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Long-term effectiveness and persistence of ustekinumab and TNF inhibitors in patients with psoriatic arthritis: final 3-year results from the PsABio real-world study

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ABSTRACT

Objectives To evaluate real-world persistence and effectiveness of the IL-12/23 inhibitor, ustekinumab or a tumour necrosis factor inhibitor (TNFi) for psoriatic arthritis over 3 years.

Methods PsABio (NCT02627768), a prospective, observational study, followed patients with PsA prescribed first-line to third-line ustekinumab or a TNFi. Persistence and effectiveness (achievement of clinical Disease Activity for PSA (cDAPSA) low disease activity (LDA)/remission and minimal disease activity/very LDA (MDA/VLDA)) were assessed every 6 months. Safety data were collected over 3 years. Analyses to compare the modes of action were adjusted on baseline differences by propensity scores (PS).

Results In 895 patients (mean age 49.8 years, 44.7% males), at 3 years, the proportion of patients still on their initial treatments was similar with ustekinumab (49.9%) and TNFi (47.8%). No difference was seen in the risk of stopping/switching; PS-adjusted hazard ratio (95% CI) for stopping/switching ustekinumab versus TNFi was 0.87 (0.68 to 1.11). In the overall population, cDAPSA LDA/remission was achieved in 58.6%/31.4% ustekinumab-treated and 69.8%/45.0% TNFi-treated patients; PS-adjusted ORs (95% CI) were 0.89 (0.63 to 1.26) for cDAPSA LDA; 0.72 (0.50 to 1.05) for remission. MDA/VLDA was achieved in 41.4%/19.2% of ustekinumab-treated and 54.2%/26.9% of TNFi-treated patients with overlapping PS-adjusted ORs. A greater percentage of TNFi-treated patients achieved effectiveness outcomes. Both treatments exhibited good long-term safety profiles, although ustekinumab-treated patients had a lower rate of adverse events (AEs) versus TNFi.

Conclusion At 3 years, there was generally comparable persistence after ustekinumab or TNFi treatment, but AE rates were lower with ustekinumab.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psoriatic arthritis (PsA) is a heterogeneous disease, with patients in routine clinical practice not adequately represented in randomised controlled trials (RCTs). Although many RCTs have demonstrated efficacy and safety of biologics, real-world data comparing treatments with different mechanisms of action, particularly over the long term, are lacking.

⇒ Published 6-month and 1-year results from the PsABio real-world observational study demonstrated similar persistence and effectiveness of ustekinumab and tumour necrosis factor inhibitors in PsA treatment.

WHAT THIS STUDY ADDS

⇒ This final 3-year analysis from the PsABio study provides long-term data and shows that treatment persistence was similar and around 50% for both modes of action. A similar proportion of patients in both treatment groups achieved the effectiveness outcomes and both treatments showed acceptable long-term safety profiles. Factors impacting treatment persistence included skin psoriasis, treatment line and concomitant use of methotrexate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These 3-year results from the PsABio study provide long-term real-world evidence on effectiveness, safety and persistence with biologics in PsA treatment, which may help inform treatment decisions in clinical practice.

INTRODUCTION

Psoriatic arthritis (PsA) is a disabling disease affecting approximately 20%–30% of patients with psoriasis.[1–3] Patients can present with musculoskeletal involvement, including arthritis, enthesitis and dactylitis.[2] Comorbidities, such as cardiovascular disease and metabolic syndrome, may render patients prone to experiencing adverse events (AEs) during treatment.[4] Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetics (tsDMARDs) and biologicals (bDMARDs).[5] Consistent with the role of interleukin (IL)−12/IL-23/IL-17 in the pathogenesis

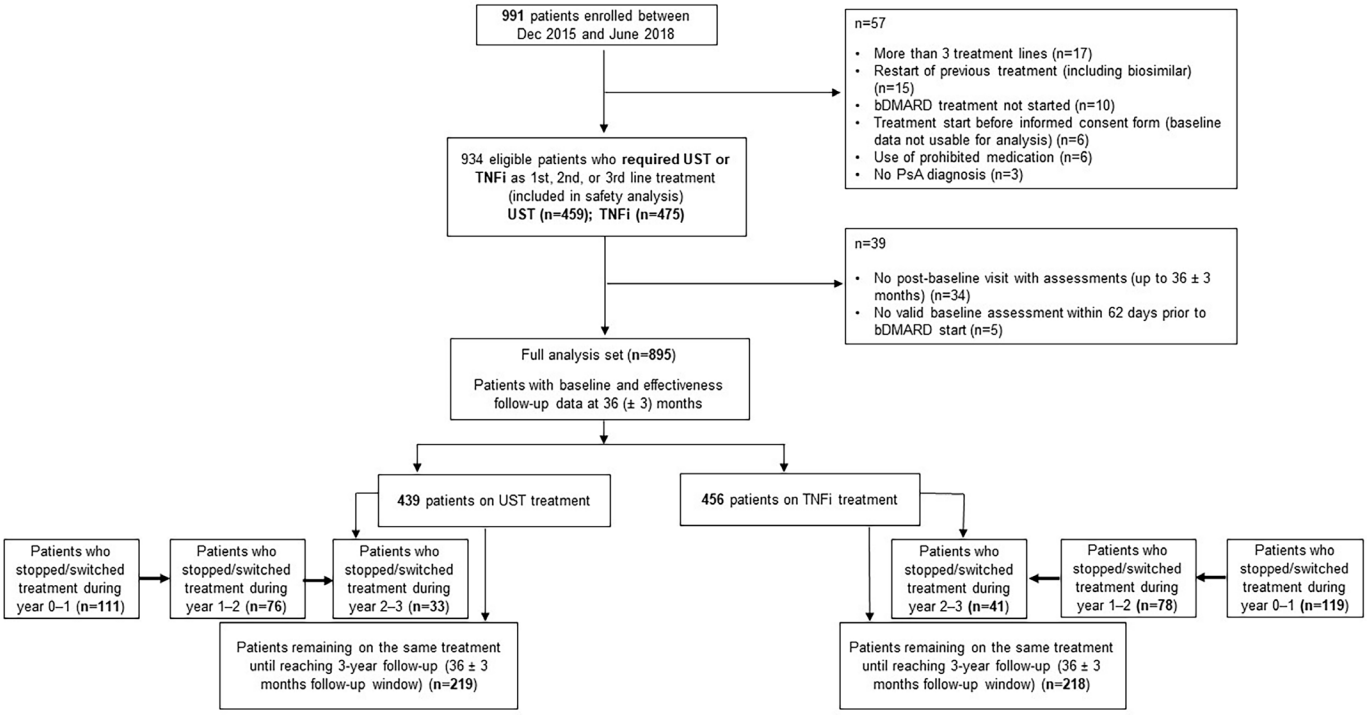

Figure 1 Patient population flow diagram.
bDMARD, biological disease-modifying antirheumatic drug; PSA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor: UST, ustekinumab.

of PsA,[6–8] bDMARDs targeting IL-12/IL-23 (p40), IL-23 (p19) and IL-17A, as well as tumour necrosis factor inhibitors (TNFi), have been approved for the treatment of PsA.[8–10]

The ultimate goal of PsA therapy is to achieve the lowest possible disease activity, defined by composite measures such as the clinical Disease Activity Index for PSA (cDAPSA) and minimal disease activity/very low disease activity (MDA/VLDA).[11–14] Treatment persistence is of critical importance for optimisation of symptom remission and functional capacity and to help reduce healthcare costs.[15] Conversely, poor persistence can lead to suboptimal outcomes.[15 16]

Ustekinumab, a fully human immunoglobulin G1 monoclonal antibody that blocks the p40 subunit of IL-23,[10 17] was the first licensed non-TNFi bDMARD therapy[18 19] that demonstrated efficacy on joints and skin, and an acceptable safety profile in patients with PsA in two phase 3 placebo-controlled trials—PSUMMIT 1[18] and PSUMMIT 2.[19] Although clinical trials provide valuable efficacy and safety data, patients in clinical trials may not represent the broader profile of patients in daily clinical practice and the results are therefore not always applicable in routine clinical care.[20 21]

Real-world and randomised controlled trial data on comparisons between treatments with different modes of action are lacking in PsA.[22] The 6-month and 1-year data from the 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 high baseline clinical disease activity and chronic widespread pain were shown to negatively influence treatment response.[23 24] Here, we present the final 3-year data on persistence, clinical effectiveness and safety from the PsABio study, aiming to provide a long-term perspective on these important clinical aspects.

