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CLINICAL SCIENCE

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

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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-line 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 6 months. In addition to descriptive statistics, propensity score (PS)-adjusted comparisons across cohorts were performed.

Results At 1 year, overall persistence was similar in the ustekinumab (n=317/438, 72.4%) and TNFi (n=321/455, 70.5%) groups. PS-adjusted HR (95% 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% of ustekinumab-treated and 67.1%/31.7% of TNFi-treated patients; PS-adjusted 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% of ustekinumab-treated and 43.1%/12.6% of 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 1 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

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.

Treatment options for PsA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying antirheumatic drugs (DMARDs): conventional synthetic DMARDs; targeted synthetic DMARDs and biological DMARDs (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 IgG1 monoclonal antibody that inhibits



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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-line 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 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; online supplemental table S1) as first-line, second-line 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 were calculated based on the sum of four components: tender joint count for 68 joints (TJC68), swollen joint count for 66 joints (SJC66) patient global assessment and patient pain, with scores ≤ 14 and ≤ 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: TJC68 ≤ 1 ; SJC66 ≤ 1 ; Leeds Enthesitis Index ≤ 1 ; skin involvement assessed as body surface area (BSA) $\leq 3\%$; Health Assessment Questionnaire Disability Index (HAQ-DI) score ≤ 0.5 ; patient global assessment ≤ 20 (Visual Analogue Scale (VAS) in mm); and patient pain VAS ≤ 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 postbaseline 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 end-point 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 time point. cDAPSA LDA always included remission and MDA always included VLDA. Between-group differences and changes over time were described using 95% CIs. 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

Table 1 Baseline demographics (effectiveness set; n=893)

	UST (n=438)	TNFi (n=455)
Age years	51.0 (12.5) (49.9; 52.2)	48.5 (12.5) (47.3; 49.7)
Female, n (%)	246 (56.2) (51.4; 60.9)	248 (54.5) (49.8; 59.1)
BMI, kg/m ²	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) (40.3; 49.8)	251 (55.2) (50.5; 59.8)
Second-line	151 (34.5) (30.0; 39.1)	149 (32.7) (28.4; 37.3)
Third-line	90 (20.5) (16.9; 24.6)	55 (12.1) (9.2; 15.4)
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) (34.9; 44.2)	251 (55.2) (50.5; 59.8)
MTX exposure ongoing at baseline	131 (29.9) (25.7; 34.4)	191 (42.0) (37.4; 46.7)
Weekly MTX dose, mg	15.3 (5.5) (14.3; 16.3)	15.0 (4.6) (14.3; 15.7)
Other treatments exposure ongoing at baseline, n (%)		
NSAIDs	240 (54.8) (50.0; 59.5)	313 (68.8) (64.3; 73.0)
Glucocorticosteroids	143 (32.6) (28.3; 37.3)	156 (34.3) (29.9; 38.8)
Comorbidities present, n (%)		
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) (34.3; 43.9)	126 (29.4) (25.2; 34.0)

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

*Hypertension, myocardial infarction, congestive heart failure, stroke or transient ischaemic attack, peripheral vascular disease, hyperlipidaemia, type 1 or type 2 diabetes or angina pectoris. bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FIRST, Fibromyalgia Rapid Screening Tool; GI, gastrointestinal; IBD, inflammatory bowel disease; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

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) (22.2; 31.7)	52 (14.8) (11.2; 18.9)
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¶, n (%)	192 (47.8) (42.8; 52.8)	204 (51.3) (46.2; 56.3)
Dactylitis**, 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 (SD) (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.

‡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.

§MDA includes VLDA.

¶Enthesitis presence defined as Leeds Enthesitis Index ≥0.

**Dactylitis presence on assessment of hands and feet.

BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire Disability Index; MDA, minimal disease activity; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease; 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.

the 12-month observation period, the LOCF effectiveness end points were imputed as non-responders for binary end points, or as showing no improvement from baseline for continuous end points.

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 UK. 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; online supplemental figure S1). Of the 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 was 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% of 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 online supplemental table S2.

Persistence

Persistence on ustekinumab and TNFi was similar at 1 year (±3 months) (figure 1A), with 72.4% of ustekinumab-treated 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 HR (95% CI) for stopping/switching bDMARD was 0.82 (0.60; 1.13). The overall observed mean time on drug was 13.1 months (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 TNFi is provided in online supplemental table S3).

Gender

Overall, as well as within both treatment cohorts, shorter drug persistence was observed in women than men (figure 1B).

