EXTENDED REPORT

# Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial

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## ABSTRACT

**Objective** Assess ustekinumab efficacy (week 24/week 52) and safety (week 16/week 24/week 60) in patients with active psoriatic arthritis (PsA) despite treatment with conventional and/or biological anti-tumour necrosis factor (TNF) agents.

**Methods** In this phase 3, multicentre, placebo-controlled trial, 312 adults with active PsA were randomised (stratified by site, weight (≤100 kg/>100 kg), methotrexate use) to ustekinumab 45 mg or 90 mg at week 0, week 4, q12 weeks or placebo at week 0, week 4, week 16 and crossover to ustekinumab 45 mg at week 24, week 28 and week 40. At week 16, patients with <5% improvement in tender/swollen joint counts entered blinded early escape (placebo→45 mg, 45 mg→90 mg, 90 mg→90 mg). The primary endpoint was ≥20% improvement in American College of Rheumatology (ACR20) criteria at week 24. Secondary endpoints included week 24 Health Assessment Questionnaire-Disability Index (HAQ-DI) improvement, ACR50, ACR70 and ≥75% improvement in Psoriasis Area and Severity Index (PASI75). Efficacy was assessed in all patients, anti-TNF-naïve (n=132) patients and anti-TNF-experienced (n=180) patients.

**Results** More ustekinumab-treated (43.8% combined) than placebo-treated (20.2%) patients achieved ACR20 at week 24 (p<0.001). Significant treatment differences were observed for week 24 HAQ-DI improvement (p<0.001), ACR50 (p≤0.05) and PASI75 (p<0.001); all benefits were sustained through week 52. Among patients previously treated with ≥1 TNF inhibitor, sustained ustekinumab efficacy was also observed (week 24 combined vs placebo: ACR20 35.6% vs 14.5%, PASI75 47.1% vs 2.0%, median HAQ-DI change −0.13 vs 0.0; week 52 ustekinumab-treated: ACR20 38.9%, PASI75 43.4%, median HAQ-DI change −0.13). No unexpected adverse events were observed through week 60.

**Conclusions** The interleukin-12/23 inhibitor ustekinumab (45/90 mg q12 weeks) yielded significant and sustained improvements in PsA signs/symptoms in a diverse population of patients with active PsA, including anti-TNF-experienced PsA patients.

## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, seronegative, inflammatory joint disease that commonly involves not only peripheral joints, but also the spine, entheses (attachment sites where tendons, ligaments and joint capsules attach to bone) and soft tissues (tendonitis and dactylitis).[1 2] PsA leads to functional impairment, reduced quality of life and increased comorbidity/mortality,[3–8] often requiring treatment with tumour necrosis factor-α(TNF) antagonists.[9]

Ustekinumab (Stelara; Janssen Biotech, Inc.; Horsham, Pennsylvania, USA), a human immunoglobulin G1κ mAb that binds to the common p40 subunit shared by IL-12 and IL-23, was approved for treatment of moderate-to-severe psoriasis based upon large phase 3 trials.[10–12] The efficacy of ustekinumab in active PsA was also evaluated in a phase 2 trial[13] and in the large phase 3 PSUMMIT 1 trial,[14] which included only patients naïve to biological anti-TNF treatments. In these anti-TNF-naïve patients, ustekinumab significantly improved active PsA signs/symptoms and demonstrated an acceptable safety profile through 1 year.[14] Results of the PSUMMIT 2 trial, including patients with and without prior exposure to anti-TNF agents, through week 60 are presented.

## METHODS

### Patients

Adult patients with active PsA for ≥6 months, despite ≥3 months of disease-modifying antirheumatic drug (DMARD) therapy, ≥4 weeks of non-steroidal anti-inflammatory drugs (NSAIDs) therapy and/or ≥8 (etanercept, adalimumab, golimumab, certolizumab-pegol) or 14 (infliximab) continuous weeks of TNF-antagonist therapy (or less if patient was intolerant of anti-TNF therapies) were eligible. The protocol specified 150–180 of 300 randomised patients must