METHODS

Study design

PsABio (NCT02627768) is a multinational, prospective, observational study of patients with PsA, designed to evaluate the persistence, effectiveness and safety of ustekinumab and TNFi as first-line to third-line in patients with PsA. The choice of bDMARD therapy was made by the treating rheumatologist, reflecting real-world clinical practice. The study duration per participant was up to 3 years, with follow-up twice yearly. This final, 3-year analysis reports comparative drug persistence data, extended effectiveness outcomes of achievement of cDAPSA LDA/remission and MDA/VLDA, as well as safety data.

Due to the COVID-19 pandemic and consequent impediments to seeing patients routinely, the study was closed prematurely, resulting in 63 patients (7.0%) not being able to reach the minimum of 1005 days for a 3-year assessment on initial treatment due to late enrolment.

Patients

Adults aged ≥18 years with PsA, starting ustekinumab or any approved TNFi (including biosimilars) as first-line, second-line or third-line treatment, were included.

Assessments

Treatment persistence

Persistence was defined as the time between initiation of first in-study bDMARD until last dose of that bDMARD plus one dispensing interval or stop/switch to another bDMARD, or study withdrawal (whichever occurred first). The focus is on the persistence of initial treatment, not subsequent treatments.

cDAPSA and MDA/VLDA

cDAPSA was calculated as described previously, with scores ≤13 and ≤4 denoting cDAPSA LDA and remission,

Table 1 Baseline demographics, clinical characteristics and comorbidities of overall patients (n=895) and remainers (n=437) (effectiveness set)

Mean (SD) (95% CI)/N (%) (95% CI)	UST overall (n=439)	TNFi overall (n=456)	UST remainers (n=219)	TNFi remainers (n=218)
Age, years (SD)	**51.1 (12.5) (49.9 to 52.2)**	**48.5 (12.6) (47.3 to 49.6)**	**51.5 (13.0) (49.8 to 53.2)**	**46.7 (12.7) (45.0 to 48.4)**
Male, n (%)	192 (43.7) (39.0 to 48.5)	208 (45.6) (41.0 to 50.3)	106 (48.4) (41.6 to 55.2)	122 (56.0) (49.1 to 62.7)
Female, n (%)	247 (56.3) (51.5 to 61.0)	248 (54.4) (49.7 to 59.0)	113 (51.6) (44.8 to 58.4)	96 (44.0) (37.3 to 50.9)
BMI, kg/m^2 (SD)	28.6 (6.2) (28.0 to 29.2)	27.8 (5.3) (27.2 to 28.3)	28.9 (6.4) (28.0 to 29.8)	27.1 (5.0) (26.5 to 27.8)
Time since initial diagnosis, years (SD)	7.5 (8.1) (6.7 to 8.3)	6.2 (6.6) (5.6 to 6.9)	7.7 (8.5) (6.5 to 8.8)	6.4 (6.7) (5.5 to 7.4)
Line of bDMARD treatment, n (%)				
First line	**198 (45.1) (40.4 to 49.9)**	**251 (55.0) (50.3 to 59.7)**	109 (49.8) (43.0 to 56.6)	129 (59.2) (52.3 to 65.8)
Second line	151 (34.4) (30.0 to 39.0)	150 (32.9) (28.6 to 37.4)	71 (32.4) (26.3 to 39.1)	69 (31.7) (25.5 to 38.3)
Third line	**90 (20.5) (16.8 to 24.6)**	**55 (12.1) (9.2 to 15.4)**	39 (17.8) (13.0 to 23.5)	20 (9.2) (5.7 to 13.8)
csDMARD exposure, n (%)				
Previous exposure	385 (87.7) (84.3 to 90.6)	422 (92.5) (89.7 to 94.8)	**189 (86.3) (81.0 to 90.6)**	**208 (95.4) (91.7 to 97.8)**
Ongoing exposure	**175 (39.9) (35.3 to 44.6)**	**252 (55.3) (50.6 to 59.9)**	**81 (37.0) (30.6 to 43.8)**	**125 (57.3) (50.5 to 64.0)**
MTX exposure ongoing	**132 (30.1) (25.8 to 34.6)**	**193 (42.3) (37.7 to 47.0)**	**55 (25.1) (19.5 to 31.4)**	**103 (47.2) (40.5 to 54.1)**
Other treatment exposure ongoing, n (%)				
NSAIDs	**240 (54.7) (49.9 to 59.4)**	**313 (68.6) (64.2 to 72.9)**	130 (59.4) (52.5 to 65.9)	152 (69.7) (63.2 to 75.7)
Steroids	144 (32.8) (28.4 to 37.4)	156 (34.2) (29.9 to 38.8)	69 (31.5) (25.4 to 38.1)	71 (32.6) (26.4 to 39.2)
PsA characteristics, n (%)				
Axial symptoms*	12 (2.7) (1.4 to 4.7)	11 (2.4) (1.2 to 4.3)	7 (3.2) (1.3 to 6.5)	7 (3.2) (1.3 to 6.5)
Oligoarticular†	96 (22.4) (18.6 to 26.7)	129 (29.0) (24.8 to 33.4)	60 (27.8) (21.9 to 34.3)	66 (31.0) (24.9 to 37.7)
Polyarticular‡	286 (66.8) (62.1 to 71.3)	284 (63.8) (59.2 to 68.3)	132 (61.1) (54.3 to 67.7)	135 (63.4) (56.5 to 69.9)
Dactylitis, n (%)	74 (18.1) (14.5 to 22.2)	90 (22.6) (18.6 to 27.0)	46 (21.3) (16.0 to 27.4)	62 (29.1) (23.1 to 35.7)
Enthesitis, n (%)	194 (47.8) (42.8 to 52.8)	204 (50.9) (45.9 to 55.9)	109 (50.7) (43.8 to 57.6)	106 (48.8) (42.0 to 55.7)
BSA, n (%)				
Clear/almost clear	106 (29.4) (24.7 to 34.4)	117 (32.8) (27.9 to 37.9)	43 (21.3) (15.9 to 27.6)	58 (29.4) (23.2 to 36.3)
<3% but not clear/almost clear	36 (10.0) (7.1 to 13.5)	54 (15.1) (11.6 to 19.3)	18 (8.9) (5.4 to 13.7)	36 (18.3) (13.1 to 24.4)
3 to 10%	124 (34.3) (29.5 to 39.5)	133 (37.3) (32.2 to 42.5)	72 (35.6) (29.0 to 42.7)	72 (36.5) (29.8 to 43.7)
>10%	**95 (26.3) (21.8 to 31.2)**	**53 (14.8) (11.3 to 19.0)**	**69 (34.2) (27.6 to 41.1)**	**31 (15.7) (11.0 to 21.6)**
cDAPSA (SD)	30.4 (20.1) (28.4 to 32.5)	29.1 (18.6) (27.2 to 31.0)	30.3 (21.7) (27.3 to 33.3)	30.3 (20.8) (27.4 to 33.2)
Swollen joint count (SD)	5.8 (8.1) (5.0 to 6.6)	5.9 (7.6) (5.2 to 6.7)	6.1 (8.5) (4.9 to 7.2)	7.0 (8.7) (5.8 to 8.3)
Tender joint count (SD)	12.3 (12.4) (11.1 to 13.6)	11.2 (10.6) (10.1 to 12.3)	12.7 (13.6) (10.8 to 14.6)	11.8 (11.6) (10.1 to 13.4)
CRP, mg/dL (SD)	1.3 (2.9) (1.0 to 1.7)	1.4 (2.6) (1.1 to 1.7)	1.7 (3.8) (1.1 to 2.3)	1.4 (1.9) (1.1 to 1.6)
Concurrent comorbidities, n (%)	**295 (67.2) (62.6 to 71.6)**	**261 (57.2) (52.6 to 61.8)**	**144 (65.8) (59.1 to 72.0)**	**113 (51.8) (45.0 to 58.6)**
Cardiometabolic disease and obesity§	72 (16.4) (13.1 to 20.2)	61 (13.4) (10.4 to 16.8)	41 (18.7) (13.8 to 24.5)	22 (10.1) (6.4 to 14.9)
Gastrointestinal disease	40 (9.1) (6.6 to 12.2)	40 (8.8) (6.3 to 11.8)	18 (8.2) (4.9 to 12.7)	13 (6.0) (3.2 to 10.0)
Depression	41 (9.3) (6.8 to 12.5)	29 (6.4) (4.3 to 9.0)	20 (9.1) (5.7 to 13.8)	14 (6.4) (3.6 to 10.5)
Anxiety or panic disorders	18 (4.1) (2.4 to 6.4)	18 (3.9) (2.4 to 6.2)	7 (3.2) (1.3 to 6.5)	9 (4.1) (1.9 to 7.7)
Neurological disease	6 (1.4) (0.5 to 3.0)	2 (0.4) (0.1 to 1.6)	2 (0.9) (0.1 to 3.3)	0
Malignancies	9 (2.1) (0.9 to 3.9)	6 (1.3) (0.5 to 2.8)	5 (2.3) (0.7 to 5.2)	2 (0.9) (0.1 to 3.3)
Chronic hepatitis	10 (2.3) (1.1 to 4.1)	1 (0.2) (0.0 to 1.2)	7 (3.2) (1.3 to 6.5)	0
Non-alcoholic fatty liver disease	18 (4.1) (2.4 to 6.4)	13 (2.9) (1.5 to 4.8)	11 (5.0) (2.5 to 8.8)	6 (2.8) (1.0 to 5.9)
Chronic obstructive pulmonary disease	9 (2.1) (0.9 to 3.9)	11 (2.4) (1.2 to 4.3)	5 (2.3) (0.7 to 5.2)	4 (1.8) (0.5 to 4.6)

