (40.5 to 50.2)	241 (54.5) (49.8 to 59.2)
Second line*	146 (34.3) (29.8 to 39.0)	148 (33.5) (29.1 to 38.1)
Third line*	87 (20.4) (**16.7 to 24.6**)	53 (12.0) (**9.1 to 15.4**)
Cardiovascular/metabolic syndrome comorbidity, n (%) (95% CI)†	176 (41.3) (36.6 to 46.2)	157 (35.5) (31.1 to 40.2)

Data are mean (SD) (95% CI of the mean) unless otherwise stated; % is that of available data. Numbers in bold indicate where significant differences exist at baseline.
*bDMARDs received before UST/TNFi in this study are presented in online supplemental table S2.
†Cardiovascular/metabolic syndrome comorbidity was numerically more frequent in the UST group.
bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

concomitant methotrexate (29.8% vs 42.3%) and NSAIDs (54.5% vs 69.5%) (table 1). Severe skin involvement (BSA >10%, 26.7% vs 14.1%) and FiRST score ≥5 (indicating more chronic widespread pain: 39.3% vs 29.0%) were significantly more prevalent in the ustekinumab group (table 2). Cardiovascular/metabolic comorbidities (41.3% vs 35.5%) were also numerically more frequent in the ustekinumab group (table 1).

Components of cDAPSA and MDA at baseline and 6 months

Observed data at baseline and for changes at 6-month follow-up (including LOCF) for the components needed to assess cDAPSA and MDA are presented in table 3. No difference was shown between the ustekinumab and TNFi groups in improvements in SJCs and TJCs, HAQ-Disability Index scores, VAS assessments of global well-being (PtGA, and PGA) and change in BSA (demonstrated by overlapping 95% CI) (table 3).

Change from baseline in composite disease activity measures

At baseline, mean (95% CI) cDAPSA levels in the ustekinumab and TNFi groups were 31.0 (28.9 to 33.1) and 29.8 (27.9 to 31.7), respectively, indicating high disease activity in both treatment groups (table 2). The mean (95% CI) change in cDAPSA from baseline at 6 months was −13.7 (−15.5 to −11.8) and −14.5 (−16.2 to −13.0), respectively. The proportions of patients achieving cDAPSA LDA (including remission) were 177/360 (49.2%; 43.9 to 54.5) vs 200/370 (54.1%; 48.8 to 59.2), cDAPSA remission 63/360 (17.5%;

Table 2 PsA clinical characteristics at baseline

	UST (n=426)	TNFi (n=442)
Psoriasis BSA, n (%) (95% CI)		
Clear/almost clear skin	99 (28.8) (24.1 to 33.9)	123 (34.1) (29.2 to 39.2)
<3% but not clear/almost clear skin	33 (9.6) (6.7 to 13.2)	58 (16.1) (12.4 to 20.3)
3%–10%	120 (34.9) (29.9 to 40.2)	129 (35.7) (30.8 to 40.9)
>10%	92 (26.7) (**22.1 to 31.8**)	51 (14.1) (**10.7 to 18.2**)
PsA characteristics, n (%) (95% CI)		
Axial involvement—pure or combined with peripheral	147 (35.4) (30.8 to 40.2)	161 (37.2) (32.6 to 41.9)
Oligoarticular	93 (22.4) (18.5 to 26.7)	125 (28.9) (24.6 to 33.4)
Polyarticular	277 (66.7) (62.0 to 71.3)	280 (64.7) (60.0 to 69.2)
Swollen joint count—66 joints (95% CI)	6.0 (8.1) (5.2 to 6.8)	5.8 (7.4) (5.1 to 6.5)
Tender joint count—68 joints (95% CI)	12.5 (12.5) (11.2 to 13.7)	11.3 (10.8) (10.3 to 12.4)
cDAPSA (95% CI)	31.0 (20.3) (28.9 to 33.1)	29.8 (18.6) (27.9 to 31.7)
Enthesitis at baseline, n (%) (95% CI)	199 (48.9) (43.9 to 53.9)	218 (51.9) (47.0 to 56.8)
Dactylitis at baseline, n (%) (95% CI)	80 (18.8) (15.2 to 22.9)	92 (20.8) (17.1 to 24.9)
Total PsAID-12 score (95% CI)	5.7 (2.2) (5.5 to 5.9)	5.5 (2.1) (5.3 to 5.7)
FiRST score ≥5, n (%) (95% CI)	160 (39.3) (**34.5 to 44.2**)	121 (29.0) (**24.7 to 33.6**)
ACPA positive, n (%) (95% CI)	3.0 (3.2) (0.7 to 9.1)	4.0 (2.9) (0.8 to 7.2)
RF positive, n (%) (95% CI)	3.0 (2.1) (0.4 to 5.9)	11 (5.8) (2.9 to 10.1)
CRP, mg/dL	1.3 (3.0) (1.0 to 1.7)	1.6 (2.9) (1.2 to 1.9)