**Table 1** Baseline patient demographics and disease characteristics among all randomised patients

| | Placebo | UST 45 mg | UST 90 mg |
|---|---|---|---|
| *All patients* (N) | 104 | 103 | 105 |
| Women | 53 (51.0) | 55 (53.4) | 56 (53.3) |
| Age (years) | 48.0 (38.5 to 56.0) | 49.0 (40.0 to 56.0) | 48.0 (41.0 to 57.0) |
| Body mass index (kg/m$^2$) | 30.5 (26.8 to 35.7) | 30.2 (25.5 to 36.9) | 30.3 (25.3 to 37.1) |
| Duration of disease (years) | | | |
| Psoriatic arthritis | 5.5 (2.3 to 12.2) | 5.3 (2.3 to 12.2) | 4.5 (1.7 to 10.3) |
| Psoriasis | 11.4 (6.0 to 22.0) | 13.3 (5.0 to 24.4) | 11.3 (4.5 to 21.4) |
| Swollen joint count (0–66) | 11.0 (7.0 to 18.0) | 12.0 (8.0 to 19.0) | 11.0 (7.0 to 17.0) |
| Tender joint count (0–68) | 21.0 (11.0 to 30.0) | 22.0 (15.0 to 33.0) | 22.0 (14.0 to 36.0) |
| CRP (mg/L) | 8.5 (4.6 to 22.0) | 13.0 (4.5 to 36.3) | 10.1 (4.8 to 19.8) |
| HAQ-DI score (0–3) | 1.3 (0.8 to 1.8) | 1.4 (0.8 to 1.9) | 1.3 (0.8 to 1.9) |
| DAS28-CRP score | 5.2 (4.4 to 5.9) | 5.6 (4.9 to 6.3) | 5.3 (4.7 to 6.0) |
| Patients with dactylitis in ≥1 digit | 38 (36.5) | 48 (46.6) | 41 (39.0) |
| Dactylitis score (1–60) | 7.0 (3.0 to 14.0) | 5.0 (2.0 to 13.0) | 7.0 (2.0 to 15.0) |
| Patients with enthesitis | 73 (70.2) | 72 (69.9) | 76 (72.4) |
| Enthesitis score (1–15) | 4.0 (2.0 to 8.0) | 6.0 (3.0 to 9.0) | 5.0 (3.0 to 8.0) |
| Patients with spondylitis/peripheral joint involvement | 22 (21.2) | 26 (25.2) | 22 (21.0) |
| BASDAI score (1–10) | 6.6 (5.8 to 7.8) | 7.6 (5.7 to 8.2) | 7.1 (5.8 to 7.9) |
| Patients with ≥3% BSA involved with psoriasis | 80 (76.9) | 80 (77.7) | 81 (77.1) |
| PASI score (0–72) | 7.9 (4.5 to 16.0) | 8.6 (4.5 to 18.3) | 8.8 (4.5 to 18.0) |
| DLQI score (0–30) | 11.0 (5.0 to 16.5) | 11.0 (6.0 to 18.0) | 10.0 (6.0 to 18.0) |
| FACIT-Fatigue score (0–52) | 28.0 (17.0 to 34.5) | 26.0 (17.0 to 33.0) | 24.5 (17.0 to 34.5) |
| SF-36 summary scores (n) | 104 | 102 | 104 |
| Mental component (0–100) | 41.8 (31.6 to 53.5) | 43.7 (33.0 to 54.6) | 41.4 (33.8 to 54.9) |
| Physical component (0–100) | 29.4 (23.3 to 36.2) | 28.0 (22.6 to 34.0) | 28.2 (21.8 to 33.6) |
| Current medication use | | | |
| Methotrexate | 49 (47.1) | 54 (52.4) | 52 (49.5) |
| Dose (mg/week), mean/median | 17.4/17.5 | 17.2/15.0 | 15.9/15.0 |
| Oral corticosteroids | 13 (12.5) | 21 (20.4) | 16 (15.2) |
| Dose (mg/day), mean/median | 8.0/7.5 | 7.0/5.0 | 7.5/7.5 |
| NSAIDs | 77 (74.0) | 72 (69.9) | 70 (66.7) |

Data are reported as n (%) or median (IQR) unless noted otherwise.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BSA, body surface area; CRP, C-reactive protein; DAS28-CRP, 28-joint disease activity score employing CRP; DLQI, Dermatology Life Quality Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, Psoriasis Area and Severity Index; pts, patients; SF-36, 36-item short-form healthy survey; UST, ustekinumab.