Variables in bold indicate non-overlapping 95% CIs.
*Pure axial PsA is defined as having only axial symptoms (presence of axial disease declared by the treating rheumatologist without requirement for imaging).
†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.
‡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.
§Hypertension, myocardial infarction, angina pectoris, congestive heart failure, stroke or transient ischaemic attack, peripheral vascular disease, hyperlipidaemia, type 1 or 2 diabetes plus BMI >30 kg/m^2.
bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; SJC66, swollen joint count for 66 joints; TJC68, tender joint count for 68 joints; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

respectively.[13 25] MDA and VLDA were based on attaining five and seven, respectively, out of seven domain cut-offs, as described previously.[26] The focus was on effectiveness of initial treatment, not subsequent treatments.

Patient-reported outcomes and assessments

The following were measured: the Health Assessment Questionnaire Disability Index; patient global assessment visual analogue scale (VAS) and patient pain VAS; 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) questionnaire[27]; EuroQol 5 Dimensions 3 Level plus VAS[28]; Fibromyalgia Rapid Screening Tool (baseline only)[29]; Bath Ankylosing Spondylitis Disease Activity Index[30] and Work Productivity and Activity Impairment questionnaires.[31]

Safety

AEs from all treatment courses throughout the study were collected by the clinical team at each visit and by spontaneous

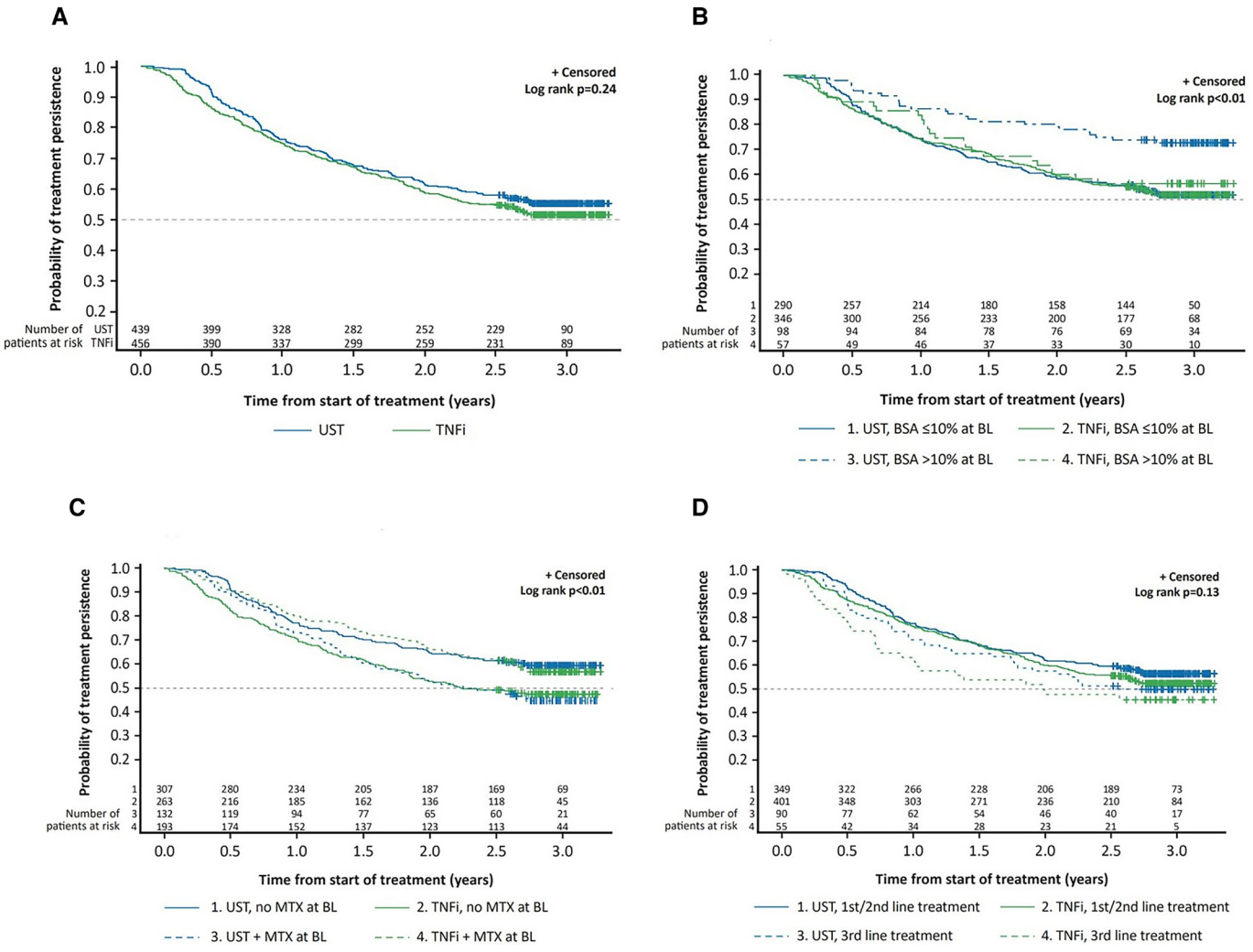

Figure 2 Kaplan-Meier plots of treatment persistence with ustekinumab versus TNFi for: (A) overall; and for baseline (B) extent of skin involvement; (C) presence/absence of MTX co-therapy; (D) treatment line.
BSA, body surface area; BL, baseline; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

reporting by patients until end of study (36±3 months)/study termination. Non-malignant AEs were assigned to initial or subsequent treatments based on the respective risk windows (defined as the time between treatment initiation and 91 days after treatment stop) in which they were reported. Hence, for a patient on several treatment cohorts, AEs were recorded as covering all treatments. All malignancies occurring from study start until end of study, independent of treatment stop, were included. As a sensitivity analysis, a 1-year lag time from initiating treatment was applied for incidence of malignancies within the different treatment groups.

Statistical analyses

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

Populations

Analyses of persistence and effectiveness were 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 36 visit window, which is up to 1200 days follow-up (including patients who switched/stopped treatment due to AEs, lack of efficacy or other reasons). Endpoint analyses used the last observation carried forward (LOCF) for patients whose last available assessment was earlier than 1005 days and for those whose last visit was cancelled due to study stop. A 36-month LOCF endpoint was created in addition to the observed case analysis. The safety set included all patients with baseline and any available follow-up data.

Analyses

As the analyses were exploratory, no predefined hypotheses were tested and no adjustment for multiplicity was applied; between-group differences and changes over time were described using 95% CIs.[32] Persistence data for ustekinumab and TNFi are presented as Kaplan-Meier (KM) curves and compared using Cox regression analysis, including propensity score (PS) to adjust for baseline imbalanced covariates; this included sex, bDMARD line, body surface area (BSA), enthesitis, PsA axial symptoms, PsA category and PsAID-12 score. To investigate their interaction with the PS-adjusted treatment effect, the Cox model was expanded with several factors, among which were concomitant methotrexate (MTX) use and skin involvement. HRs, with 95% CI, are presented.