Data are mean (SD) (95% CI of the mean) unless otherwise stated; % is that of available data. Numbers in bold indicate where significant differences exist at baseline.
ACPA, anti-citrullinated protein antibody; BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; CRP, C-reactive protein; FiRST, Fibromyalgia Rapid Screening Tool; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease questionnaire; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

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Table 3 Change in PSA outcome variables needed for assessing cDAPSA and MDA

Variable	UST Baseline	TNFi Baseline	UST Change at 6 months	TNFi Change at 6 months
cDAPSA	31.0 (28.9 to 33.1)	29.8 (27.9 to 31.7)	−13.7 (−15.5 to −11.8)	−14.6 (−16.2 to −13.0)
Tender joint count—68 joints	12.5 (11.2 to 13.7)	11.3 (10.3 to 12.4)	−5.3 (−6.4 to −4.2)	−5.7 (−6.6 to −4.8)
Swollen joint count—66 joints	6.0 (5.2 to 6.8)	5.8 (5.1 to 6.5)	−3.7 (−4.4 to −3.0)	−3.7 (−4.4 to −3.1)
HAQ-DI assessment	1.1 (1.1 to 1.2)	1.2 (1.1 to 1.2)	−0.25 (−0.3 to −0.2)	−0.34 (−0.4 to −0.3)
Physician Global Assessment of Disease—VAS, mm	53.5 (51.6 to 55.3)	54.7 (52.7 to 56.6)	−23.3 (−25.7 to −20.8)	−24.9 (−27.3 to −22.6)
Patient Global Assessment of Disease— VAS, mm	61.1 (58.8 to 63.5)	61.1 (58.7 to 63.4)	−20.7 (−23.5 to −18.0)	−25.2 (−28.2 to −22.3)
Patient assessment of pain—VAS*, mm	60.6 (58.1 to 63.0)	61.2 (58.9 to 63.5)	−19.1 (−21.9 to −16.2)	−24.4 (−27.2 to −21.6)
Total enthesitis score (LEI)	2.6 (2.4 to 2.8)	2.6 (2.4 to 2.8)	−1.4 (−1.6 to −1.2)	−1.5 (−1.7 to −1.2)
Psoriasis BSA distribution, n (%) (95% CI)				
Clear/almost clear skin	99 (28.8) (24.1 to 33.9)	123 (34.1) (29.2 to 39.2)	312 (59.1) (54.8 to 63.3)	335 (63.6) (59.3 to 67.7)
<3% but not clear/almost clear	33 (9.6) (6.7 to 13.2)	58 (16.1) (12.4 to 20.3)	70 (13.3) (10.5 to 16.5)	85 (16.1) (13.1 to 19.6)
3%–10%	120 (34.9) (29.9 to 40.2)	129 (35.7) (30.8 to 40.9)	133 (25.2) (21.5 to 29.1)	93 (17.6) (14.5 to 21.2)
>10%	92 (26.7) (22.1 to 31.8)	51 (14.1) (10.7 to 18.2)	13 (2.5) (1.3 to 4.2)	14 (2.7) (1.5 to 4.4)
Psoriasis BSA improvement† from baseline, n (%)	–	–	184 (53.5) (48.1 to 58.9)	166 (46.0) (40.8 to 51.3)

Data are observed mean (95% CI) at month 6 (last observation carried forward), unless otherwise indicated.
*There was a significantly higher percentage of UST patients with chronic widespread pain (FiRST score).
†Improvement: at least one category.
BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire Disability Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VAS, visual analogue scale.