have been previously treated with biological anti-TNF agents. Active PsA was defined as ≥5/66 swollen and ≥5/68 tender joints at screening/baseline, screening C-reactive protein (CRP) ≥6.0 mg/L (modified to ≥3.0 mg/L after study start; upper limit of normal 10 mg/L) and active/documented history of plaque psoriasis. A history of active tuberculosis (TB) was prohibited, but patients with newly documented latent TB or anti-TNF-experienced patients with a history of treated latent TB within 3 years were eligible with initiation of appropriate treatment. Concomitant methotrexate (MTX) was permitted if started ≥3 months prior to study start and at a stable dose (≤25 mg/week) for ≥4 weeks. Concomitant NSAIDs and oral corticosteroids (≤10 mg prednisone/day) were permitted if stable for ≥2 weeks. Allowed concomitant medications were to remain stable through week 52. Patients could not have previously received any anti-IL-12/23 agent or abatacept. Receipt of alefacept within 3 months and/or B cell and T cell-depleting agents (including rituximab), efalizumab or natalizumab within 12 months of screening excluded patient participation. DMARDs other than MTX were not allowed within 4 weeks prior to or during trial participation (see online supplement).

## Study design

In the phase 3, multicentre, randomised, placebo-controlled PSUMMIT 2 study (NCT01077362, EudraCT 2009-012265-60), patients who met the ClASsification Criteria for Psoriatic ARthritis (CASPAR)[15] were randomly assigned to receive ustekinumab 45 mg, 90 mg or placebo at week 0, week 4 and every 12 weeks (q12 weeks) thereafter. Randomisation was accomplished using dynamic central randomisation, employing an algorithm implemented in an interactive voice/web response system, and was stratified by study site, baseline body weight (≤100 kg, >100 kg) and baseline MTX usage (yes/no). The randomisation method was minimisation with a biased-coin assignment (1:1:1). At week 16, patients with <5% improvement in tender and swollen joints entered blinded early escape (EE); patients receiving placebo switched to ustekinumab 45 mg, those receiving ustekinumab 45 mg increased to 90 mg and patients receiving ustekinumab 90 mg continued with blinded 90 mg dosing. Placebo patients who did not EE crossed over to receive ustekinumab 45 mg at week 24, week 28 and week 40 (see online supplement).

## Assessments

Clinical efficacy was primarily assessed using the American College of Rheumatology (ACR) response criteria[16]; response per the 28-joint disease activity score employing C-reactive protein (DAS28-CRP), that is, European League Against Rheumatism (EULAR) response of good or moderate and

DAS28-CRP score <2.6[17–20]; and the Psoriasis Area and Severity Index (PASI) score (0–72)[21] among patients with ≥3% of body surface area (BSA) affected by psoriasis at baseline. Physical function was measured using the Health Assessment Questionnaire-Disability Index (HAQ-DI),[22] a ≥0.3 unit improvement (decrease), which is considered clinically important in PsA.[23]

Additional assessments included (1) dactylitis—assessed in 20 digits of the hands and feet on a scale of 0 to 3 (0=no dactylitis; 3=severe dactylitis); (2) entheseal tenderness/pain—scored in 15 body sites (0=absent; 1=present) using the PsA-modified (to include left and right insertion of the plantar fascia) Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)[24]; and (3) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)—a self-assessment tool for ankylosing spondylitis[25] administered to patients with baseline spondylitis and peripheral joint involvement; note that the BASDAI has not been validated in PsA. A BASDAI decrease of 50% or two points is considered clinically meaningful in ankylosing spondylitis.[26]

Patient quality of life was assessed using the 36-item short-form (SF-36) health survey[27] and, among patients with ≥3% BSA affected by psoriasis at baseline, the Dermatology Life Quality Index (DLQI).[28] Fatigue during the previous week was measured using the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire.[29] Safety evaluations included adverse events (AEs) and routine laboratory analyses; immunogenicity determinations are detailed online.