Observed effectiveness outcomes (MDA including VLDA/VLDA and cDAPSA LDA including remission/remission) were summarised at each assessment timepoint by proportion of

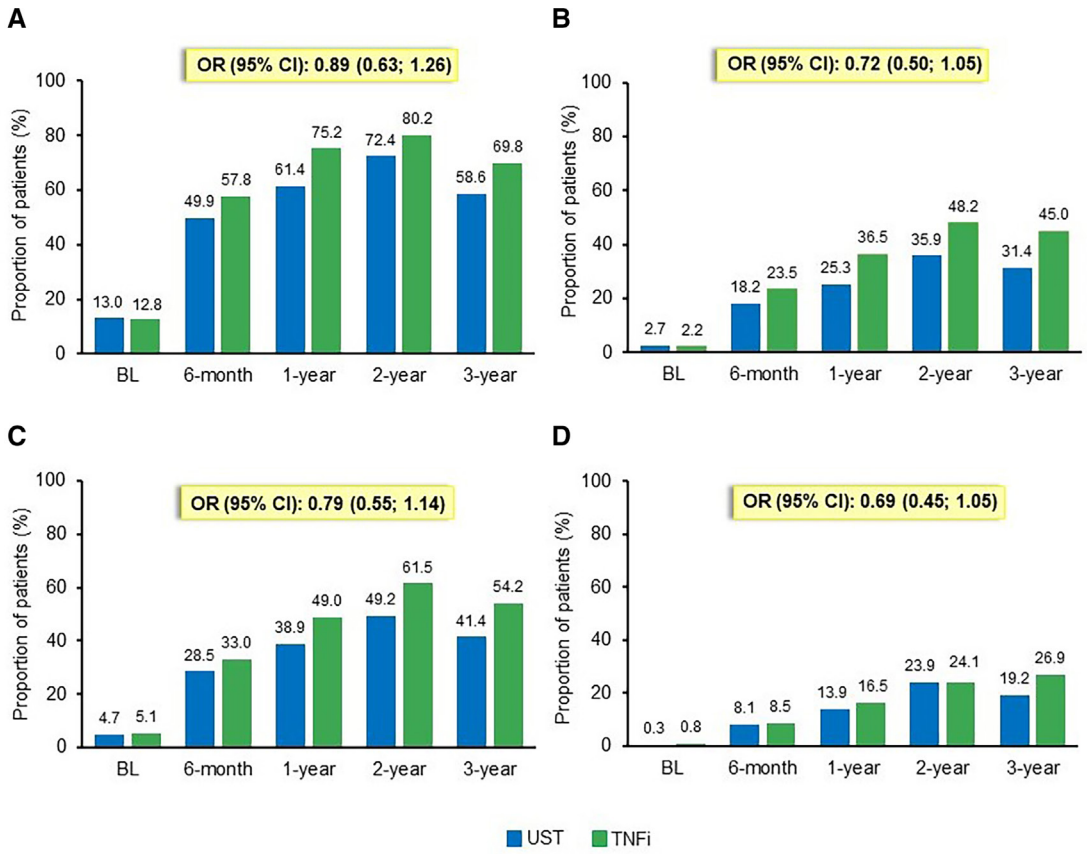

Figure 3 Observed proportions of patients and PS-adjusted ORs (95% CI) achieving: (A) cDAPSA LDA*; (B) cDAPSA remission; (C) MDA; and (D) VLDA with ustekinumab or TNFi up to 3 years (overall LOCF analysis).
The overall analysis included patients switching/stopping their original treatment during the 3-year observation period. The PS-adjusted ORs resulting from the overall analysis included non-response imputation in case of stop/switch initial treatment. *Includes remission.
BL, baseline; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; LOCF, last observation carried forward; LDA, low disease activity; MDA; minimal disease activity; PS, propensity score; TNFi, tumour necrosis factor inhibitors; UST, ustekinumab; VLDA, very low disease activity.

patients achieving the outcomes and compared using logistic regression, including PS adjustment for baseline imbalanced covariates. Cohort comparison was done among patients who stayed on their initial ustekinumab or TNFi treatment until the end of study (remainer analysis), and who switched/stopped their original treatment, imputed as non-responders (overall analysis). Patients who were not able to reach the 3-year follow-up due to late enrolment, or due to sponsor study termination, were included as remainers if they were still on their initial treatment at the time the study was stopped. Descriptive statistics included the LOCF endpoint created in case of missing 3-year effectiveness data, for example, due to COVID-19.

In the persistence analysis (time to stopping first study drug), patients who were lost to follow-up but remained on their initial treatment were included as censored observations. Patients who were lost to follow-up after having completed at least 1005 days on their initial treatment were included as remainers.

RESULTS

Patient disposition

In total, 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. Of 991 patients, 57 were not eligible and were excluded from the study. Therefore, 934 patients were included in the safety analysis (ustekinumab n=459; TNFi n=475); of these, 14 (1.5%) terminated study participation due to the COVID-19 pandemic. Of 934 patients, 895 (ustekinumab n=439; TNFi n=456) had baseline and follow-up effectiveness data up to 3 years and were included in the overall effectiveness analysis set; 219 (49.9%) ustekinumab-treated and 218 (47.8%) TNFi-treated patients were included in the remainer analysis (figure 1).

Demographics, baseline/clinical characteristics

In both the overall and remainer groups, ustekinumab and TNFi groups had clinically relevant differences in baseline 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 MTX and NSAIDs than those in the TNFi group. More patients in the ustekinumab group had severe skin involvement compared with the TNFi group, as assessed by BSA at baseline (table 1).

Persistence

Throughout the 3-year study period, 83.6%, 61.5% and 49.9% of patients stayed on ustekinumab, and 80.0%, 62.1% and 47.8% of patients stayed on TNFi for 1, 2 or 3 or more years, respectively. Observed data (KM curve) showed similar probability of stopping/switching of initial treatment in ustekinumab and TNFi cohorts (figure 2A). Mean (95% CI) duration of initial treatment was 24.7 (23.5 to 25.8) months for ustekinumab and 24.1 (22.9 to 25.3) months for TNFi; the treatment duration in remainers was 35.3 (35.0 to 35.6) for both cohorts. After