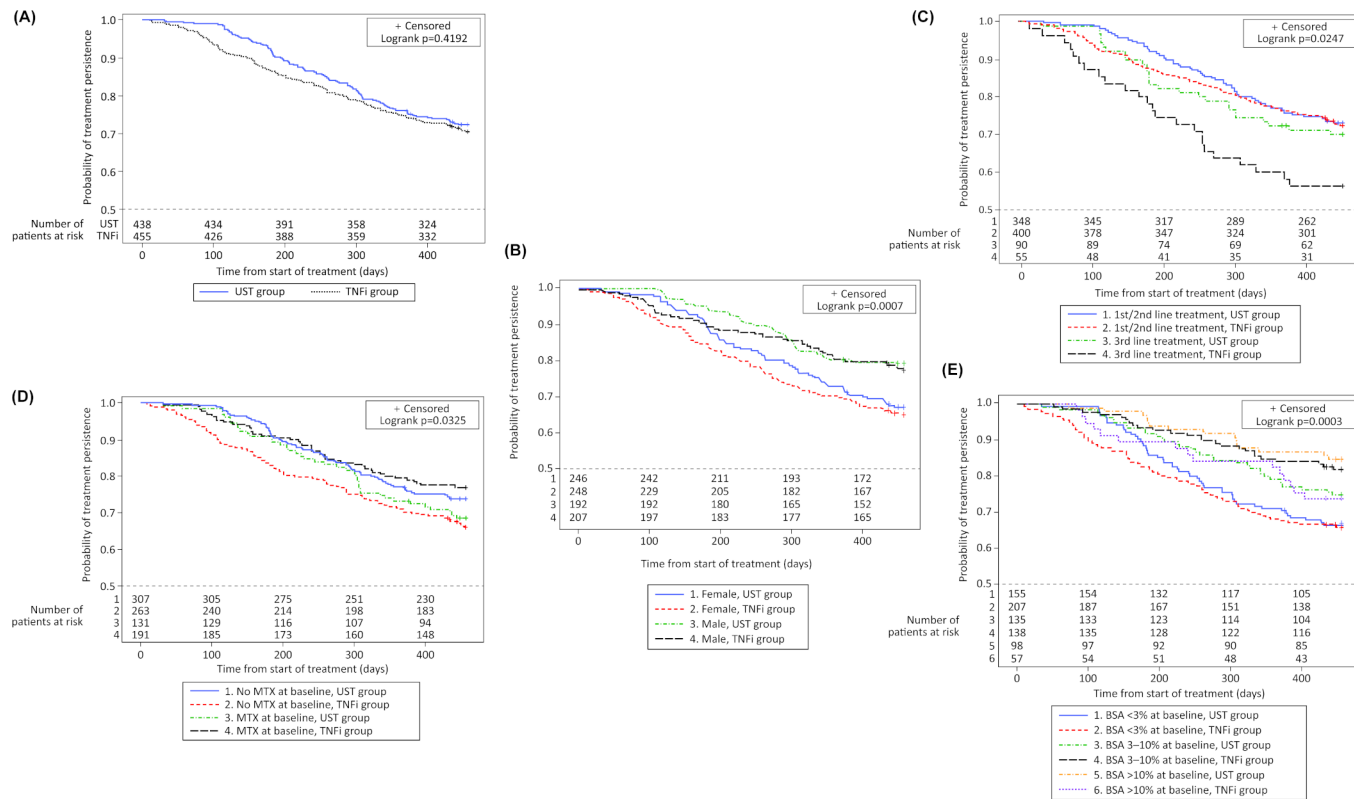


Figure 1 Kaplan-Meier plots of treatment persistence with ustekinumab versus TNFi (A) Overall, (B) By sex, (C) By treatment line, (D) By presence/absence of methotrexate and (E) By extent of skin involvement at baseline. BSA, body surface area; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

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 (95% CI 0.50; 1.38)) for patients with axial involvement (defined as presence of axial disease declared by the treating rheumatologist without requirement for imaging) 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-line/second-line treatment than in patients with third-line treatment, with TNFi third-line treatment being associated with numerically shorter persistence than all other lines including ustekinumab third-line treatment (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 the mean weekly MTX dose between ustekinumab 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 months and 12 months is 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 six in both cohorts. PS-adjusted treatment comparison between the ustekinumab and TNFi groups showed similar improvement in total PsAID-12 (regression coefficient (0.14, 95% CI -0.22; 0.51), and in individual domains, except skin

