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**Persistence and effectiveness of the IL-12/23 pathway inhibitor ustekinumab or tumour necrosis factor inhibitor treatment in patients with psoriatic arthritis: 1-year results from the real-world PsABio study**

Laure Gossec<sup>1,2</sup> [ORCID ID: 0000-0002-4528-310X], Stefan Siebert<sup>3</sup> [ORCID ID: 0000-0002-1802-7311], Paul Bergmans<sup>4</sup>, Kurt de Vlam<sup>5</sup> [ORCID ID: 0000-0003-3848-5122], Elisa Gremese<sup>6</sup>, Beatriz Joven-Ibáñez<sup>7</sup>, Tatiana V Korotaeva<sup>8</sup> [ORCID ID: 0000-0003-0579-1131], Frederic Lavie<sup>9</sup>, Wim Noël<sup>10</sup>, Michael T Nurmohamed<sup>11</sup> [ORCID ID: 0000-0002-6274-1934], Petros P Sfikakis<sup>12</sup>, Elke Theander<sup>13</sup> [ORCID ID: 0000-0002-6533-2263], Josef S Smolen<sup>14</sup>

<sup>1</sup>Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France; <sup>2</sup>Rheumatology Department, Pitié-Salpêtrière Hospital, AP-HP Sorbonne Université, Paris, France; <sup>3</sup>University of Glasgow, United Kingdom; <sup>4</sup>Janssen-Cilag BV, Breda, Netherlands; <sup>5</sup>University Hospitals Leuven, Belgium; <sup>6</sup>Fondazione Policlinico A Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>7</sup>University Hospital 12 de Octubre, Madrid, Spain; <sup>8</sup>VA Nasonova Research Institute of Rheumatology, Moscow, Russian Federation; <sup>9</sup>The Janssen Pharmaceutical Companies of Johnson & Johnson, Paris, France; <sup>10</sup>Janssen Pharmaceutica NV, Beerse, Belgium; <sup>11</sup>Reade and VU University Medical Center, Amsterdam, Netherlands; <sup>12</sup>National and Kapodistrian University of Athens Medical School, Athens, Greece; <sup>13</sup>Janssen, Solna, Sweden; <sup>14</sup>Medical University of Vienna, Vienna, Austria

**Corresponding author:**

Professor Laure Gossec

Hôpital Pitié-Salpêtrière, Service de Rhumatologie, 47–83 Boulevard de l'Hôpital, 75013

Paris France

Tel: +33142178421

Email: laure.gossec@aphp.fr

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***Key messages:***

**What is already known about this subject?**

- Although many randomised controlled trials have demonstrated efficacy and safety of biologics in psoriatic arthritis (PsA), real-world data comparing them, particularly over the long term, are lacking.
- The PsABio real-world observational study provided comparative data on ustekinumab and tumour necrosis factor inhibitors (TNFi) in PsA treatment over 6 months and indicated similar efficacy.

**What does this study add?**

- We provide 1-year analyses from the PsABio study.
- Drug persistence was similar at 1 year following treatment initiation (72.4% with ustekinumab and 70.5% with TNFi).
- Drug effectiveness and safety were also similar for ustekinumab and TNFi at 1 year.

**How might this impact on clinical practice or future developments?**

- Efficacy, safety and persistence are important considerations when making treatment decisions in PsA.
- These 1-year results from the PsABio study provide real-world evidence on factors which may impact treatment selection and help inform treatment decisions in clinical practice.

## **Abstract**

**Objective:** We evaluated real-world treatment persistence and effectiveness at 1 year following initiation of IL-12/23 inhibitor ustekinumab or a tumour necrosis factor inhibitor (TNFi) for psoriatic arthritis (PsA).

**Methods:** PsABio (NCT02627768), a prospective, observational study, followed patients with PsA prescribed first- to third-line ustekinumab or TNFi. Drug persistence, effectiveness (achievement of clinical Disease Activity Index for Psoriatic Arthritis [cDAPSA] low disease activity [LDA]/remission and minimal disease activity/very low disease activity [MDA/VLDA]), and safety were assessed every six months. In addition to descriptive statistics, propensity score (PS)-adjusted comparisons across cohorts were performed.

**Results:** At 1 year, overall persistence was similar in ustekinumab (n=317/438, 72.4%) and TNFi (n=321/455, 70.5%) groups. PS-adjusted hazard ratio (95% confidence interval [CI]) for stopping/switching ustekinumab versus TNFi was 0.82 (0.60; 1.13). cDAPSA LDA (including remission)/remission was achieved in 55.9%/22.1% ustekinumab- and 67.1%/31.7% TNFi-treated patients; PS-adjusted odds ratios (ORs) (95% CI) were 0.80 (0.57; 1.10) for cDAPSA LDA and 0.73 (0.49; 1.07) for remission. MDA/VLDA was achieved in 34.2%/11.9% ustekinumab- and 43.1%/12.6% TNFi-treated patients; PS-adjusted ORs (95% CI) were 0.89 (0.63; 1.26) for MDA and 0.90 (0.54; 1.49) for VLDA. The safety profiles were similar in both groups.

**Conclusion:** In the real-world PsABio study, after one year of treatment, although unadjusted persistence was numerically slightly higher for ustekinumab versus TNFi and unadjusted effectiveness was numerically slightly higher for TNFi versus ustekinumab, the PS-adjusted comparisons demonstrated comparable overall persistence, effectiveness and safety for both modes of action in PsA.

## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated disease, affecting approximately 20–30% of patients with psoriasis.[1,2] Patients may present with various musculoskeletal and other manifestations such as arthritis, enthesitis, dactylitis, spondyloarthritis, and skin and nail disease.[1]

Treatment options for PsA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying antirheumatic drugs (DMARDs): conventional synthetic (csDMARDs); targeted synthetic (tsDMARDs), and biological (bDMARDs).[3] As the interleukin (IL)-12, IL-23 and IL-17 axes are critical pathways in the pathogenesis of PsA,[4–6] bDMARDs directed against IL-12/IL-23 (p40), IL-23 (p19) and IL-17A, as well as tumour necrosis factor inhibitors (TNFi), have been shown to be effective.[6–8] Ustekinumab, a fully human immunoglobulin G1 monoclonal antibody that inhibits IL-12/IL-23[9], was the first licensed non-TNFi bDMARD therapy in psoriasis and PsA and combines efficacy against disease activity in joints and skin with a favourable safety profile.[7,10,11]

Owing to the significant disease heterogeneity, number of available drugs and limited head-to-head clinical trials in PsA,[12,13] treatment selection is challenging. Treatment persistence is important when managing patients who require long-term treatment, in whom poor adherence (the degree of conformity to treatment recommendations relating to dose and frequency) and poor persistence can lead to suboptimal outcomes.[14,15] Research has shown that the main reasons for switching to a different biologic are lack of effectiveness and adverse events (AEs),[16–19] with patients who switched subsequently recording lower response rates and drug persistence than with their initial bDMARD.[16] Female sex, smoking,[15,17,20] presence of comorbidities[18,21] and higher number of prior therapies are factors associated with poor persistence.[17] Adherence, an influencing factor for persistence,[22] was found to be higher in patients with longer PsA duration (>9 years).[23,24] One study reported that 1-year continuation and low disease activity were predictive of 12-year persistence, indicating that better initial treatment adherence may lead to long-term persistence.[25]

Data on comparisons of different treatment modes of action are lacking in PsA.[19] A retrospective Swedish registry study with a maximum follow-up of 10.6 years demonstrated favourable persistence with ustekinumab versus adalimumab across treatment lines.[26]

Six-month data from the prospective, observational PsABio cohort study of ustekinumab and TNFi treatment in patients with PsA indicated that later line of treatment, female sex and comorbidities as well as baseline disease impact, high clinical disease activity, and chronic widespread pain were shown to negatively influence treatment response.[27]

Here we present data on persistence, the primary outcome of PsABio, as well as clinical effectiveness, disease impact and safety after 1 year of follow-up.

## **METHODS**

### **Study design**

PsABio (NCT02627768) is an observational, multinational study of patients with PsA treated with first- to third-line ustekinumab or a TNFi by their rheumatologist, reflecting real-world practice. The study duration per participant was up to 3 years, with follow-up twice yearly. This 1-year analysis reports the first PsABio comparative drug persistence data, extended effectiveness outcomes regarding achievement of low disease activity (LDA) or remission using clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA)/definitions and minimal disease activity/very low disease activity (MDA/VLDA) as well as the patient-reported 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) measure, and safety data.

### **Patients**

Adults with PsA, who required ustekinumab or any approved TNFi (including biosimilars; **Table S1**) as first, second or third-line treatment, were included.

### **Assessments**

## Persistence

Treatment persistence was defined as the time between initiation of bDMARD until last dose plus one dispensing interval or stop/switch to another bDMARD, or study withdrawal. For calculation of average persistence, data cut-off date for patients remaining on initial treatment was included.

## cDAPSA and MDA/VLDA

cDAPSA was calculated based on the sum of four components: 68 TJC, 66 SJC; patient global assessment and patient pain, with scores  $\leq 14$  and  $\leq 4$  denoting cDAPSA LDA and remission, respectively.[28,29] MDA and VLDA were based on attaining five and seven, respectively, out of the following seven domain cut-offs: tender joint count for 68 joints (68 TJC  $\leq 1$ ); swollen joint count for 66 joints (66 SJC  $\leq 1$ ); Leeds Enthesitis Index ( $\leq 1$ ); skin involvement assessed as body surface area (BSA  $\leq 3\%$ ); Health Assessment Questionnaire Disability Index (HAQ-DI) score  $\leq 0.5$ ; patient global assessment ( $\leq 20$ , visual analogue scale [VAS] in mm); and patient pain VAS ( $\leq 15$ ).[30]

## Patient-reported disease impact measure PsAID-12

The PsAID-12 is a validated, self-administered, weighted questionnaire that assesses the impact of PsA on patients' lives.[31] Each question is answered using a numerical rating scale, from 0 (none/no difficulty/very well) to 10 (extreme/extreme difficulty/very poorly).

## Safety

Details of AEs, serious AEs and AEs of special interest (for ustekinumab defined as malignancies, serious and opportunistic infections and serious neurological disorders) were collected from the first use of ustekinumab or a TNFi in the study. All AEs that started during initial and subsequent treatments in the risk window (defined as the time between treatment initiation and 91 days after treatment stop) were reported.

## Statistical analyses

The sponsor (Janssen Pharmaceuticals NV, Beerse, Belgium) oversaw the development of the statistical plan, data validation and all statistical analyses.

### Populations

The safety set included all patients with baseline and any available follow-up data. Analysis of persistence and effectiveness was based on the effectiveness set, comprising all patients with baseline data and any post-baseline effectiveness data up to the upper limit of the Month 12 visit window, which is up to 15 months follow-up (including patients who switched/stopped treatment due to AEs, lack of efficacy or other reasons). For patients whose last available assessment was earlier than the lower limit of the 12-month visit window, the endpoint analysis used the last observation carried forward (LOCF).

### Analyses

The analysis was exploratory. No predefined hypotheses were tested and no adjustment for multiplicity was applied. Observed values and changes from baseline of effectiveness outcomes (MDA/VLDA and cDAPSA LDA/remission) were summarised at each assessment timepoint. cDAPSA LDA always included remission and MDA always included VLDA. Between-group differences and changes over time were described using 95% confidence intervals (CI). Persistence for ustekinumab and TNFi was described by Kaplan–Meier statistics and log-rank test for the effectiveness set, as well as by relevant baseline subgroups.

In addition to the descriptive statistics, comparative analyses were performed to investigate the differences between treatment cohorts in terms of persistence and effectiveness, including propensity score (PS) adjustment for imbalanced baseline demographic and disease-related covariates. In these analyses, for patients who switched/stopped their initial treatment during the 12-month observation period, the LOCF effectiveness endpoints were imputed as non-responders for binary endpoints, or as showing no improvement from baseline for continuous endpoints.



## RESULTS

### Patients

A total of 991 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 United Kingdom. For this 1-year analysis, 893 patients were included in the effectiveness analysis set (ustekinumab n=438; TNFi n=455) and 927 patients in the safety set (ustekinumab n=457; TNFi n=470; **Figure S1**). Of 438 patients receiving ustekinumab, 341 (77.9%) were on a 45 mg dose, 96 (21.9%) were on a 90 mg dose and 1 (0.2%) patient on another dose.