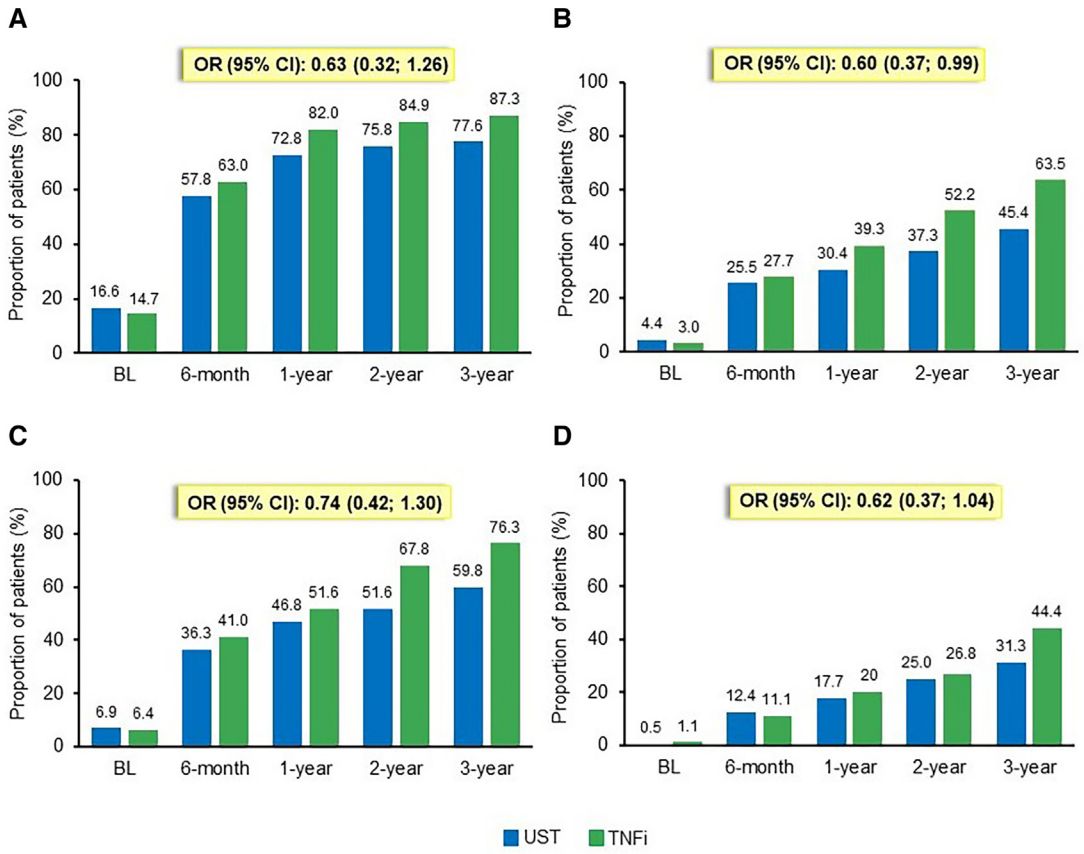

Figure 4 Observed proportions of patients and PS-adjusted ORs (95% CI) achieving: (A) cDAPSA LDA*; (B) cDAPSA remission; (C) MDA; and (D) VLDA with ustekinumab or TNFi up to 3 years (remainer LOCF analysis).
Results reflect 3-year LOCF data from assessments for patients still under initial treatment at 3 years. *Includes remission.
BL, baseline; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; LOCF, last observation carried forward; LDA, low disease activity; MDA; minimal disease activity; PS, propensity score; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

PS adjustment for baseline imbalances, no difference in the risk of stopping/switching was detected for ustekinumab versus TNFi; HR (95%CI) 0.87 (0.68 to 1.11). Reasons for stopping/switching were related to safety and tolerability in 17% (ustekinumab) and 24% (TNFi) of patients, and effectiveness in 83% (ustekinumab) and 76% (TNFi) of stopping/switching patients. Duration of initial treatment was most marked for patients with severe skin involvement (BSA>10%) on ustekinumab treatment, versus patients with mild (BSA <3%) or moderate (BSA 3%–10%) skin involvement. Patients with severe skin involvement (BSA >10%) treated with ustekinumab were on initial treatment for longer than patients with severe skin involvement on TNFi; HR (risk of stopping/switching) for ustekinumab (BSA >10%) vs TNFi (BSA>10%) was 0.48 (0.27; 0.88) (figure 2B). Of ustekinumab-treated and TNFi-treated patients with severe skin involvement (BSA >10%), 72.6% and 58.5%, respectively, were persistent with their treatment for 3 years. Mean duration of treatment in the ustekinumab with severe skin involvement subgroup (figure 2B) was longer than the overall group (figure 2A). Furthermore, skin improvement (>10%) at 1 year was associated with a higher persistence than no skin improvement (data not shown). Of the ustekinumab-treated and TNFi-treated patients with mild-to-moderate skin involvement (BSA <10%), 27.4% and 41.5%, respectively, persisted with treatment for 3 years. After PS adjustment, no difference in the risk of stopping/switching was detected for ustekinumab (BSA <3%) vs TNFi (BSA <3%) in patients with mild skin involvement; HR 1.09 (0.77 to 1.55). No difference in the risk of stopping/switching was observed for patients with moderate skin involvement (ustekinumab (BSA 3%–10%) vs TNFi (BSA 3%–10%); HR 0.97 (95% CI 0.63 to 1.49)).

Treatment with ustekinumab monotherapy (without MTX) was associated with reduced risk of stopping/switching compared with TNFi monotherapy; HR 0.65 (0.48 to 0.89). Treatment with TNFi combination therapy (with MTX) was associated with reduced risk of stopping/switching compared with ustekinumab combination therapy; HR 1.35 (0.93 to 1.95). Patients on ustekinumab monotherapy and TNFi combination therapy had comparable persistence (figure 2C). Patients on ustekinumab monotherapy persisted longer than patients on ustekinumab combination therapy, while the opposite was observed in the TNFi group. Better drug persistence was observed in patients with first-line/second-line bDMARD treatment than in patients with third-line treatment. TNFi third-line was associated with shorter persistence than all other treatment lines, including ustekinumab third-line; HR 0.82 (0.68 to 1.11) (figure 2D).

Effectiveness

At 3 years, in the overall analysis, the mean (95% CI) decrease in cDAPSA from baseline was –15.9 (–18.0 to –13.7) for ustekinumab and –18.4 (–20.4 to –16.3) for TNFi. In the overall population, cDAPSA LDA/remission was achieved in 58.6%/31.4% of ustekinumab-treated and 69.8%/45.0% of TNFi-treated patients; PS-adjusted ORs (95% CI) were 0.89 (0.63 to 1.26) for cDAPSA LDA and 0.72 (0.50 to 1.05) for remission (figure 3).

Table 2 Overview of adverse events (safety set)

n (%) (95% CI)	UST (n=494)*	TNFi (n=557)*
Patients with ≥1 AE	171 (34.6) (30.4 to 39.0)	221 (39.7) (35.6 to 43.9)
Patients with ≥1 bDMARD-related AE†	84 (17.0) (13.8 to 20.6)	121 (21.7) (18.4 to 25.4)
Patients with ≥1 SAE	31 (6.3) (4.3 to 8.8)	40 (7.2) (5.2 to 9.7)
Patients with ≥1 bDMARD-related SAE†	7 (1.4) (0.6 to 2.9)	12 (2.2) (1.1 to 3.7)
Patients with ≥1 AE leading to withdrawal of study drug	43 (8.7) (6.4 to 11.5)	59 (10.6) (8.2 to 13.5)
Patients with ≥1 bDMARD-related AE leading to withdrawal of study drug	32 (6.5) (4.5 to 9.0)	50 (9.0) (6.7 to 11.7)
Patients with ≥1 AE leading to permanent discontinuation from the study	3 (0.6) (0.1 to 1.8)	8 (1.4) (0.6 to 2.8)
Patients with ≥1 bDMARD-related AE leading to permanent discontinuation from the study	2 (0.4) (0.0 to 1.5)	6 (1.1) (0.4 to 2.3)
Patients with ≥1 AE leading to death	1 (0.2) (0.0 to 1.0)	1 (0.2) (0.0 to 1.0)
Patients with ≥1 serious or opportunistic infections	6 (1.2) (0.4 to 2.6)	5 (0.9) (0.3 to 2.1)
COVID-19	1 (0.2) (0.0 to 1.1)	0
Erysipelas	1 (0.2) (0.0 to 1.1)	0
Pneumonia	1 (0.2) (0.0 to 1.1)	1 (0.2) (0.0 to 1.0)
Pyelonephritis	1 (0.2) (0.0 to 1.1)	0
Bronchitis	0	1 (0.2) (0.0 to 1.0)
Diverticulitis	0	1 (0.2) (0.0 to 1.0)
Influenza	0	1 (0.2) (0.0 to 1.0)
Pleurisy	0	1 (0.2) (0.0 to 1.0)
Postoperative wound infection	1 (0.2) (0.0 to 1.1)	0
Skin infection	1 (0.2) (0.0 to 1.1)	0
Patients with ≥1 cardiac AE	6 (1.2) (0.4 to 2.6) Acute myocardial infarction Acute coronary syndrome Aortic valve stenosis Bradycardia Cardiac arrest Extrasystoles	10‡ (1.8) (0.9 to 3.3) Atrial fibrillation Myocardial infarction Acute myocardial infarction Myocardial ischaemia Arrhythmia Cardiac flutter Palpitations Supraventricular tachycardia Tachyarrhythmia Tachycardia Ventricular extrasystoles

*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. Due to overlapping risk windows, the sum of 'n' numbers for ustekinumab and TNFi groups is greater than 934 patients included in the safety set.
†Refers to AEs or SAEs that could be related to a bDMARD, according to study investigator.
‡One patient had more than one condition listed.
AE, adverse event; bDMARD, biological disease-modifying antirheumatic drug; SAE, serious AE; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

PS-adjusted ORs (95% CI) point towards a similarity of effectiveness between the cohorts. The MDA/VLDA achievements followed a similar pattern to what is described above, where MDA/VLDA was achieved in 41.4%/19.2% of ustekinumab-treated and 54.2%/26.9% of TNFi-treated patients with overlapping PS-adjusted ORs. PS-adjusted ORs (95% CI) were 0.79 (0.55 to 1.14) for MDA and 0.69 (0.45 to 1.05) for VLDA (figure 3). While ORs for achieving treatment targets were overlapping, a numerically higher percentage of TNFi-treated patients achieved treatment targets. The remainer analysis showed similar results (figure 4).