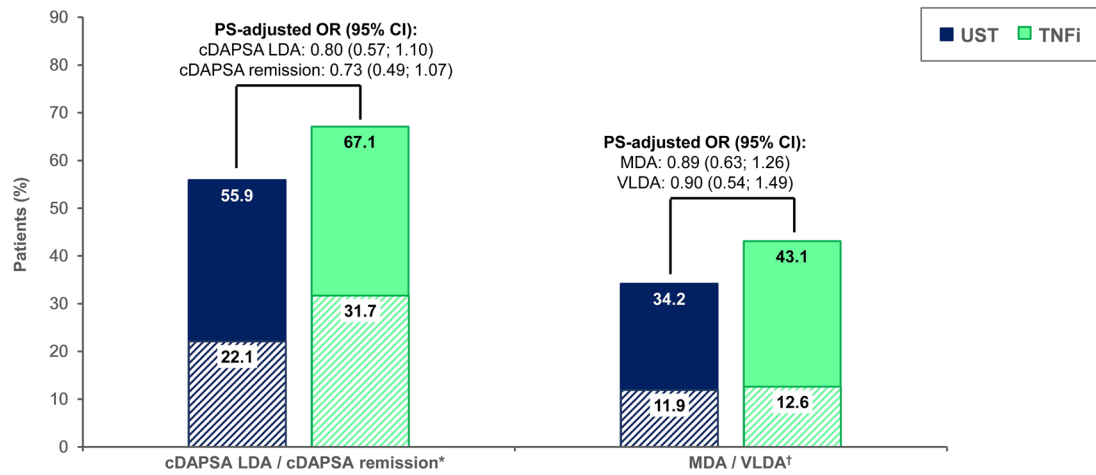


Figure 2 Disease outcomes at month 12 for patients with PsA receiving ustekinumab or TNFi. *Main (solid) bar represents cDAPSA LDA (including remission; cDAPSA ≤13) and inset (hashed) bar represents cDAPSA remission ≤4. †Main (solid) bar represents MDA (including VLDA) and inset (hashed) bar represents VLDA. cDAPSA, clinical disease activity in psoriatic arthritis; LDA, low disease activity; MDA, minimal disease activity; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; VLDA, very low disease activity.

problems, where more improvement was observed with ustekinumab than TNFi (−0.55, 95% CI −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, for example, difficulties participating in social activities and overall coping, improved with both treatments (online supplemental table S4).

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 two ustekinumab-treated and two TNFi-treated patients. Cardiovascular AEs were reported by two ustekinumab-treated and six TNFi-treated 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, an unexplained sudden death occurred in one patient in the ustekinumab group, and one patient in the TNFi group died due to pneumonia (online supplemental table S5).

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

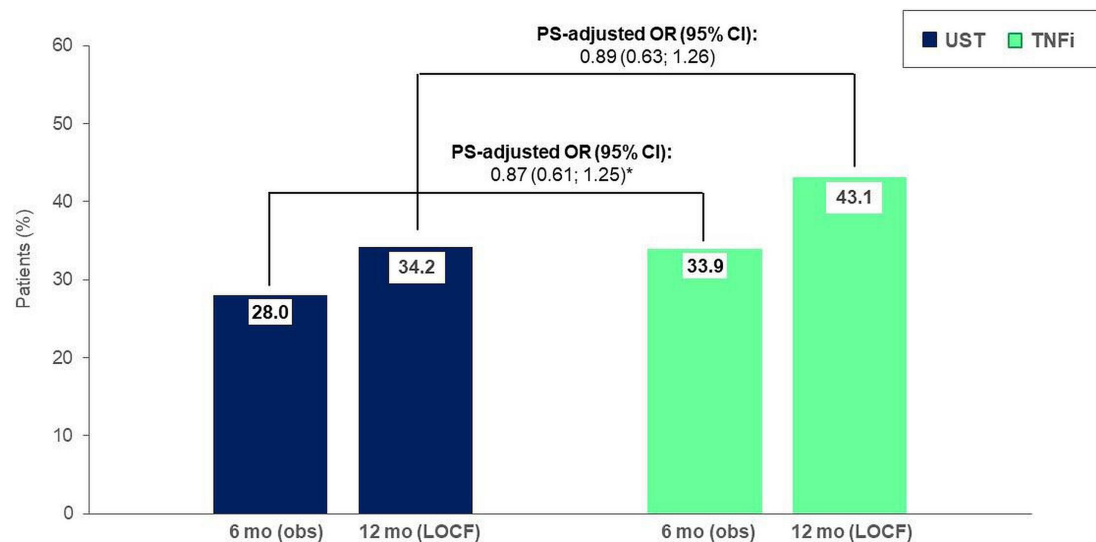


Figure 3 Proportion of patients achieving MDA at month 6 (observed) and month 12 (LOCF) and PS-adjusted ORs. *The 6-month PS-adjusted OR 95% CI are from the 6-month analysis. LOCF, last observation carried forward; MDA, minimal disease activity; mo, month; obs, observed; PS, propensity score.