### Demographics, baseline/clinical characteristics

Patients in the ustekinumab group were older, had more comorbidities and were more likely to have had previous bDMARD exposure, but fewer patients were on concurrent methotrexate (MTX) and NSAIDs than those in the TNFi group. Ustekinumab was given as first-line treatment in 45.0%, second-line in 34.5% and third-line in 20.5% patients versus 55.2%, 32.7% and 12.1% on TNFi, respectively (**Table 1**). More patients in the ustekinumab versus TNFi group had severe skin involvement as assessed by BSA at baseline (**Table 2**). Details regarding the types of previous bDMARD treatments are provided in **Table S2**.

**Table 1. Baseline demographics (effectiveness set; n=893, one-year follow-up)**

	<b>UST (n=438)</b>	<b>TNFi (n=455)</b>
Age years	51.0 (12.5) [ <b>49.9; 52.2</b> ]	48.5 (12.5) [ <b>47.3; 49.7</b> ]
Female, n (%)	246 (56.2) [51.4; 60.9]	248 (54.5) [49.8; 59.1]
BMI, kg/m <sup>2</sup>	28.6 (6.2) [27.9; 29.2]	27.7 (5.3) [27.2; 28.2]
Disease duration since initial diagnosis, years	7.5 (8.1) [6.7; 8.3]	6.2 (6.6) [5.6; 6.9]
Line of bDMARD treatment, n (%)		
First-line	197 (45.0) [ <b>40.3; 49.8</b> ]	251 (55.2) [ <b>50.5; 59.8</b> ]
Second-line	151 (34.5) [30.0; 39.1]	149 (32.7) [28.4; 37.3]
Third-line	90 (20.5) [ <b>16.9; 24.6</b> ]	55 (12.1) [ <b>9.2; 15.4</b> ]
csDMARD exposure, n (%)		
Previous exposure	384 (87.7) [84.2; 90.6]	421 (92.5) [89.7; 94.8]
Ongoing exposure at baseline	173 (39.5) [ <b>34.9; 44.2</b> ]	251 (55.2) [ <b>50.5; 59.8</b> ]
Methotrexate exposure ongoing at baseline	131 (29.9) [ <b>25.7; 34.4</b> ]	191 (42.0) [ <b>37.4; 46.7</b> ]
Other treatments exposure ongoing at baseline, n (%)		
NSAIDs	240 (54.8) [ <b>50.0; 59.5</b> ]	313 (68.8) [ <b>64.3; 73.0</b> ]
Glucocorticosteroids	143 (32.6) [28.3; 37.3]	156 (34.3) [29.9; 38.8]
Once-weekly MTX dose, mg (SD)	15.3 (5.5) [14.3; 16.3]	15.0 (4.6) [14.3; 15.7]
Comorbidities present, n (%)	301 (68.7) [64.1; 73.0]	277 (60.9) [56.2; 65.4]
Cardiovascular disease/metabolic syndrome*	184 (42.0) [37.3; 46.8]	162 (35.6) [31.2; 40.2]
Anxiety or panic disorders	18 (4.1) [2.5; 6.4]	18 (4.0) [2.4; 6.2]
Depression	40 (9.1) [6.6; 12.2]	29 (6.4) [4.3; 9.0]

GI disease or medical history of IBD	55 (12.6) [9.6; 16.0]	49 (10.8) [8.1; 14.0]
FiRST score suggestive of chronic widespread pain (scores ≥5)	163 (39.0) <b>[34.3; 43.9]</b>	126 (29.4) <b>[25.2; 34.0]</b>

\*Hypertension, myocardial infarction, congestive heart failure, stroke or transient ischemic attack, peripheral vascular disease, hyperlipidemia, type 1 or 2 diabetes or angina pectoris. Data are mean (standard deviation) [95% CI of the mean] unless otherwise stated; % is that of available data. Variables in bold indicate non-overlapping 95% CI.

BMI, body mass index; bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GI, gastrointestinal; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

FiRST, Fibromyalgia Rapid Screening Tool.

**Table 2: PsA clinical characteristics at baseline (effectiveness set)**

PsA characteristics	UST (n=438)	TNFi (n=455)
Psoriasis BSA, n (%)		
Clear/almost clear skin	102 (28.7) [24.1; 33.7]	116 (33.0) [28.1; 38.1]
<3% but not clear/almost clear skin	34 (9.6) [6.7; 13.1]	53 (15.0) [11.5; 19.2]
3–10%	124 (34.9) [30.0; 40.1]	131 (37.2) [32.2; 42.5]
>10%	95 (26.8) <b>[22.2; 31.7]</b>	52 (14.8) <b>[11.2; 18.9]</b>
Axial involvement* – pure or combined with peripheral, n (%)	153 (35.8) [31.3; 40.6]	166 (37.4) [32.9; 42.1]
Oligoarticular†, n (%)	96 (22.5) [18.6; 26.7]	129 (29.1) [24.9; 33.5]
Polyarticular‡, n (%)	286 (67.0) [62.3; 71.4]	283 (63.7) [59.1; 68.2]
SJC66	5.9 (8.2) [5.1; 6.8]	5.8 (7.5) [5.1; 6.6]
TJC68	12.5 (12.7) [11.2; 13.8]	11.0 (10.5) [9.9; 12.0]
cDAPSA, n (%)	30.6 (20.2) [28.5; 32.7]	29.3 (18.6) [27.3; 31.2]
Remission	10 (2.8) [1.3; 5.1]	7 (2.0) [0.8; 4.0]
Low	36 (10.1) [7.1; 13.6]	39 (11.0) [7.9; 14.7]
Moderate	141 (39.4) [34.3; 44.7]	149 (41.9) [36.7; 47.2]
High	171 (47.8) [42.5; 53.1]	161 (45.2) [40.0; 50.6]
MDA§, n (%)	16 ( 4.3) [2.5; 7.0]	18 ( 5.1) [3.0; 7.9]
VLDA, n (%)	1 ( 0.3) [0.0; 1.4]	2 ( 0.5) [0.1; 2.0]

Enthesitis <sup>¶</sup> , n (%)	192 (47.8) [42.8; 52.8]	204 (51.3) [46.2; 56.3]
Dactylitis <sup>‡</sup> , n (%)	74 (17.7) [14.1; 21.7]	90 (21.8) [17.9; 26.1]
PsAID-12 total score	5.8 (2.1) [5.5; 6.0]	5.5 (2.1) [5.3; 5.7]
HAQ-DI	1.1 (0.7) [1.1; 1.2]	1.2 (0.7) [1.1; 1.2]

Data are mean (standard deviation) [95% CI of the mean] unless otherwise stated; % is that of available data. Variables in bold indicate non-overlapping 95% CI.