In looking at swollen joint count in isolation, overall, ustekinumab and TNFi patients had comparable improvements in swollen joint count at both 1 and 3 years of treatment, with both treatments appearing to be effective. A similar trend was observed in patients in the remainer groups of both treatments (online supplemental table 1). The percentage of patients with enthesitis decreased from baseline after both 1 and 3 years of either ustekinumab or TNFi treatment. Both treatment groups had comparable effectiveness in both the overall and remainer analyses (online supplemental figure 1). After 1 and 3 years, the percentage of patients with dactylitis decreased from baseline following either ustekinumab or TNFi treatment. Both ustekinumab and TNFi treatment led to comparable decreases in the percentages of patients with dactylitis in both overall and remainer analyses (online supplemental figure 1).

Safety

At least one (non-neoplasm) AE was recorded in 34.6% of ustekinumab-treated and 39.7% of TNFi-treated patients, with 6.3% and 7.2%, respectively, recording at least one serious AE (SAE; table 2). In total, five patients in both arms reported COVID-19 infection; one patient in the ustekinumab group and none in the TNFi group reported serious COVID-19 infection. The low numbers of serious COVID-19 infections are likely due to issues with testing at the start of the pandemic and mild cases of COVID-19 being unreported. During follow-up years 2 and 3, malignancies were recorded in 3/494 (0.6%) ustekinumab and 4/557 (0.7%) TNFi patients when a lag time of 1 year was applied (table 3). Ustekinumab-treated patients had a lower rate of clinically relevant AEs versus TNFi-treated patients in several subgroups defined by baseline characteristics (figure 5A). While no clinically relevant differences were detected for SAEs (figure 5B), the rate of infections was lower with ustekinumab versus TNFi for the overall group and for some subgroups (figure 5C).

DISCUSSION

The long-term results from the prospective, non-interventional, multinational PsABio study provide comparative real-world data on treatment persistence, effectiveness and safety of biological therapy in patients with PsA. Overall, for ustekinumab and TNFi treatments, comparable percentages of patients persisted for 1, 2 or 3 or more years, respectively.

While there were no notable differences in persistence between the ustekinumab and TNFi groups, differences were observed in the underlying rationales for stopping/switching. More patients in the TNFi group stopped/switched treatments due to reasons

Table 3 Malignancies in the PsABio population distinguished by time period since treatment initiation (safety set)

	UST			TNFi		
	0–6 months (n=457)	7–12 months (n=467)	>12 months* (n=494)	0–6 months (n=489)	7–12 months (n=502)	>12 months* (n=557)
n (%)	3 (0.6)	2 (0.4)	3 (0.6)	2 (0.4)	3 (0.6)	4 (0.7)
Events	Cutaneous T-cell lymphoma Parathyroid tumour Bowen's disease	Lung neoplasm Meningioma	Colon cancer Malignant neoplasm of eye Prostate cancer	Lung adenocarcinoma Myelodysplastic syndrome	Renal oncocytoma Basal cell carcinoma Squamous cell carcinoma	Bladder neoplasm Colon cancer Malignant urinary tract neoplasm Squamous cell carcinoma

The total number of patients is higher than the number in the full analysis set because the same patients were included several times for adverse event evaluation if they were switchers.
*Usually only malignancies diagnosed after a lag time of 12 months are attributable to a newly initiated treatment.
TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

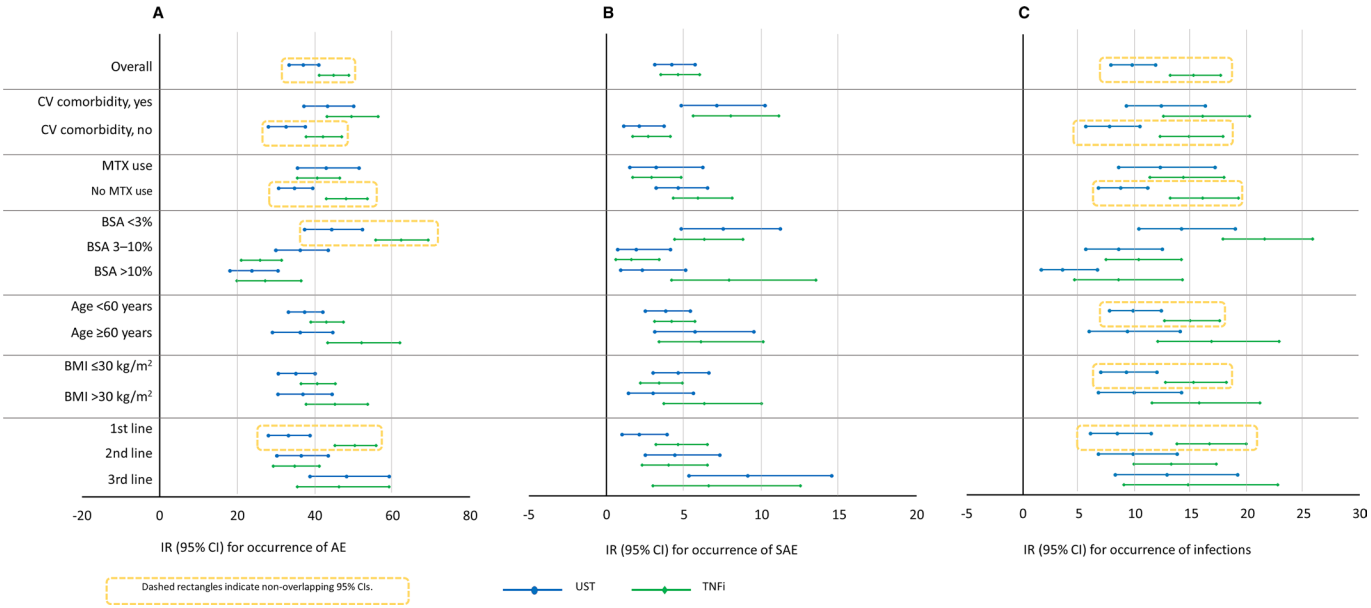

Figure 5 Exposure-adjusted incidence rate per 100 patient-years at risk (95% CI) in patients receiving ustekinumab and TNFi for the occurrence of (A) adverse events; (B) serious adverse events and (C) infections.
AE, adverse event; BMI, body mass index; BSA, body surface area; CV, cardiovascular; IR, incidence rate; MTX, methotrexate; SAE, serious adverse event; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

related to safety/tolerability. In the ustekinumab group, skin response was an important reason for prolonged persistence, with more patients in the ustekinumab group stopping/switching due to lack of effectiveness. This is consistent with our observation that a numerically higher percentage of patients in the TNFi group achieved effectiveness outcomes. However, effectiveness is typically impacted by the same factors as persistence, and adjustments for imbalanced baseline characteristics are needed for a robust comparison of different drugs used in real-world settings.

The similarity in drug persistence observed here for ustekinumab and TNFi, after 3 years of follow-up, is consistent with our findings from the 1-year analysis.[24] Previously it was shown that female sex, older age, chronic widespread pain, depression, high number of comorbidities and later line of bDMARD treatment reduce persistence.[15 24 33 34] In the real-world situation, where there is no randomisation, these factors are not equally distributed among the cohorts, because they are already considered in the choice of treatments for individual patients (channelling bias). In PsABio, there were clinically relevant differences in several baseline characteristics. Older patients, and those presenting a higher number of comorbidities and greater treatment failure (represented by a later line of bDMARD treatment) were channelled towards ustekinumab. Thus, the overall observed persistence analysis is prone to conferring disadvantage onto the ustekinumab group; however, ustekinumab patients had more severe skin involvement and improvements in skin resolution are likely to have a major impact on treatment persistence, therefore, PS-adjusted calculation of HR (95% CI) for counteracting these differences was applied. Nevertheless, given the differences between these populations, direct comparisons between ustekinumab and TNFi treatments should be interpreted with caution.