13.7 to 21.8) vs 81/370 (21.9%; 17.8 to 26.5), MDA 104/385 (27.0%; 22.6 to 31.7) vs 120/376 (31.9%; 27.2 to 36.9), and VLDA 34/410 (8.3%; 5.8 to 11.4) vs 38/395 (9.6%; 6.9 to 13.0) at 6 months in the ustekinumab and TNFi groups, respectively (figure 2A). The PS-adjusted ORs of ustekinumab versus TNFi for achieving cDAPSA LDA/remission, MDA or VLDA indicated similar effectiveness (figure 2B). The outcomes observed in the FAS and completer sets were similar to those observed in the main analysis (online supplemental table S4). Composite disease activity measures by treatment line are shown in figure 3.

Predicting a state of cDAPSA LDA or MDA

Baseline variables and treatment group (ustekinumab or TNFi) were investigated as predictors of response, defined as reaching cDAPSA LDA or MDA by month 6 of follow-up. Treatment with either therapy (mode of action) was not associated with any of the model outcomes. Table 4 presents results from the final model, illustrating that previously described negative predictors of good treatment response are confirmed in the total PsABio cohort (eg, line of treatment, female sex, comorbidities),[25–28] but also new potential negative predictors are identified, such as high baseline impact of disease activity (PsAID-12) or high baseline cDAPSA or FiRST score.[29 30] Exposure to oral glucocorticosteroids also decreased the odds.

Higher body mass index (BMI) and higher cDAPSA at baseline did not significantly affect these treatment outcomes in the ustekinumab cohort in contrast to the TNFi cohort, where higher BMI acted as a negative predictor. Enthesitis appeared as a negative factor in the ustekinumab cohort only, dactylitis as a positive predictor for MDA in the TNFi cohort. Female sex did not significantly impair the response to TNFi, as it did in the ustekinumab cohort. Generally, the differences between the cohorts were small, and differences compared with the total cohort were mainly due to lower statistical power (table 4).

Concomitant treatment with csDMARDs/methotrexate was not associated with higher likelihood of cDAPSA LDA or MDA in either cohort.

Changes from baseline in health-related quality of life

Figure 4A shows the changes from baseline to month 6 in health state from EuroQoL 5-dimension 3-level questionnaire (EQ5D-3L) score (ustekinumab: +8.6 (95% CI 5.9 to 11.2), TNFi: +11.8 (95% CI 9.0 to 14.6)) and PsAID-12 score (ustekinumab: −1.8 (95% CI −2.04 to −1.59), TNFi: −1.9 (95% CI −2.13 to −1.69)). For both the ustekinumab and TNFi groups, achievement of cDAPSA remission/LDA or MDA at 6 months was associated with significant and clinically relevant improvement in EQ5D-3L, VAS and PsAID-12 scores, and thus impact of the disease on patients' lives (figure 4B).

Adverse events

Safety data were similar between the ustekinumab and TNFi groups; 17.9% of patients in the ustekinumab and 20.9% in the TNFi group experienced at least one AE, and 3.5% and 1.6%, respectively, experienced at least one serious AE (online supplemental table S5).

DISCUSSION

The observational PsABio study provides important information on the efficacy of ustekinumab and TNFi in a real-world cohort of patients with PsA; study data indicated similar effectiveness for ustekinumab and TNFi. PsABio demonstrated that approximately half of all patients but also half of those patients in whom previous therapies had an insufficient response and who received UST or TNFi as second- or third-line treatments, can achieve cDAPSA LDA, with many also reaching MDA or remission.