\*Pure axial PsA is defined as having only axial involvement (presence of axial disease declared by the treating rheumatologist without requirement for imaging), while combined axial PsA includes axial involvement and at least one of the following: distal interphalangeal joint involvement, monoarticular or oligoarticular PsA, polyarticular PsA, and arthritis mutilans. 2.1% of patients in the UST group and 3.2% in the TNFi group had pure axial PsA with inflammatory back pain.

<sup>†</sup>Either TJC68 and SJC66 are both non-missing and patient has <5 swollen or <5 tender joint counts, or in case TJC68 and/or SJC66 are missing monoarticular or oligoarticular PsA is indicated by the investigator.

<sup>‡</sup>Either TJC68 and SJC66 are both non-missing and patient has ≥5 swollen and ≥5 tender joint counts, or in case TJC68 and/or SJC66 are missing polyarticular PsA is indicated by the investigator.

<sup>§</sup>MDA includes VLDA.

<sup>¶</sup>Enthesitis presence defined as Leeds Enthesitis Index ≥0.

<sup>‡</sup>Dactylitis presence on assessment of hands and feet.

BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; CI, confidence interval; HAQ, Health Assessment Questionnaire; MDA, minimal disease activity; PsA, psoriatic arthritis; PsAID-12, Psoriatic Arthritis Impact of Disease score; SJC66, swollen joint count for 66 joints; TJC68, tender joint count for 68 joints; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

## Persistence

Persistence on ustekinumab and TNFi was similar at 1 year ( $\pm 3$  months) (**Figure 1A**), with 72.4% of ustekinumab- and 70.5% of TNFi-treated patients remaining on their initial treatment. Patients stopped/switched treatment predominantly due to lack of effectiveness (ustekinumab 76.9%; TNFi 69.4%) or safety/AEs (ustekinumab 12.4%; TNFi 28.4%); others switched due to patient's/physician's preference, access to the drug or for guideline reasons. The PS-adjusted Cox persistence analysis confirmed the observed finding: ustekinumab versus TNFi hazard ratio (95% CI) for stopping/switching bDMARD was 0.82 (0.60; 1.13). The overall observed mean time on drug was 13.1 months (standard deviation [SD] 3.5) for patients receiving ustekinumab versus 12.7 months (SD 4.2) for patients receiving a TNFi (a breakdown of treatment durations for individual TNFis is provided in Table S3).

Gender: Overall, as well as within both treatment cohorts, shorter drug persistence was observed in women than men (**Figure 1B**). Comparing the treatment cohorts by means of a PS-adjusted Cox persistence analysis, no interaction was observed of the factor sex and the treatment cohort.

Axial involvement: PS-adjusted Cox analysis showed no difference in persistence between ustekinumab versus TNFi (HR 0.83 [0.50–1.38]) for patients with axial involvement at baseline.

bDMARD line: Although the PS-adjusted Cox proportional hazard model did not show an overall significant interaction between the treatment lines and the treatment cohorts, the Kaplan-Meier graphs clearly showed better drug persistence in patients with first-/second line treatment than in patients with third-line treatment, with TNFi third-line being associated with numerically shorter persistence than all other lines including ustekinumab third-line (**Figure 1C**).

Monotherapy: The observed better persistence on ustekinumab monotherapy versus TNFi monotherapy (**Figure 1D**) was confirmed in the PS-adjusted Cox persistence analysis that showed a ustekinumab versus TNFi HR (95% CI) of 0.61 (0.42;0.90). In patients co-treated

with MTX, the observed ustekinumab and TNFi difference in persistence was not confirmed in the PS-adjusted Cox model (HR: 1.37; 95% CI: 0.83; 2.26). There was no notable difference in mean, weekly MTX dose between UST and TNFi treatment groups (15.3 mg [SD 5.5] and 15.0 mg [SD 4.6], respectively).

**Skin involvement:** In the observed analysis, patients with more skin involvement at baseline persisted longer on their biologic than those with less skin involvement, in particular on ustekinumab (**Figure 1E**). This was partly confirmed in the PS-adjusted Cox persistence analysis that showed a trend ( $p=0.0632$ ) towards an interaction between the factor skin involvement and the treatment cohort, with longer persistence on ustekinumab in patients with baseline BSA>10% (HR: 0.41; 95% CI: 0.19; 0.89).

### **Effectiveness**

The observed proportion of patients achieving cDAPSA LDA/remission at 1 year was 55.9%/22.1% for the ustekinumab group and 67.1%/31.7% for the TNFi group; PS-adjusted ORs (95% CI) for ustekinumab versus TNFi were 0.80 (0.57; 1.10) for cDAPSA LDA and 0.73 (0.49; 1.07) for cDAPSA remission. Across all lines of treatment, the observed proportion of patients achieving MDA/VLDA was 34.2%/11.9% in the ustekinumab group and 43.1%/12.6% in the TNFi group (**Figure 2**); PS-adjusted ORs (95% CI) for ustekinumab versus TNFi treatment were 0.89 (0.63; 1.26) for MDA and 0.90 (0.54; 1.49) for VLDA. The proportion of patients on ustekinumab or TNFi who achieved MDA at 6 and 12 months are shown in **Figure 3**.

### **PsAID-12**

From baseline to 1 year, both treatments improved disease impact measured by PsAID-12 (total and individual domain scores) (**Figure 4**), with the majority of the improvement occurring by month 6 in both cohorts. PS-adjusted treatment comparison between ustekinumab and TNFi groups showed similar improvement in total PsAID-12 (regression coefficient [95% CI]: 0.14 [-0.22; 0.51]), and in individual domains, except Skin Problems, where more improvement

was observed with ustekinumab than TNFi (-0.55 [-1.04; -0.06]). Within both groups, improvements in PsAID-12 and HAQ-DI showed moderate/strong positive correlation (ustekinumab:  $r=0.63$ , TNFi:  $r=0.70$ ). Non-clinical aspects of PsAID-12, e.g. difficulties participating in social activities and overall coping, improved with both treatments (**Table S3**).