Several previous studies demonstrated superior persistence for ustekinumab in patients with PsA. For example, a retrospective Swedish registry study of 3918 patients with PsA for a maximum of 10.6 years demonstrated favourable treatment persistence with ustekinumab versus adalimumab across treatment lines.[35] While we cannot directly compare retrospective analyses of national registries or claims databases to a prospective observational study such as PsABio, the subgroup analyses in PsABio are in line with the above-mentioned study results. In the PsABio study, 51% of patients stopped/switched their initial treatment at 3 years, with similar mean persistence for ustekinumab and TNFi. A single-centre study by Murray *et al* has recently reported a higher level of persistence for TNFi treatment, >50% after 1 and 12 years of follow-up.[36] While our long-term data complements these results, further work will need to be done to understand why these results are different; however, given the larger sample size and expanded breadth of our TNFi cohort, we are confident that the results reported here are meaningful.

We also present the data outlining the influence of factors such as extent of skin involvement, line of treatment and monotherapy (without MTX), demonstrating the importance of understanding these population dynamics. Here, the KM curves, log-rank test and PS-adjusted HR (95% CI) demonstrate results, which may be of higher value for the practising rheumatologist in supporting treatment choices for patient subgroups than just the overall undifferentiated KM statistics.

At 3 years, more TNFi-treated patients with BSA <10% persisted with treatment compared with patients with BSA<10% in the ustekinumab group. Patients with BSA>10% at baseline had longer persistence on ustekinumab than patients with BSA<10% on ustekinumab and all patients on TNFi. A greater number of ustekinumab-treated patients with BSA <10% persisted with treatment (72.6%) compared with the overall population; this highlights the importance of effective psoriasis management for patients with PsA with severe skin involvement. These observations are in line with other studies where a relationship between skin involvement and treatment persistence has been observed. This is expected, as psoriasis can significantly affect morbidity, and successfully treating skin symptoms improves patients' health-related quality of life.[37] Interestingly, ustekinumab has previously been shown to have greater drug

survival than adalimumab after a 1-year and 2-year period in patients with psoriasis; however, in a subset of psoriasis patients with PsA, adalimumab had greater drug survival compared with ustekinumab.[38] While these observations are not completely in line with what we have reported in this study or in other studies,[35] it does provide some evidence as to why patients on ustekinumab with severe skin involvement had longer persistence than the overall population and why a numerically greater percentage of TNFi-treated patients achieved certain effectiveness outcomes in our study, given the focus on PsA.

Out of the four groups examined, patients on ustekinumab monotherapy had the greatest persistence over a 3-year period. Patients on ustekinumab monotherapy (without MTX) and those on TNFi+MTX combination therapy persisted longer than patients on ustekinumab+MTX combination therapy and those on TNFi monotherapy, respectively. That patients on ustekinumab monotherapy persisted longer than those on TNFi monotherapy, is consistent with our 1-year results.[24] This may be due to several reasons: patients treated with a TNFi may more frequently develop neutralising antidrug antibodies, especially without MTX co-therapy, but with ustekinumab the risk of such antidrug antibodies is described as minimal.[39] MTX, when given with ustekinumab, may contribute to AEs and reduce patients' treatment satisfaction. TNFi with MTX was more effective for skin involvement than without MTX; however, ustekinumab was effective for skin involvement regardless of MTX cotherapy.

In the observed analysis, a clinically relevant proportion of patients who remained on their respective treatments at 3 years achieved well-established composite effectiveness outcomes with ustekinumab and TNFi. PS-adjusted treatment comparisons showed similar results for MDA/VLDA, cDAPSA LDA or remission among the treatment cohorts; however, in general more TNFi-treated patients achieved effectiveness outcomes. Almost 15% more TNFi-treated patients achieved cDAPSA remission and MDA compared with ustekinumab-treated patients. Starting with a high disease activity (cDAPSA at baseline ~30), patients in both cohorts achieved LDA—and even remission—quickly, often within 6 months. While the observed data appeared to suggest TNFi is more effective than ustekinumab, after PS adjustment, ORs indicated a similar effectiveness between the cohorts. Ustekinumab and TNFi appeared to have comparable effectiveness in terms of improvements seen in swollen joint counts, enthesitis and dactylitis, with these results suggesting both treatments can be effective at improving musculoskeletal manifestations of PsA. Previous work, reported in the ECLIPSA study, suggested ustekinumab was more effective at reducing enthesitis in patients with PsA; however, in our study, we saw comparable improvement in both treatment groups.[40] Differences in the size of study populations, baseline characteristics of patients, and study duration may account for these divergent results. The effectiveness shown by the two phase 3 placebo-controlled trials examining the use of ustekinumab in PsA is indirectly supported by the results from this analysis.[18 19 39] As we only studied the effectiveness of initial treatment in PsABio, a separate analysis focusing on the effectiveness of treatment sequences in routine care might be of interest to clinicians but is out of scope for this paper.

The 3-year results demonstrated good long-term safety of both ustekinumab and TNFi in real-world PsA patients presenting with several comorbidities. Both groups reported similar AE and SAE rates; however, when reporting exposure-adjusted AE rates per 100 patient-years, ustekinumab was associated with lower rates of AEs and infections compared with TNFi overall, and in some patient subgroups. Non-overlapping CIs suggest these differences may indeed be of importance, although the non-randomised setting and lack of methods controlling for multiplicity testing preclude firm conclusions. While safety data relating to ustekinumab and TNFi have been published previously,[18 19 41] there is a dearth of real-world data focused specifically on patients with PsA, particularly long-term data.[10] The benefit of the data presented here is that they are long-term, real-world results of patients suffering from PsA with underlying comorbidities, and receiving ustekinumab and TNFi treatment, respectively, and as such may be more representative of what may happen in clinical practice. PsABio is the only observational study in real-world care comparing biologics with different modes of action in patients with PsA, and will facilitate the tailoring of treatment strategies for patients.

In conclusion, 3-year results from the PsABio study demonstrated that, supporting our previous observations, ustekinumab and TNFi in general performed as effective and well tolerated first-line to third-line biological treatments for PsA in real-world clinical practice, demonstrating safety over a year.[24] Adjusting for imbalances of outcome-modifying baseline characteristics, such as line of treatment, extent of skin involvement and monotherapy, resulted in identification of subgroups with a higher probability of long-term drug persistence and lower rates of AEs with ustekinumab. In line with our study results, patients with high levels of skin involvement, and in whom MTX use is contraindicated, may be attractive candidates for treatment with ustekinumab rather than TNFi.

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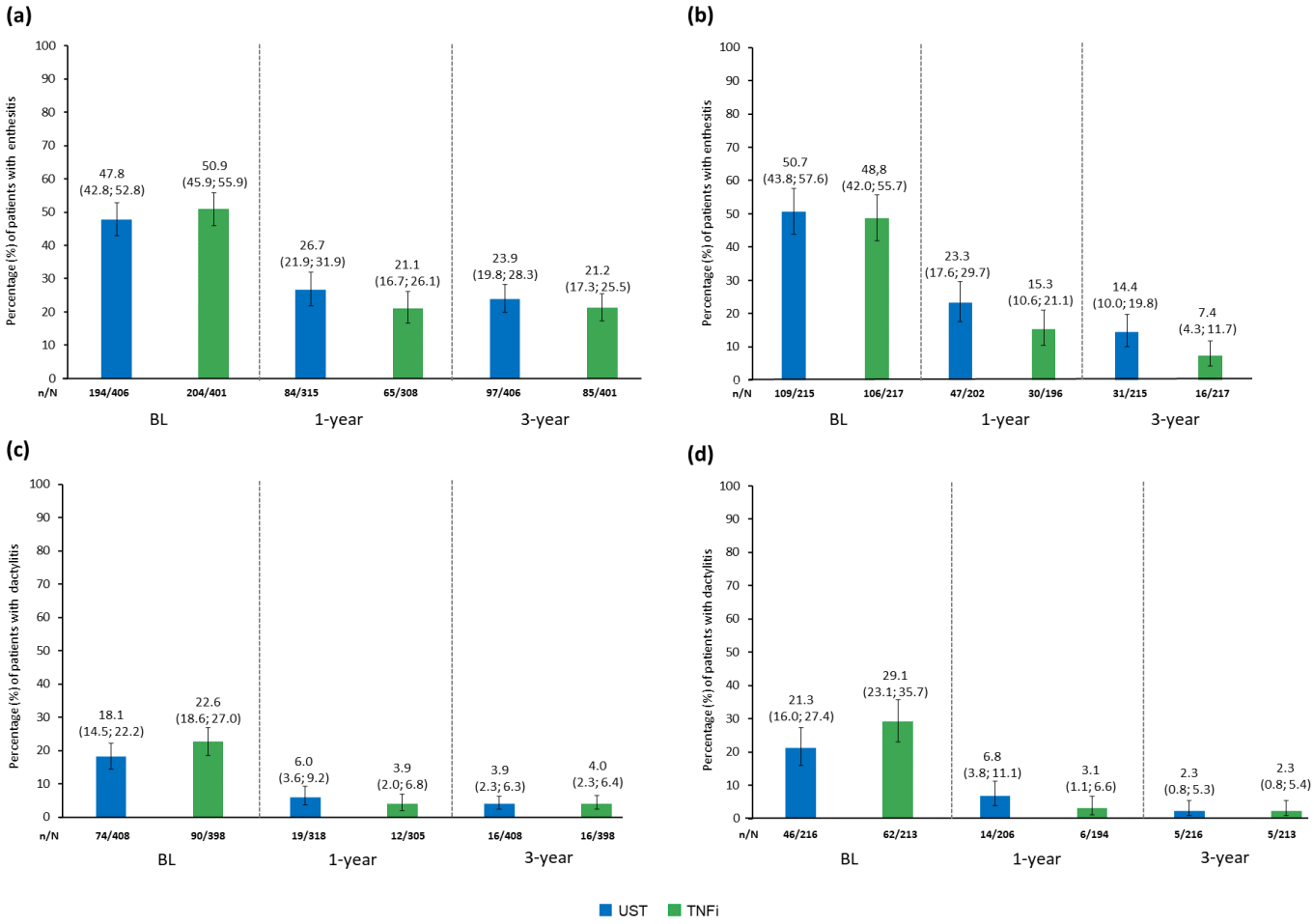
Supplementary Material