### Statistical analysis

The primary endpoint was the proportion of patients with ≥20% improvement in ACR (ACR20) response at week 24. Major clinical secondary endpoints, all at week 24, included change in HAQ-DI, and proportions of patients achieving ≥75% improvement in PASI (PASI75), ≥50% improvement in ACR (ACR50) and ≥70% improvement in ACR (ACR70) criteria. To control for multiplicity for the primary and major secondary endpoint analyses, the latter were performed sequentially, contingent upon the success of the primary endpoint analysis. Primary and major secondary analyses were intent-to-treat.

Patients who used prohibited medication or discontinued study agent because of lack of efficacy were considered non-responders for binary endpoints and had baseline values carried forward for continuous endpoints through week 52. For patients who qualified for EE at week 16, week 16 data were carried forward through week 24. After week 24, available data were used for EE patients. Patients with missing week 24 data were considered non-responders for ACR and PASI responses and had the last observation carried forward for the week 24 change in HAQ-DI. Otherwise, missing data were not imputed. Treatment differences at week 24 were assessed using Cochran–Mantel–Haenszel tests for binary variables and analyses of variance on the van der Waerden normal scores[30] for continuous variables. Both tests adjusted for baseline MTX use (also see online supplement).

## RESULTS

### Disposition and baseline characteristics

Patient disposition and baseline demographic and disease characteristics are shown in online supplementary figure S1 and table 1, respectively. Among the anti-TNF-experienced patients, >70% had an inadequate response to or were intolerant of prior anti-TNF treatment and >50% had received ≥2 anti-TNF agents (see online supplementary table S1).

### Joints, dactylitis and enthesitis

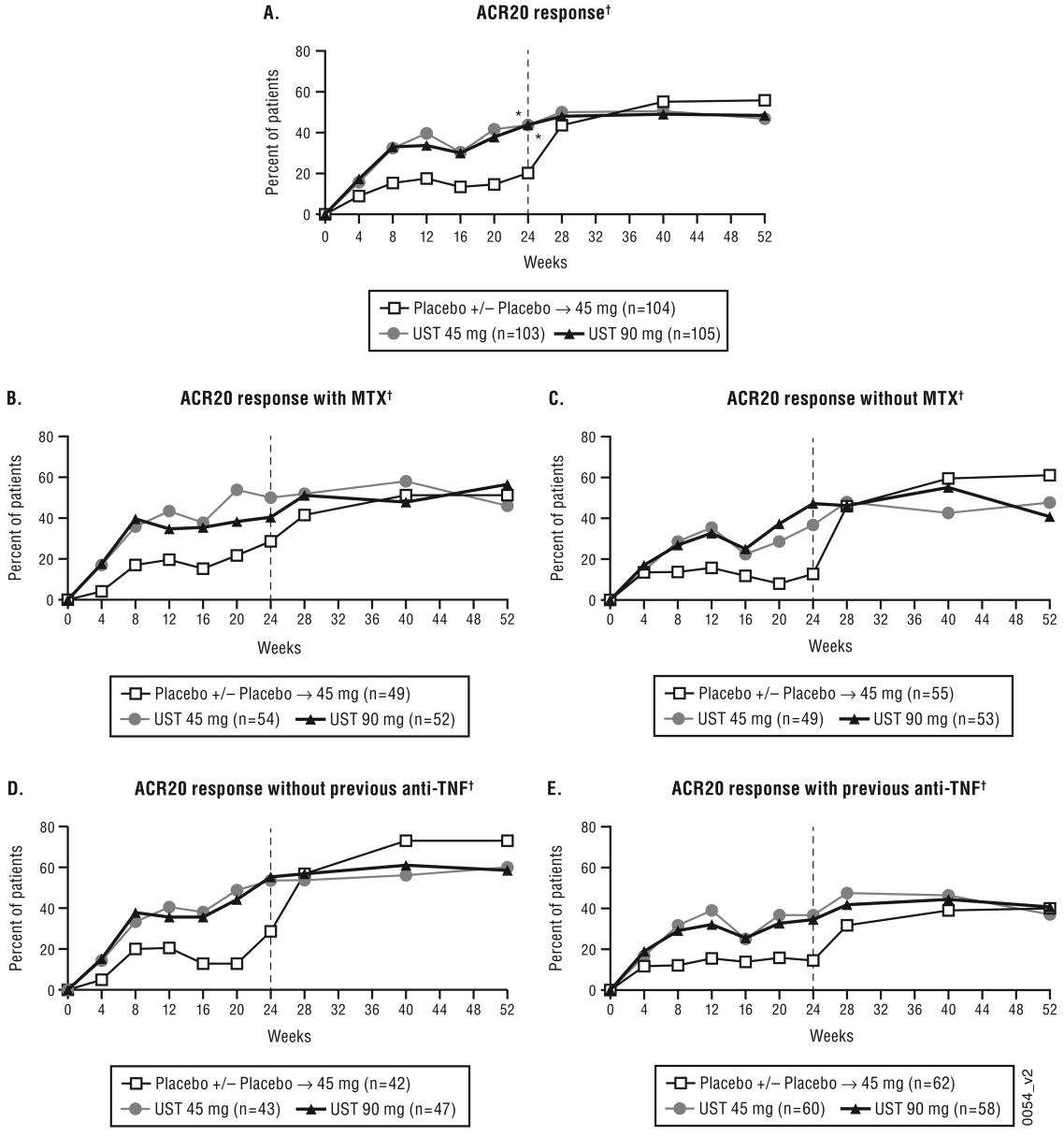
Significantly higher proportions of ustekinumab-treated (43.8%–combined, 43.7%–45 mg, 43.8%–90 mg) than placebo-treated (20.2%) patients achieved week 24 ACR20 response (all $p<0.001$). Significant differences were observed for the more stringent ACR50 response at week 24 (20.2%–combined, 17.5%–45 mg, 22.9%–90 mg vs 6.7% placebo; all $p<0.05$); numerical but not significant differences were observed for ACR70 response. Response rates were sustained through week 52 (see online supplementary table S3, figure 1A; recall that EE rules were not applied after week 24). At week 24, ACR20 response was achieved regardless of concomitant MTX therapy or body weight, although the treatment difference appeared numerically larger in patients not receiving MTX versus those receiving MTX and in patients weighing >100 kg vs ≤100 kg, in both cases due to a higher placebo response rate in patients receiving MTX or weighing ≤100 kg (table 2, figure 1B,C).