## **Safety**

At least one AE was reported for 24.4% of all patients receiving ustekinumab and 28.7% of patients receiving a TNFi, with 4.5% and 3.4%, respectively, reporting at least one serious AE. Three patients reported at least one serious infection in both treatment groups; there were three cases of pneumonia in patients receiving a TNFi and one case each of cellulitis, skin infection and staphylococcal bacteraemia in the ustekinumab group. A similar proportion of patients reported malignancies (excluding non-melanoma skin cancer; ustekinumab:  $n=4$ ; TNFi:  $n=3$ , all single events) within the first year. Non-melanoma skin cancer was reported in 2 ustekinumab- and 2 TNFi-treated patients. Cardiovascular AEs were reported by 2 ustekinumab and 6 TNFi patients over 1 year but none were major and all were arrhythmias. Of note, all but two patients experiencing cardiovascular AEs had a medical history of cardiovascular disease/metabolic syndrome. During the first year of the study, one patient in the ustekinumab group experienced unexplained sudden death and one patient in the TNFi group died due to pneumonia (**Table S4**).

## **DISCUSSION**

The prospective PsABio study aims to provide comparative real-world data on treatment persistence of biologic therapy in patients with PsA. After 1 year of follow-up, drug persistence was similar for ustekinumab or a TNFi in the PS-adjusted analysis, although observed data showed slightly better persistence for ustekinumab versus TNFi. These results are in contrast to the results from recent retrospective database studies showing that patients with PsA who initiated IL-12/23 inhibitor treatment had significantly longer treatment persistence and lower discontinuation rate compared with those initiating a TNFi during 1-year follow-up[32] and those initiating adalimumab during 10-year follow-up[26]. Likewise, the subgroup of patients

with PsA in the PSOLAR study, a registry study of 12,095 patients with psoriasis, showed better drug persistence with ustekinumab versus TNFi.[19] This difference in results of adjusted analyses between the PsABio study and the other studies could be due to various reasons: prospective non-interventional study setting, as done here, is different from retrospective claims database or registry analysis; the ustekinumab population in the current study was heavily affected by comorbidities, chronic widespread pain, late lines of bDMARD treatment, which may have impacted drug persistence with ustekinumab in this prospective patient cohort versus the other studies, and these or additional non-assessed imbalances may not have been fully adjusted for. Also, in this study in PsA, active psoriasis was not required and many patients had clear or almost clear skin, potentially reducing the advantage of ustekinumab treatment compared to TNFis.

The current study also showed lower drug persistence in women versus men with both treatments. Third-line TNFi treatment was associated with more reduced persistence than all other lines including ustekinumab third-line. This observation supports previous reports, and the strategy of changing the biologic treatment mode of action, instead of cycling through treatments with the same pathophysiological target.[11,17,19]

Minimal or no skin involvement was strongly associated with low persistence in both cohorts. Patients with the greatest skin involvement at baseline showed longer persistence in both treatment groups, although persistence with TNFi was shorter than with ustekinumab in patients with BSA >10%, which may indicate the importance of skin improvement for patients. This effect is also seen with the greater improvement in PsAID-12 score in patients with higher baseline BSA. These observations are consistent with other studies showing a relationship between skin involvement and treatment persistence in PsA. This is expected, as the burden of psoriasis can significantly impact morbidity, and patients' health-related quality of life depends on successful treatment of skin symptoms.[33]



The differential importance of MTX co-therapy on persistence with ustekinumab versus TNFi demonstrated in this real-world study supports results from the long-term SPIRIT-H2H extension randomised controlled trial data.[12] While ustekinumab persistence is independent of co-therapy with MTX, TNFi persistence without MTX is shorter than with MTX and shorter than ustekinumab with/without MTX. This may be interpreted as a function of several mechanisms: patients receiving a TNFi may develop neutralising anti-drug antibodies when MTX is not given; with ustekinumab, the risk of such anti-drug antibodies is described as minimal.[34] Other reasons may include MTX co-therapy with TNFi being more effective for skin involvement and likely selection bias in this real-world study as more patients on TNFi versus ustekinumab were on MTX at baseline.

PS-adjusted treatment effectiveness (cDAPSA LDA/remission or MDA/VLDA) was not different for TNFi and ustekinumab at 6 months and 1 year although the observed proportions were higher with TNFi versus ustekinumab. Also, PsAID-12 scores improved in all domains between baseline and 1 year with both treatments.

Both ustekinumab and TNFi treatment have a favourable safety profile in this real-world study of PsA patients presenting with several comorbidities. Although reported AE and serious AE rates were similar for both groups, more patients in the TNFi group stopped/switched treatment due to AEs than in the ustekinumab group; at the same time more patients in the ustekinumab versus TNFi group stopped/switched due to lack of efficacy.

We did not evaluate outcomes in the individual dose groups of ustekinumab versus TNFi group because some patients were overdosed and others underdosed depending on their body weight (in particular, obese patients weighing just over 100 kg). Moreover, some rheumatologists may have used a lower dose when the patient's disease was better controlled; therefore, analysis of different dose groups may introduce bias. Similar complexities of dosing apply as well to TNF inhibitors.

PsABio is the only prospective real-world study comparing biologics with different modes of action in patients with PsA. The prospective open design allows the analysis and publication of data as it accumulates, permitting early detection of differences. The study captures data from a real-world population across eight different countries, each with their own local guidelines and treatment preferences; data which will apply to routine patient care and management. The limitation is that the comparison between treatment cohorts had to be based on PS adjustment and not on randomisation, due to a probable selection bias in treatment choice.

This study has confirmed the strong impact of treatment line, gender and baseline extent of skin disease on persistence and demonstrated the effectiveness of ustekinumab or TNFi-based treatments in PsA, not only on physician-derived but also patient-reported outcomes, such as disease impact. The final 3-year data from the PsABio study may provide further insights, such as information about factors that may predict long-term persistence at an early stage of treatment.