Supplementary Figure 1. Percentage of patients with enthesitis (a) overall analysis; (b) remainer analysis or dactylitis; (c) overall analysis; (d) remainer analysis



Data shown as percentage of patients with enthesitis or dactylitis at baseline, 12 months, and 36 months (LOCF).

Error bars represent 95% CI.

The overall analysis included patients switching/stopping their original treatment during the 3-year observation period. The remainer analysis reflects 3-year data from assessments for patients still under initial treatment at 3 years.

BL, baseline; CI, confidence intervals; TNFi, tumour necrosis factor inhibitors; UST, ustekinumab

Supplementary Table 1. Mean swollen joint counts at baseline, 1 year and 3 years for overall patients (n=895) and remainers (n=437) (LOCF analysis)

Mean (SD)[95%CI]	UST overall (n=439)	TNFi overall (n=456)	UST remainers (n=219)	TNFi remainers (n=218)
Swollen joint count at baseline	n=439 5.8 (8.1) [5.0; 6.6]	n=456 5.9 (7.6) [5.2; 6.7]	n=219 6.1 (8.5) [4.9; 7.2]	n=218 7.0 (8.7) [5.8; 8.3]
Swollen joint count at 1 year Change from baseline at 1 year	n=298 1.8 (3.8) [1.3; 2.2] -4.4 (7.9) [-5.5; -3.5]	n=293 1.2 (2.4) [0.9; 1.5] -4.7 (6.9) [-5.5; -3.9]	n=190 1.5 (3.5) [1.0; 2.0] -4.7 (8.3) [-5.9; -3.5]	n=185 0.9 (1.9) [0.7; 1.2] -5.7 (7.8) [-6.9; -4.6]
Swollen joint count at 3 years Change from baseline at 3 years	n=384 2.0 (4.8) [1.5; 2.4] -3.9 (7.9) [-4.7; -3.1]	n=373 1.5 (4.2) [1.1; 2.0] -4.4 (7.6) [-5.2; -3.6]	n=204 0.7 (2.4) [0.3; 1.0] -5.4 (8.2) [-6.5; -4.3]	n=196 0.9 (4.0) [0.3; 1.5] -6.2 (9.0) [-7.4; -4.9]

The overall analysis included patients switching/stopping their original treatment during the 3-year observation period. The remainer analysis reflects 3-year data from assessments for patients still under initial treatment at 3 years.

CI, confidence interval; LOCF, last observation carried forward; SD, standard deviation; TNFi, tumour necrosis factor inhibitors; UST, ustekinumab

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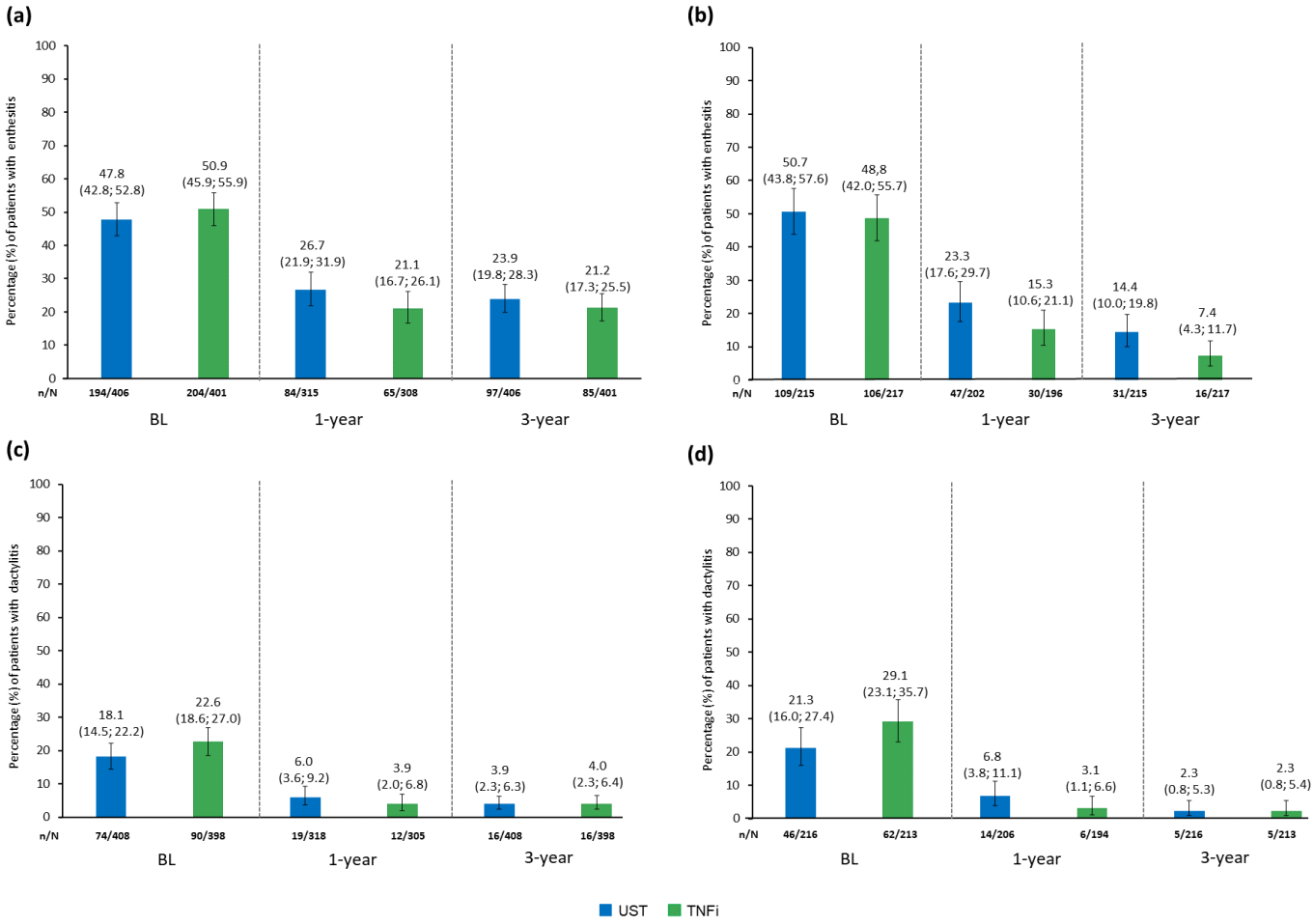
Supplementary Figure 1. Percentage of patients with enthesitis (a) overall analysis; (b) remainer analysis or dactylitis; (c) overall analysis; (d) remainer analysis



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