The question of how biologics other than TNFi perform in routine care remains unanswered, and the PsABio study aims to address this. In the current analysis, we have shown that overall and unadjusted, 28% of patients on ustekinumab achieved the goal of MDA at 6 months compared with 32% of patients receiving a TNFi. This compares with 30%–71% of patients in previous smaller real-world studies of ustekinumab,[31–35] 50%–60% of TNFi-treated patients,[5] and 11%–34% of patients with PsA in placebo-controlled Phase 3 studies of biological therapies.[14 36–39] After PS adjustment for imbalances in potential baseline confounders, both TNFi and ustekinumab had

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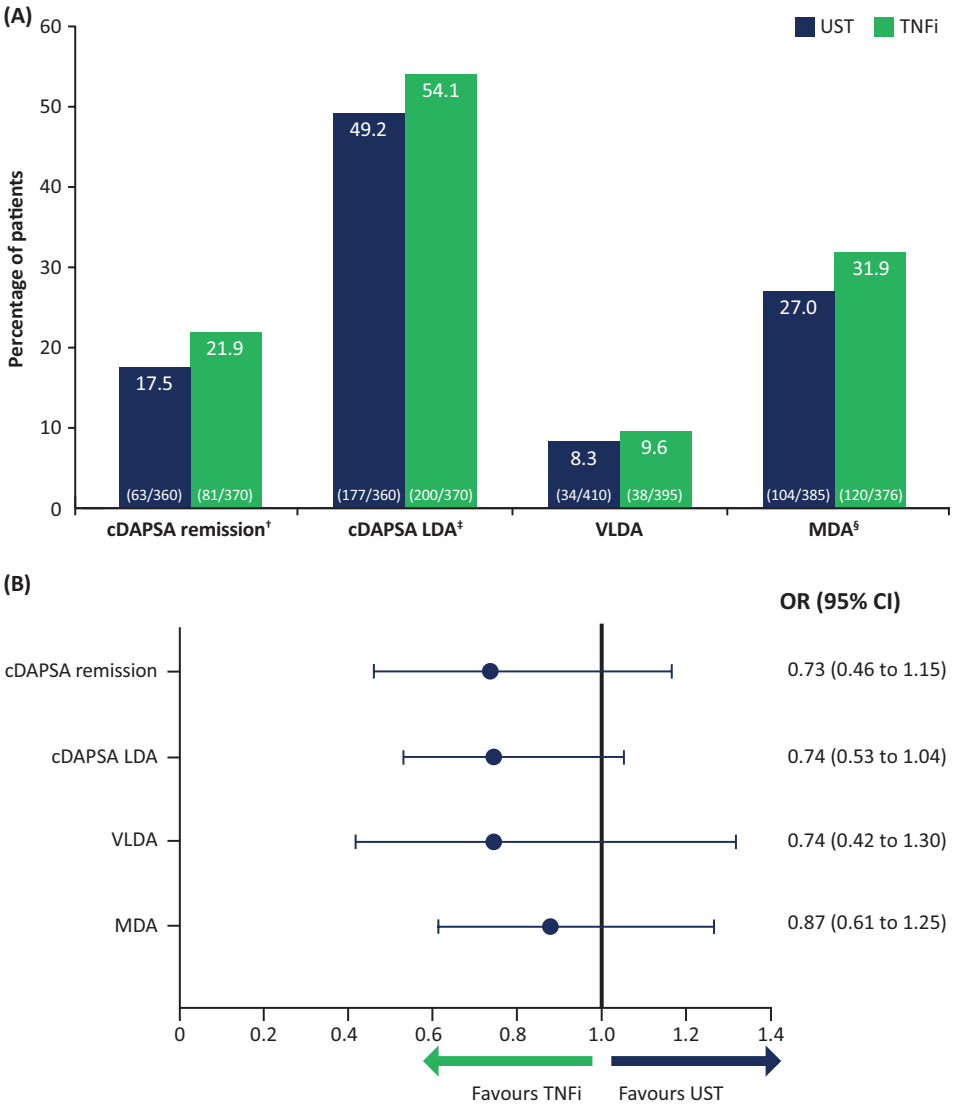