## **Conclusion**

Real-world results from the PsABio study have demonstrated generally comparable drug persistence, efficacy and safety following 1 year of treatment with ustekinumab or a TNFi, after PS adjustment for counteracting imbalanced baseline characteristics caused by channeling bias. Patients in this study were more likely to remain on ustekinumab than TNFi when extensive skin disease was present and when MTX was not used as concomitant treatment. On unadjusted analysis, women had lower treatment persistence with both treatments versus men, indicating they may require more comprehensive multidimensional therapy.

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Cello Health MedErgy drafted the initial version of the manuscript and provided medical writing support throughout its development.

### **Competing interests**

**LG** reports research grants from: Amgen, Galapagos, Lilly, Pfizer, Sandoz, Sanofi; consulting fees from: AbbVie, Amgen, BMS, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Samsung Bioepis, Sanofi-Aventis, UCB. **SS** reports non-financial support from Janssen during the conduct of the study; grants from: Boehringer-Ingelheim, Bristol-Myers Squibb; personal fees from: AbbVie, Biogen, Novartis; grants and personal fees from: Amgen (previously Celgene), GlaxoSmithKline, Janssen, UCB; all outside the submitted work. **PB** reports personal fees from Janssen, Johnson & Johnson during the conduct of the study. **KdV** reports personal fees from Janssen. **EG** reports payment or honoraria from Abbvie, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, Sanofi. **BJI** has nothing to disclose. **TVK** reports consulting fees from MCD, Pfizer, Janssen, BiOCAD, Abbvie, Novartis, Sandoz, Lilly. **FL** reports non-financial support and other from Janssen during the conduct of the study. **WN** is an employee of and owns stock at Johnson & Johnson. **MTN** reports grants and non-financial support from Janssen during the conduct of the study; grants from: BMS, Amgen, Pfizer; grants and personal fees from: Abbvie, Eli Lilly; all outside the submitted work. **PS** reports non-financial support from Janssen during the conduct of the study; grants from: UCB; personal fees from: MSD; grants and personal fees from: Abbvie, Lilly, Pfizer, Novartis; all outside the submitted work. **ET** reports other fees from Janssen during the conduct of the study and outside the submitted work. **JSS** reports grants to his institution from: Abbvie, Astro, AstraZeneca, Janssen, Lilly, Merck Sharpe & Dohme,

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### **Author contributions**

LG, SS, PB, JSS, TVK, EG, BJI, WN, PS, KdV, ET, FL contributed to conceptualization of the study; LG, SS, PB, TVK, EG, WN, PS, KdV, MTN, ET, FL contributed to the development of study design, data curation and methodology; PB, ET, FL, MTN, KdV contributed to formal data analysis and validation of results; FL, WN provided funding acquisition and financial support for the project; LG, SS, TVK, EG, BJI, MTN, PS, KdV, ET conducted the research; SS, EG, MTN, PS, ET, FL planned, directed and coordinated research activity; BJI, MTN, PS, KdV, EG provided resources and analysis tools; PB contributed to programming and implementation of computer programs; SS, ET, FL, MTN, PS, WN, KdV, EG provided supervision of the research including mentorship; LG, SS, PB, BJI, ET, MTN, TVK, KdV, EG contributed to data visualization and presentation; LG, PB, EG, WN, MTN, ET contributed to preparing and writing the manuscript. All authors reviewed, provided critical review at each stage and approved the final version of the manuscript.

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**Disclaimer**

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**Patient and public involvement**

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication**

Not required.

**Ethics approval**

This study complied with ethics requirements as specified by the Independent Ethics Committee/Institutional Review Board and by local regulations. Each participant signed a participation agreement/informed consent form in line with local regulations and trial sponsor policy, before data collection.

**Data sharing statement**

Access to anonymised individual participant-level data will not be provided for this trial as it meets one or more of the exceptions described on <https://yoda.yale.edu/> under “Data Use Agreement - Janssen Pharmaceuticals DUA”.

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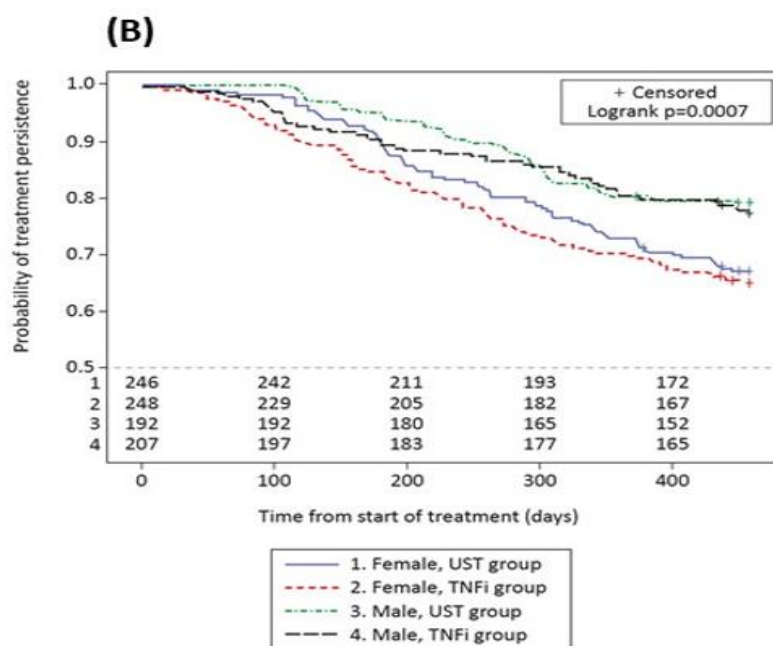
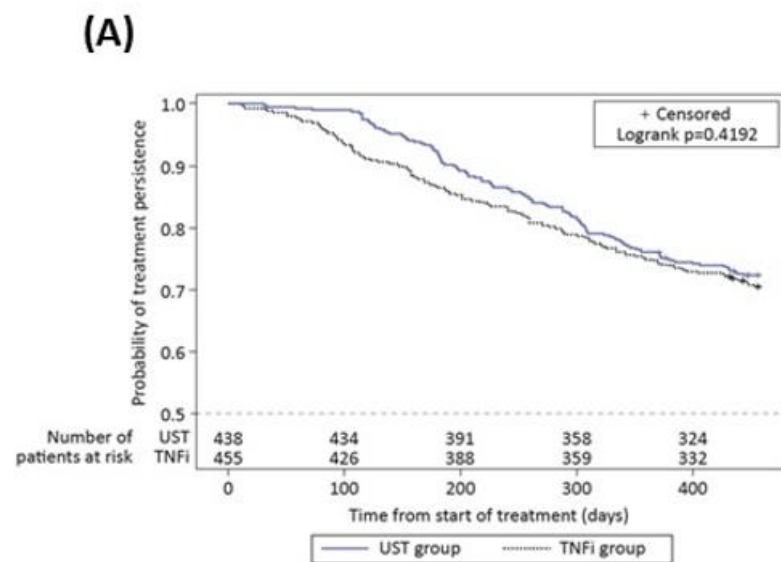
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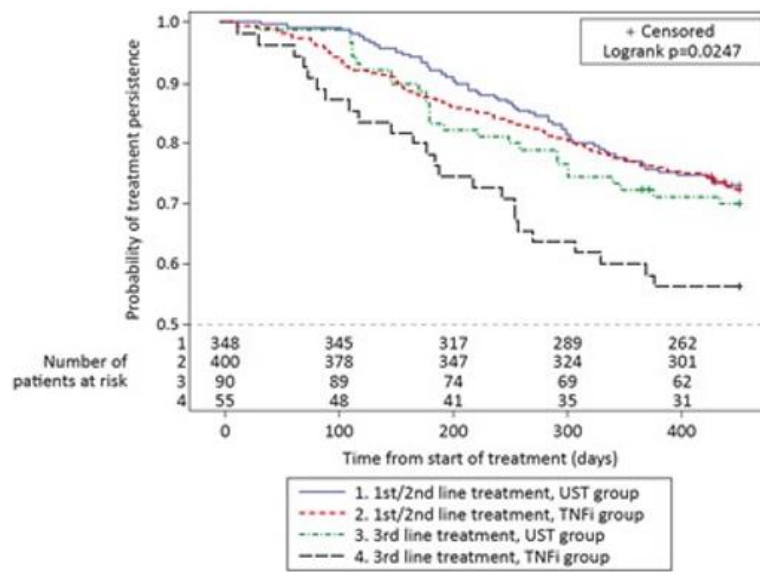