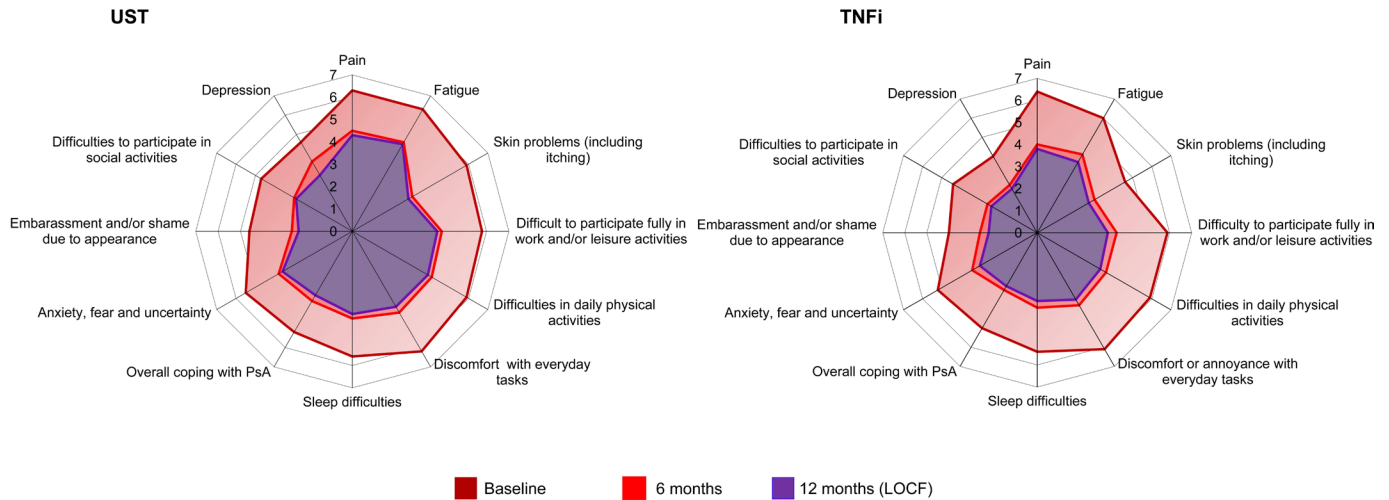


Figure 4 Mean PsAID-12 overall and domain scores at baseline and 1 year with ustekinumab (n=438) and TNFi (n=455). UST: mean (95% CI) total score improved from 5.8 (5.5; 6.0) at baseline to 3.9 (3.6; 4.1) at 6 months and 3.7 (3.4; 3.9) at 1 year. TNFi: mean (95% CI) total score improved from 5.5 (5.3; 5.7) at baseline to 3.4 (3.2; 3.7) at 6 months and 3.1 (2.9; 3.4) at 1 year. LOCF, last observation carried forward; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

significantly longer treatment persistence and lower discontinuation rates compared with those initiating a TNFi during 1 year follow-up³² and those initiating adalimumab during 10 years 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 with TNFi.

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 third-line ustekinumab treatment. 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 a 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 antidrug antibodies when MTX is not given; with ustekinumab, the risk of such antidrug 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 patients with PsA presenting with several comorbidities. Although reported AEs 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 the TNFi group, as some patients received doses that were too high or too low relative to 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 or escalated the dose when disease activity was less well controlled; therefore, analysis of different dose groups may introduce bias. Similar complexities of dosing also apply to TNFi.

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 they accumulate, 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 channelling 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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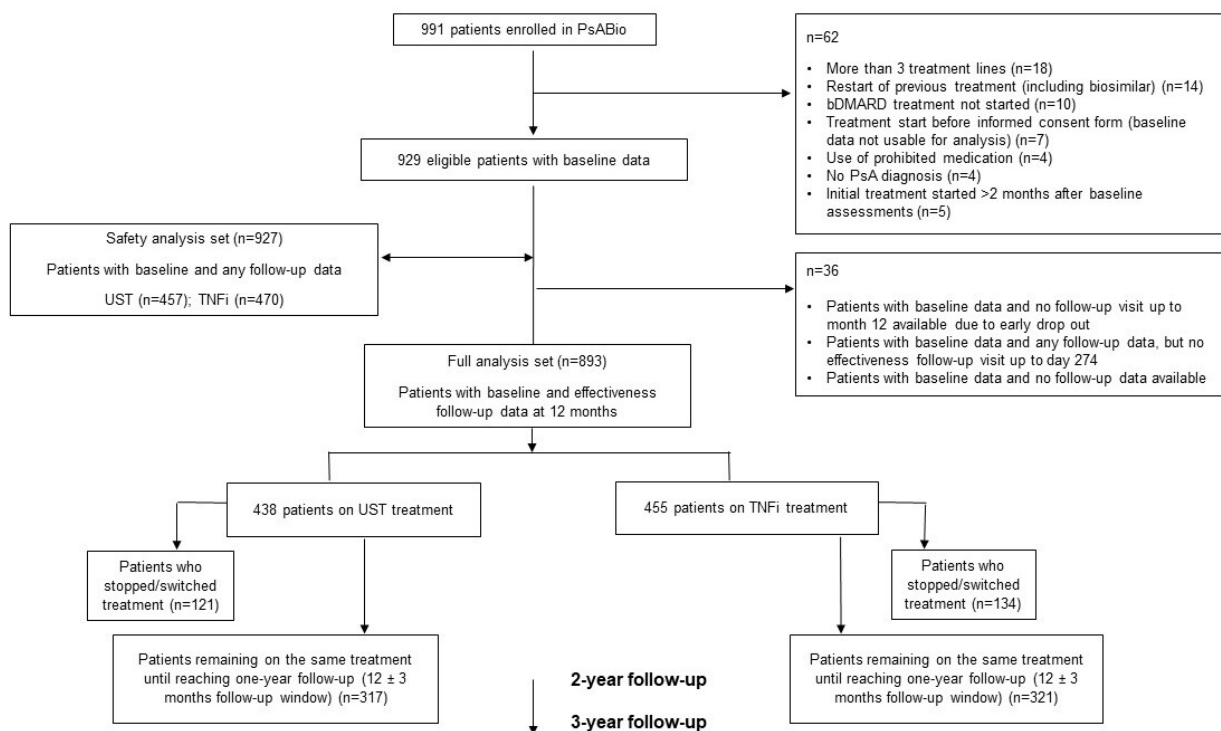