Figure 2 Disease outcomes at month 6 (A) observed percentages*; (B) PS-adjusted ORs (95% CI) of ustekinumab versus TNFi outcomes. *Observed percentages including non-responder imputation of patients who stopped or switched initial treatment. †cDAPSA remission ≤4. ‡Including remission; cDAPSA ≤13. §Including VLDA. cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PS, propensity score; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

a comparable effect on disease activity measures, including achievement of MDA, cDAPSA-LDA and change in cDAPSA.[40] In PsABio, participants in the ustekinumab group were more often receiving it as third-line biologic, and were older than the TNFi group, with longer disease duration. Additionally, a higher proportion of patients had more severe skin involvement, comorbidities or chronic widespread pain. Based on these baseline characteristics, the ustekinumab group could be regarded as more refractory to treatment than the TNFi comparison group which reduces the likelihood of a good response; prespecified PS adjustment for the baseline differences was performed for a fair statistical comparison between groups.

While the predictors of treatment success in our study generally agree with previous publications for TNFi (eg, line of treatment, female sex, comorbidities),[25–28] we highlight some new and modifiable negative predictors, such as high disease impact (PsAID-12) and high clinical disease activity as well as signs of chronic, widespread pain. These results reflect the complex and multifactorial influences on the outcomes with treatment. Effective early intervention may avoid the evolution of patients' disease towards these unfavourable states. Generally, ustekinumab and TNFi effectiveness are predicted by similar factors with some exceptions, such as higher BMI, higher cDAPSA and chronic widespread pain, negatively influencing mainly TNFi but not ustekinumab, while TNFi did not seem to be impacted by female sex, cardiovascular comorbidities or enthesitis, in contrast to ustekinumab.

Previous studies reported that 30%–60% of patients treated with biological therapy achieved a state of remission/LDA or MDA.[29 30 32] Moreover, there is evidence that earlier-stage treatment for PsA can result in more patients achieving remission.[41] Approximately half of patients in PsABio achieved LDA, with associated improvement in quality of life and disease impact.

The present analysis has several strengths and limitations. Here, 6-month data are presented; additional publications at later follow-up will provide further information on longer-term effectiveness, persistence and safety. A recent paper pointed towards high rates of persistence, LDA and remission in PsA patients on TNFi after 1 and 12 years of follow-up. Our long-term data will complement these results.[42] A strength of PsABio is that it consists

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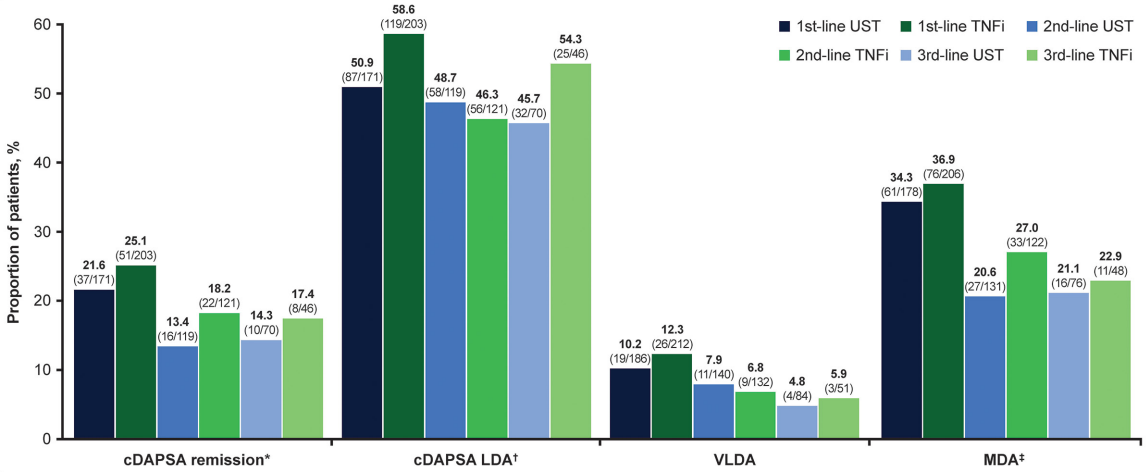