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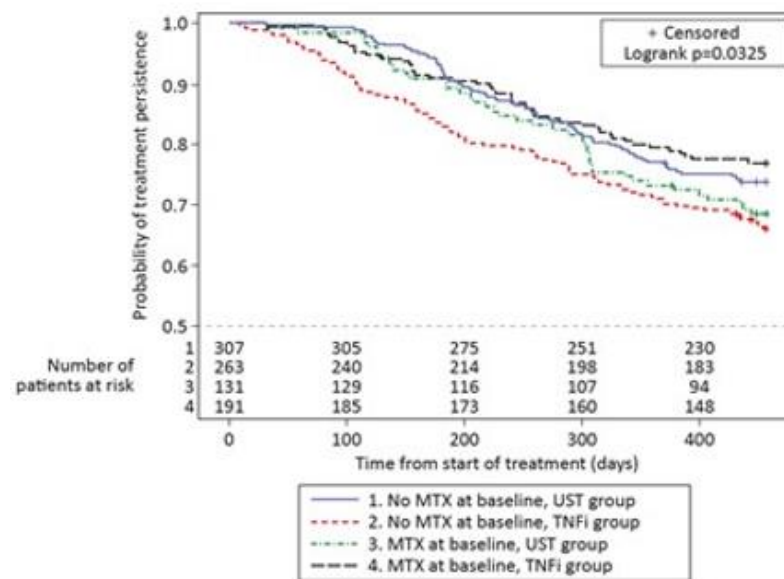
**Figure 1.** Kaplan–Meier plots of treatment persistence with ustekinumab versus TNFi (A) overall, (B) by sex, (C) by treatment line, (D) by presence/absence of methotrexate and (E) by extent of skin involvement at baseline

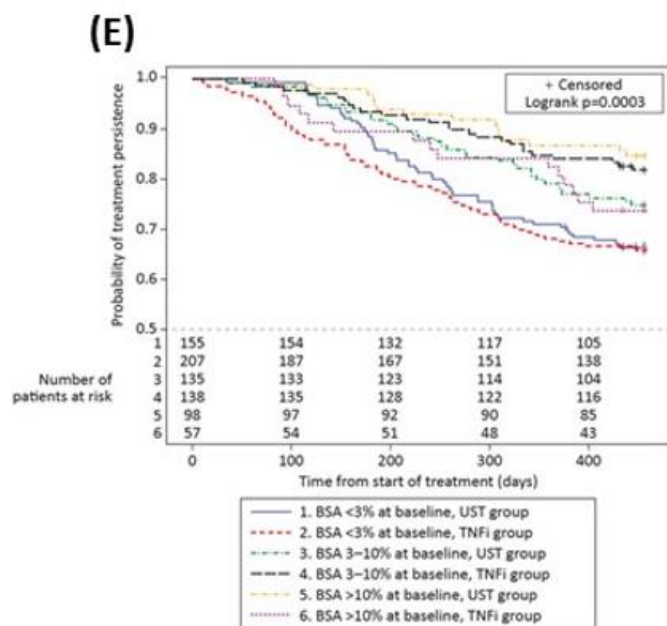


(C)



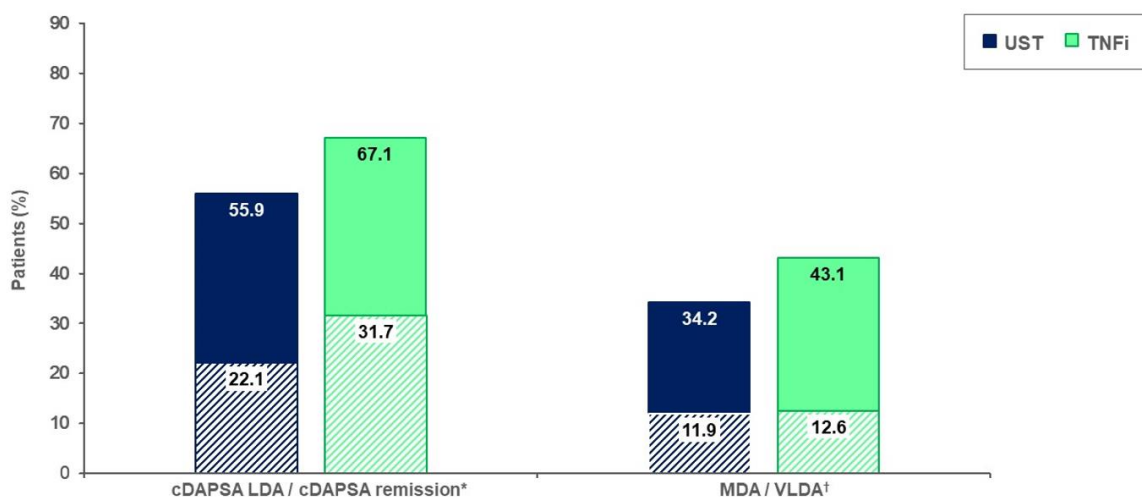
(D)