Table S1. TNFi (including biosimilars) started at baseline in the PsABio study effectiveness set)

TNFi (branded or biosimilar), n (%)	All lines (n=455)	First-line (n=251)	Second-line (n=149)	Third-line (n=55)
Etanercept	148/455 (32.5)	95/148 (64.2)	45/148 (30.4)	8/148 (5.4)
Adalimumab	115/455 (25.3)	63/115 (54.8)	42/115 (36.5)	10/115 (8.7)
Golimumab	86/455 (18.9)	51/86 (59.3)	27/86 (31.4)	8/86 (9.3)
Certolizumab	71/455 (15.6)	24/71 (33.8)	26/71 (36.6)	21/71 (29.6)
Infliximab	35/455 (7.7)	18/35 (51.4)	9/35 (25.7)	8/35 (22.9)

TNFi, tumour necrosis factor inhibitor.

Table S2. Previous bDMARD agent exposure (including biosimilars) of patients initiating second- or third-line treatment in PsABio (effectiveness set)

n (%)	UST cohort	TNFi cohort
Total	241	204
Adalimumab	79 (32.8)	64 (31.4)
Etanercept	74 (30.7)	60 (29.4)
Infliximab	29 (12.0)	33 (16.2)
Golimumab	31 (12.9)	16 (7.8)
Certolizumab	18 (7.5)	7 (3.4)
Ustekinumab	not allowed	14 (6.9)
Other	10 (4.1)	10 (4.9)

bDMARD, biological disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

Table S3. Observed duration of initial treatment line for ustekinumab- and TNFi-treated (including biosimilars) patients up to 1 year in the PsABio study (effectiveness set)

N, months (mean) [SD]	All lines	First-line	Second-line	Third-line
UST	438 (13.1) [3.5]	197 (13.5) [3.2]	151 (12.8) [3.6]	90 (12.5) [4.0]
TNFi (branded or biosimilar), any	455 (12.7) [4.2]	251 (13.1) [3.8]	149 (12.5) [4.4]	55 (11.1) [5.0]
Infliximab	35 (13.6) [3.4]	18 (14.2) [2.8]	9 (13.9) [2.3]	8 (11.8) [5.2]
Adalimumab	115 (12.2) [4.5]	63 (12.6) [4.2]	42 (12.0) [4.8]	10 (10.8) [5.3]
Golimumab	86 (13.9) [2.9]	51 (14.0) [2.8]	27 (13.9) [2.9]	8 (13.5) [4.3]
Etanercept	148 (12.4) [4.3]	95 (12.6) [4.0]	45 (11.8) [4.9]	8 (12.7) [3.3]
Certolizumab	71 (11.9) [4.8]	24 (13.0) [4.0]	26 (12.9) [4.5]	21 (9.5) [5.3]

Duration of treatment line is shown in months.

SD, standard deviation; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

Table S4. PsAID-12 scores by baseline characteristic subgroup

Mean (95% CI)	UST		TNFi	
	Baseline	Unadjusted change from baseline at 1 year (LOCF)	Baseline	Unadjusted change from baseline at 1 year (LOCF)
Biologic line				
First	5.51 (5.19; 5.82)	-2.14 (-2.49 ; -1.79)	5.44 (5.15; 5.72)	-2.41 (-2.72; -2.09)
Second	6.05 (5.69; 6.41)	-2.14 (-2.55 ; -1.72)	5.57 (5.19; 5.95)	-2.37 (-2.79; -1.94)
Third	5.84 (5.33; 6.35)	-1.81 (-2.45 ; -1.17)	5.34 (4.52; 6.15)	-1.89 (-2.62; -1.16)
Sex*				
Male	5.27 (4.95; 5.59)	-2.35 (-2.70 ; -1.99)	4.89 (4.56; 5.23)	-2.49 (-2.83; -2.15)
Female	6.14 (5.86; 6.43)	-1.86 (-2.20 ; -1.52)	5.95 (5.67; 6.23)	-2.20 (-2.53; -1.87)
Enthesitis				
Yes	5.95 (5.66; 6.24)	-2.19 (-2.51 ; -1.86)	5.89 (5.61; 6.17)	-2.65 (-2.98; -2.31)
No	5.51 (5.19; 5.83)	-1.98 (-2.36 ; -1.59)	4.99 (4.65; 5.32)	-2.02 (-2.35; -1.68)
Psoriasis BSA, %				
<3	5.66 (5.32; 6.00)	-1.60 (-2.03 ; -1.18)	4.97 (4.63; 5.31)	-1.89 (-2.25; -1.52)
3–10	5.44 (5.05; 5.83)	-2.16 (-2.59 ; -1.74)	5.78 (5.43; 6.14)	-2.99 (-3.38; -2.59)
>10	6.15 (5.70; 6.60)	-2.93 (-3.43 ; -2.43)	6.13 (5.55; 6.71)	-2.86 (-3.49; -2.23)
Joint involvement [†]				
Mono/oligoarticular	5.07 (4.56; 5.58)	-1.96 (-2.47 ; -1.45)	4.82 (4.38; 5.25)	-2.18 (-2.66; -1.70)
Polyarticular	5.98 (5.75; 6.22)	-2.21 (-2.51 ; -1.92)	5.78 (5.52; 6.04)	-2.47 (-2.75; -2.18)
FiRST score*				
<5	5.15 (4.87; 5.44)	-2.18 (-2.50 ; -1.87)	5.10 (4.83; 5.36)	-2.44 (-2.71; -2.16)
≥5	6.72 (6.43; 7.00)	-1.95 (-2.38 ; -1.53)	6.49 (6.15; 6.83)	-2.09 (-2.57; -1.61)