Figure 3 Disease outcomes at month 6 (observed percentages). Observed percentages (intention-to-treat analysis set) including non-responder imputation. *cDAPSA remission ≤4. †Including remission; cDAPSA ≤13. ‡Including VLDA. cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PS, propensity score; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

of a large, prospectively followed population with PsA receiving bDMARDs with two different modes of action. The real-world nature of PsABio also has the advantage of providing data from a less tightly selected patient population than randomised controlled trials.[15] However, as PsABio is non-randomised, the treatment groups need to be balanced using PS adjustment, owing to documented confounding data or bias by the rheumatologists' selection strategies. A potential limitation of this is that PS matching may not succeed in fully adjusting for unknown or unmeasured differences in baseline characteristics.[43]

An inherent problem in the present study is confounding by indication, occurring when the indication to prescribe a particular treatment is based on the severity of the illness or associated disease characteristics including multimorbidity.[44] Baseline findings of later biologic use, more severe skin involvement and more chronic widespread pain (FiRST score ≥5) in

Table 4 Factors associated with reaching the treatment targets of MDA and cDAPSA LDA, in the total PsABio cohort and in the ustekinumab cohort and TNFi cohort

	Total cohort		Ustekinumab cohort		TNFi cohort	
Test variable (baseline state)	MDA	cDAPSA LDA	MDA	cDAPSA LDA	MDA	cDAPSA LDA
No of patients, n*	621	614	315	306	306	308
Coefficient of determination, R^2	0.32	0.32	0.36	0.36	0.35	0.35
Line of bDMARD: first-line versus second-/third-line	1.69 (1.13 to 2.53)	1.23 (0.84 to 1.78)	1.83 (1.02 to 3.29)	0.87 (0.50 to 1.50)	1.78 (0.99 to 3.22)	1.78 (1.02 to 3.09)
Sex: female versus male	0.50 (0.33 to 0.75)	0.60 (0.41 to 0.88)	0.34 (0.19 to 0.63)	0.40 (0.22 to 0.70)	0.58 (0.31 to 1.06)	0.80 (0.45 to 1.41)
CV comorbidity/metabolic syndrome: present versus not present	0.49 (0.32 to 0.76)	0.63 (0.42 to 0.93)	0.44 (0.23 to 0.83)	0.47 (0.26 to 0.84)	0.54 (0.30 to 1.00)	0.80 (0.46 to 1.41)
Body mass index: per 1 kg/m^2	0.97 (0.94 to 1.01)	0.97 (0.93 to 0.99)	0.97 (0.91 to 1.03)	0.99 (0.94 to 1.04)	0.98 (0.93 to 1.04)	0.94 (0.89 to 0.99)
cDAPSA: per 10 score unit higher	0.75 (0.64 to 0.88)	0.75 (0.66 to 0.85)	0.89 (0.73 to 1.08)	0.86 (0.72 to 1.02)	0.58 (0.44 to 0.76)	0.64 (0.52 to 0.79)
PsAID-12 score: per one score unit higher	0.86 (0.77 to 0.97)	0.87 (0.79 to 0.97)	0.84 (0.71 to 0.99)	0.82 (0.69 to 0.96)	0.88 (0.74 to 1.03)	0.92 (0.79 to 1.07)
Enthesitis: present at baseline versus not present	0.60 (0.40 to 0.92)	0.57 (0.38 to 0.84)	0.32 (0.17 to 0.62)	0.43 (0.24 to 0.78)	1.23 (0.66 to 2.27)	0.83 (0.47 to 1.49)
Dactylitis: present at baseline versus not present	1.05 (0.64 to 1.74)	1.16 (0.72 to 1.86)	0.56 (0.25 to 1.23)	0.64 (0.31 to 1.32)	2.15 (1.04 to 4.45)	2.01 (0.99 to 4.04)
Psoriasis body surface area						
<3% vs 3%–10%	0.89 (0.57 to 1.41)	1.66 (1.08 to 2.56)	1.17 (0.59 to 2.33)	2.08 (1.09 to 3.97)	0.61 (0.32 to 1.16)	1.33 (0.71 to 2.47)
<3% vs >10%	0.70 (0.40 to 1.24)	1.49 (0.88 to 2.52)	1.26 (0.57 to 2.78)	2.32 (1.11 to 4.84)	0.33 (0.13 to 0.86)	0.95 (0.42 to 2.17)
NSAID treatment: yes versus no	0.65 (0.42 to 1.01)	0.73 (0.49 to 1.09)	0.84 (0.40 to 1.74)	0.77 (0.41 to 1.45)	0.61 (0.34 to 1.12)	0.64 (0.37 to 1.11)
Use of oral corticosteroids: yes versus no	0.50 (0.27 to 0.92)	0.47 (0.27 to 0.80)	0.51 (0.21 to 1.25)	0.40 (0.16 to 0.86)	0.45 (0.19 to 1.08)	0.49 (0.23 to 1.03)
FiRST score: per unit increase	0.88 (0.78 to 0.98)	0.85 (0.77 to 0.95)	0.85 (0.72 to 1.00)	0.86 (0.74 to 1.00)	0.88 (0.74 to 1.05)	0.82 (0.70 to 0.96)