BSA, body surface area; BL, baseline; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

**Figure 2.** Disease outcomes at Month 12 for patients with PsA receiving UST or TNFi

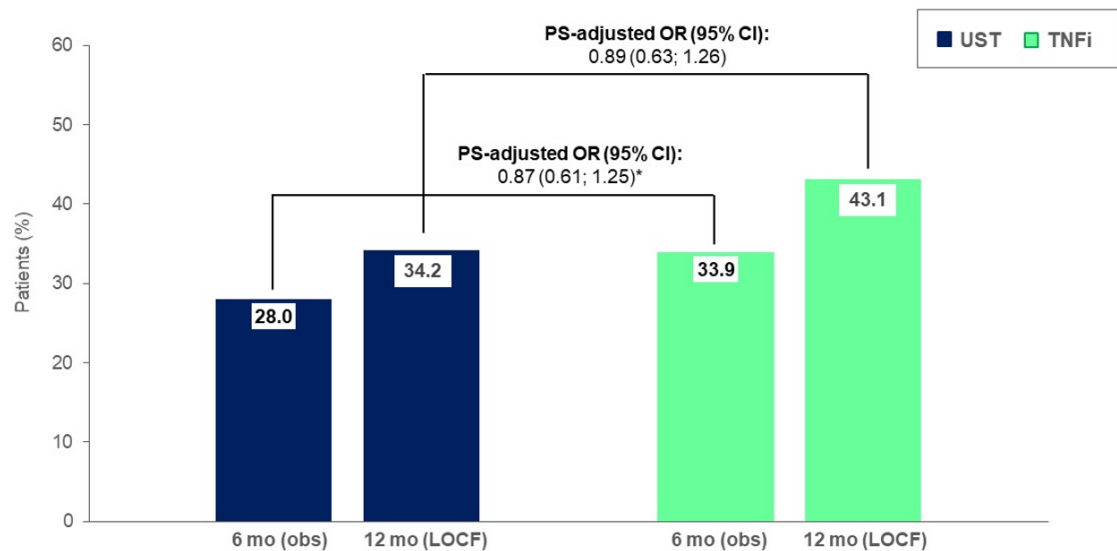


\*Main (solid) bar represents cDAPSA LDA (including remission; cDAPSA  $\leq 13$ ) and inset (hashed) bar represents cDAPSA remission  $\leq 4$ .

†Main (solid) bar represents MDA (including VLDA) and inset (hashed) bar represents VLDA.

cDAPSA, clinical Disease Activity in Psoriatic Arthritis; CI, confidence interval; LDA, low disease activity; MDA, minimal disease activity; OR, odds ratio; PS, propensity score; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

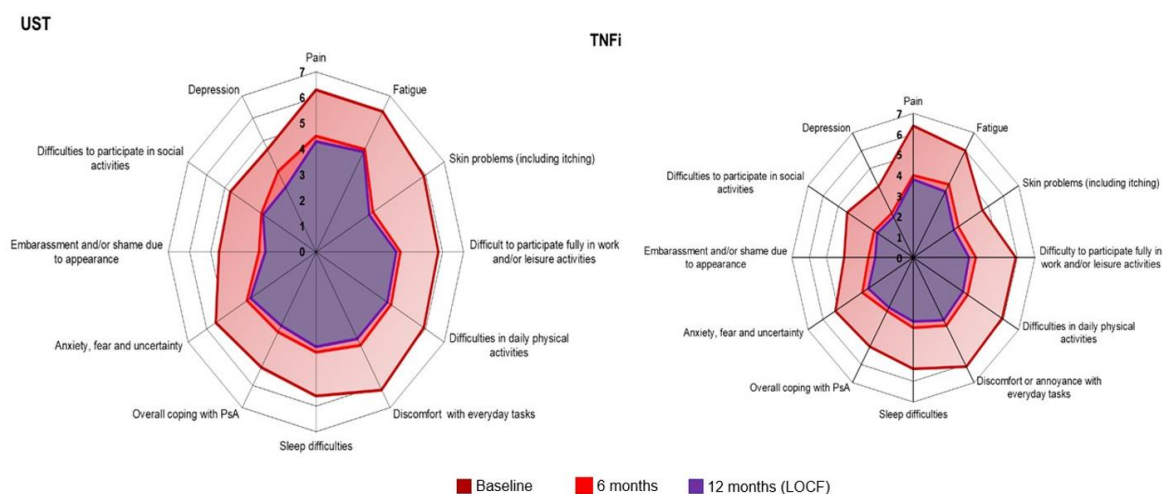
**Figure 3.** Proportion achieving MDA at Months 6 (observed) and 12 (LOCF) and PS-adjusted odds ratios



\*The 6-month PS-adjusted OR (95% CI) are from the 6-month analysis.[33]

CI, confidence interval; LOCF, last observation carried forward; MDA, minimal disease activity; mo, month; obs, observed; OR, odds ratio; PS, propensity score; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

**Figure 4.** Mean PsAID-12 overall and domain scores at baseline and 1 year with ustekinumab (n=438) and TNFi (n=455)



UST: mean (95% CI) total score improved from 5.8 (5.5; 6.0) at BL to 3.9 (3.6; 4.1) at 6 months and 3.7 (3.4; 3.9) at 1 year.

TNFi: mean (95% CI) total score improved from 5.5 (5.3; 5.7) at BL to 3.4 (3.2; 3.7) at 6 months and 3.1 (2.9; 3.4) at 1 year.