*At BL and 1 year, a clinically relevant difference was observed between female patients and patients with FiRST score ≥5 (chronic widespread pain) and male patients and those with FiRST score <5. [†]Polyarticular patients were significantly more impacted at BL, but not 1 year.

BSA, body surface area; CI, confidence interval; FiRST, Fibromyalgia Rapid Screening Tool; LOCF, last observation carried forward.

Table S5. Overview of adverse events frequency (ustekinumab versus TNFi)

n (%)	UST (n= 467)*	TNFi (n= 502)*
Patients with ≥1 AE	114 (24.4)	144 (28.7)
Patients with ≥1 drug related AE [†]	53 (11.3)	74 (14.7)
Patients with ≥1 SAE	21 (4.5)	17 (3.4)
Patients with ≥1 drug related SAE [†]	3 (0.6)	6 (1.2)
Patients with ≥1 severe adverse event	18 (3.9)	14 (2.8)
Patients with ≥1 AE leading to withdrawal of study drug	30 (6.4)	38 (7.6)
Patients with ≥1 drug related AE leading to withdrawal of study drug	21 (4.5)	29 (5.8)
Patients with ≥1 AE leading to permanent discontinuation of the study	4 (0.9)	6 (1.2)
Patients with ≥1 drug related AE leading to permanent discontinuation of the study	0	4 (0.8)
Patients with serious infections		
Pneumonia	0	3 (0.6)
Cellulitis	1 (0.2)	0
Skin infection	1 (0.2)	0
Staphylococcal bacteraemia	1 (0.2)	0
Malignancy (excluding non-melanoma skin cancer)	4 (0.9)	3 (0.6)
	Cutaneous T-cell lymphoma Parathyroid tumour Lung neoplasm Meningioma	Lung adenocarcinoma Myelodysplastic syndrome Renal oncocytoma
Non-melanoma skin cancer	1 (0.2)	2 (0.4)
	Bowen's disease	Basal cell carcinoma Squamous cell carcinoma
Cardiovascular AEs [‡]	2 (0.4)	6 (1.1)
	Extrasystoles	Atrial fibrillation

	Bradycardia	Cardiac flutter Supraventricular tachycardia Tachyarrhythmia Tachycardia Arrhythmia
Death	1 (0.2)	1 (0.2)

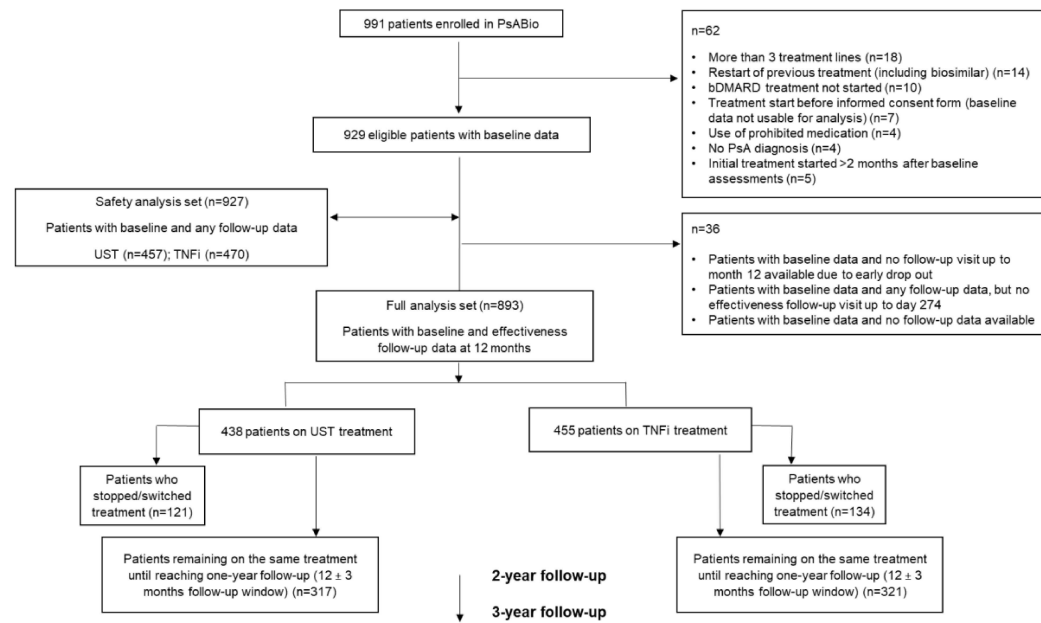
*AEs were summarised under the initial treatment line as well as under all treatments that started within a 91-day safety period after the initial treatment line prior to the AE. Therefore, the same patient could be assigned to both columns.