Data are OR (95% CI) unless otherwise stated.
*The n for the cohorts indicate the number of patients included in the respective model. Numbers are lower than total UST or TNFi patient cohorts due to missing variable data, such as missing patient-reported outcomes and skin assessments in some patients.
bDMARD, biological disease-modifying antirheumatic drug; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; CV, cardiovascular; FiRST, Fibromyalgia Rapid Screening Tool; LDA, low disease activity; MDA, minimal disease activity; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease questionnaire; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

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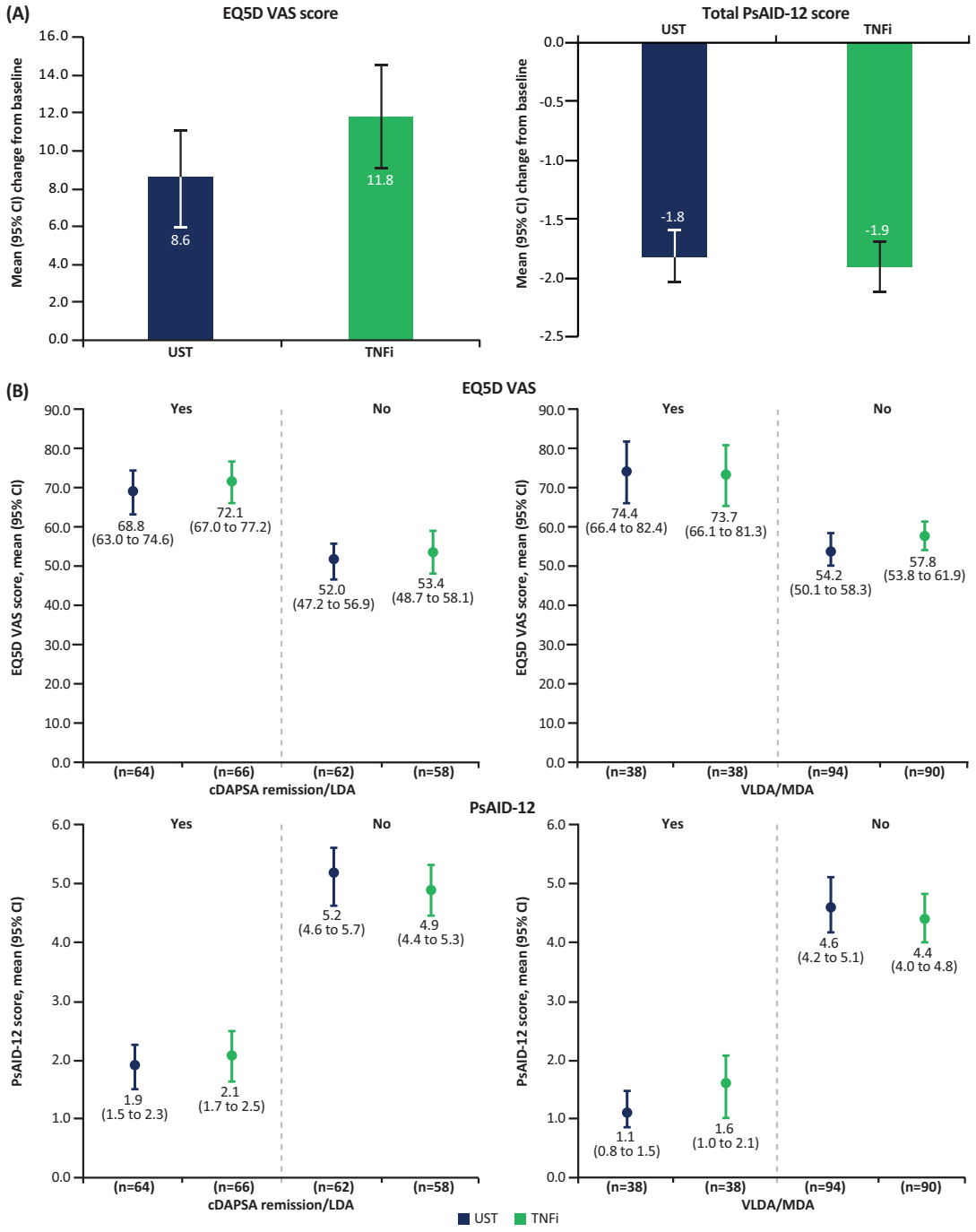