†Refers to AEs or SAEs that could be related to a biologic disease-modifying antirheumatic drug, according to study investigator.

*One TNFi-treated patient experienced 3 events (2 atrial fibrillation and 1 tachyarrhythmia) at 0–6 months. The same patient experienced 1 further event of atrial fibrillation at 6–12 months. All other events experienced by 1 patient each. Due to the observational nature of the study, no further information on the cardiac events could be retrieved.

AE, adverse event; SAE; serious adverse event.

Figure S1. Patient population flow diagram



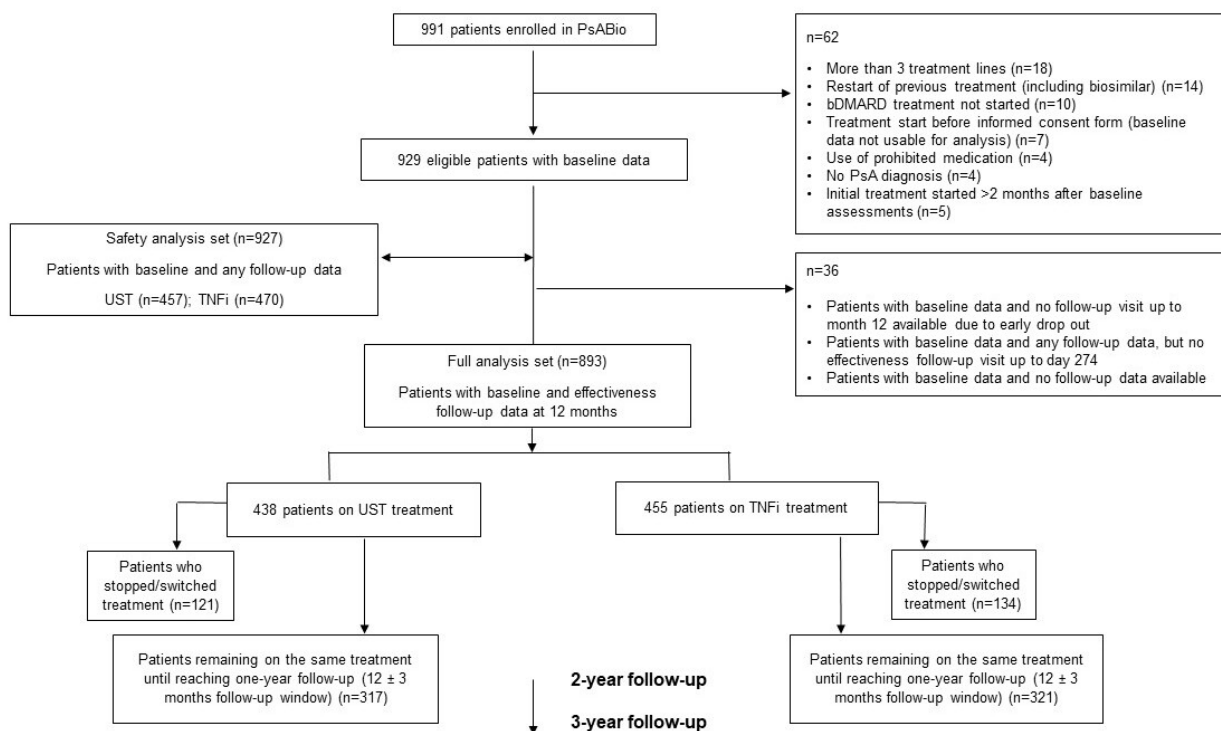


Table S1. TNFi (including biosimilars) started at baseline in the PsABio study effectiveness set)

TNFi (branded or biosimilar), n (%)	All lines (n=455)	First-line (n=251)	Second-line (n=149)	Third-line (n=55)
Etanercept	148/455 (32.5)	95/148 (64.2)	45/148 (30.4)	8/148 (5.4)
Adalimumab	115/455 (25.3)	63/115 (54.8)	42/115 (36.5)	10/115 (8.7)
Golimumab	86/455 (18.9)	51/86 (59.3)	27/86 (31.4)	8/86 (9.3)
Certolizumab	71/455 (15.6)	24/71 (33.8)	26/71 (36.6)	21/71 (29.6)
Infliximab	35/455 (7.7)	18/35 (51.4)	9/35 (25.7)	8/35 (22.9)

TNFi, tumour necrosis factor inhibitor.

Table S2. Previous bDMARD agent exposure (including biosimilars) of patients initiating second- or third-line treatment in PsABio (effectiveness set)

n (%)	UST cohort	TNFi cohort
Total	241	204
Adalimumab	79 (32.8)	64 (31.4)
Etanercept	74 (30.7)	60 (29.4)
Infliximab	29 (12.0)	33 (16.2)
Golimumab	31 (12.9)	16 (7.8)
Certolizumab	18 (7.5)	7 (3.4)
Ustekinumab	not allowed	14 (6.9)
Other	10 (4.1)	10 (4.9)

bDMARD, biological disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

Table S3. Observed duration of initial treatment line for ustekinumab- and TNFi-treated (including biosimilars) patients up to 1 year in the PsABio study (effectiveness set)

N, months (mean) [SD]	All lines	First-line	Second-line	Third-line
UST	438 (13.1) [3.5]	197 (13.5) [3.2]	151 (12.8) [3.6]	90 (12.5) [4.0]
TNFi (branded or biosimilar), any	455 (12.7) [4.2]	251 (13.1) [3.8]	149 (12.5) [4.4]	55 (11.1) [5.0]
Infliximab	35 (13.6) [3.4]	18 (14.2) [2.8]	9 (13.9) [2.3]	8 (11.8) [5.2]
Adalimumab	115 (12.2) [4.5]	63 (12.6) [4.2]	42 (12.0) [4.8]	10 (10.8) [5.3]
Golimumab	86 (13.9) [2.9]	51 (14.0) [2.8]	27 (13.9) [2.9]	8 (13.5) [4.3]
Etanercept	148 (12.4) [4.3]	95 (12.6) [4.0]	45 (11.8) [4.9]	8 (12.7) [3.3]
Certolizumab	71 (11.9) [4.8]	24 (13.0) [4.0]	26 (12.9) [4.5]	21 (9.5) [5.3]

Duration of treatment line is shown in months.

SD, standard deviation; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

Table S4. PsAID-12 scores by baseline characteristic subgroup

Mean (95% CI)	UST		TNFi	
	Baseline	Unadjusted change from baseline at 1 year (LOCF)	Baseline	Unadjusted change from baseline at 1 year (LOCF)
Biologic line				
First	5.51 (5.19; 5.82)	-2.14 (-2.49 ; -1.79)	5.44 (5.15; 5.72)	-2.41 (-2.72; -2.09)
Second	6.05 (5.69; 6.41)	-2.14 (-2.55 ; -1.72)	5.57 (5.19; 5.95)	-2.37 (-2.79; -1.94)
Third	5.84 (5.33; 6.35)	-1.81 (-2.45 ; -1.17)	5.34 (4.52; 6.15)	-1.89 (-2.62; -1.16)
Sex*				
Male	5.27 (4.95; 5.59)	-2.35 (-2.70 ; -1.99)	4.89 (4.56; 5.23)	-2.49 (-2.83; -2.15)
Female	6.14 (5.86; 6.43)	-1.86 (-2.20 ; -1.52)	5.95 (5.67; 6.23)	-2.20 (-2.53; -1.87)
Enthesitis				
Yes	5.95 (5.66; 6.24)	-2.19 (-2.51 ; -1.86)	5.89 (5.61; 6.17)	-2.65 (-2.98; -2.31)
No	5.51 (5.19; 5.83)	-1.98 (-2.36 ; -1.59)	4.99 (4.65; 5.32)	-2.02 (-2.35; -1.68)
Psoriasis BSA, %				
<3	5.66 (5.32; 6.00)	-1.60 (-2.03 ; -1.18)	4.97 (4.63; 5.31)	-1.89 (-2.25; -1.52)
3–10	5.44 (5.05; 5.83)	-2.16 (-2.59 ; -1.74)	5.78 (5.43; 6.14)	-2.99 (-3.38; -2.59)
>10	6.15 (5.70; 6.60)	-2.93 (-3.43 ; -2.43)	6.13 (5.55; 6.71)	-2.86 (-3.49; -2.23)
Joint involvement [†]				
Mono/oligoarticular	5.07 (4.56; 5.58)	-1.96 (-2.47 ; -1.45)	4.82 (4.38; 5.25)	-2.18 (-2.66; -1.70)
Polyarticular	5.98 (5.75; 6.22)	-2.21 (-2.51 ; -1.92)	5.78 (5.52; 6.04)	-2.47 (-2.75; -2.18)
FiRST score*				
<5	5.15 (4.87; 5.44)	-2.18 (-2.50 ; -1.87)	5.10 (4.83; 5.36)	-2.44 (-2.71; -2.16)
≥5	6.72 (6.43; 7.00)	-1.95 (-2.38 ; -1.53)	6.49 (6.15; 6.83)	-2.09 (-2.57; -1.61)

*At BL and 1 year, a clinically relevant difference was observed between female patients and patients with FiRST score ≥5 (chronic widespread pain) and male patients and those with FiRST score <5. [†]Polyarticular patients were significantly more impacted at BL, but not 1 year.

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