Figure 4 Efficacy of ustekinumab and TNFi on HR-QoL and disease impact to month 6 (A) mean (95% CI) change from baseline (B) by achievement of cDAPSA remission/LDA or VLDA/MDA*. *Yes/no represents achievement of cDAPSA remission/LDA and VLDA/MDA at 6 months. For PsAID-12, lower scores represent lower impact of psoriatic arthritis, with a minimal important difference for the PsAID-12 of −3.0 points.[46] cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; EQ5D, EuroQol 5-Dimension Questionnaire; HR-QoL, health-related quality of life; LDA, low disease activity; MDA, minimal disease activity; PsAID-12, 12-Item Psoriatic Arthritis Impact of Disease Questionnaire; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VAS, visual analogue scale; VLDA, very low disease activity.

ustekinumab-treated patients compared with TNFi, raises the possibility of confounding by indication. Moreover, TNFi drugs were grouped, whereas there may be differences in efficacy between different class members, although to our knowledge this has not been definitively demonstrated.[45] The use of etanercept in 32% of our patients could still pose questions relating to effectiveness on skin outcomes. However, this represents clinical practice and among others, the Murray *et al* study demonstrates no difference in effectiveness or persistence in PsA for etanercept vs adalimumab.[42] Other biologic modes of action, such as IL-17 inhibitors, were not available when PsABio was planned, and were not included. However, two trials comparing IL-17 inhibitors with a TNF blocker have since been published; these failed to show superiority of IL-17 blockade over TNF inhibition (or vice versa) regarding American College of Rheumatology criteria response rates, further substantiating the current study.[13 14] Thus, data from PsABio provide new insights regarding important open research questions on patients with PsA selected for biologic

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treatment in routine care. No similar large-scale, real-world data comparing different biologics exist.

In conclusion, after 6 months of treatment in a routine care setting, ustekinumab and TNFi, when used as a first-line, second-line or third-line bDMARD, demonstrated a significant DAPSA score improvement from baseline, with similar achievement of MDA, cDAPSA-LDA or cDAPSA remission in patients with PsA. This translated into a considerable enhancement of health-related quality of life, and a major reduction of disease impact on daily functioning, independently of ustekinumab or TNFi use. Both baseline high disease activity and severe impact of the disease were modifiable negative predictive factors which might support early effective intervention in patients with PsA. Publication of later follow-up data will further evaluate a longer-term comparison of ustekinumab with TNFi.

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