At week 24, significantly higher proportions of ustekinumab-treated than placebo-treated patients achieved a DAS28-CRP/EULAR response (all $p<0.001$; see online supplementary table S2); responses were sustained through week 52 (see online supplementary table S3), with continued improvement over time (see online supplementary figures S2A,B). Ustekinumab treatment also yielded a significantly higher proportion of patients with DAS28-CRP score <2.6 at week 24. By week 52, 19.6% of ustekinumab-treated patients had a DAS28-CRP score <2.6.

Among the 221 randomised patients with baseline enthesitis, significantly lower proportions of ustekinumab-treated than placebo-treated patients had residual enthesitis at week 24 (all $p<0.05$; see online supplementary table S2). Patients treated with ustekinumab 90 mg exhibited significantly greater improvement in enthesitis (MASES) at week 24 versus placebo ($p<0.01$). Numeric, but not significant, improvement was observed among the smaller number (n=127) of patients with baseline dactylitis in the 90 mg group versus placebo. By week 52, median percent improvements in dactylitis and enthesitis scores among ustekinumab-treated patients were 95.0% and 50.0%, respectively (see online supplementary table S3 and figures S3A,B). Among patients with baseline concomitant spondylitis, numerically greater BASDAI response rates among ustekinumab-treated than placebo-treated patients at week 24 were generally observed (see online supplementary table S2).

### Skin disease

In patients with ≥3% BSA baseline psoriasis skin involvement, significantly (all $p<0.001$) greater proportions of ustekinumab-treated than placebo-treated patients achieved PASI75 response or ≥90% improvement in PASI score (PASI90) at week 24 (table 2, figure 2A, see online supplementary table S2). By week 52, 60.6% and 43.7% of ustekinumab-treated patients achieved PASI75 and PASI90 responses, respectively (figure 2A; online supplementary table S3). At week 24, PASI75 response was achieved regardless of concomitant MTX therapy or body weight, although the treatment difference appeared numerically larger in patients not receiving MTX versus those receiving MTX and in patients weighing >100 vs ≤100 kg, both resulting from higher placebo response rates in patients receiving MTX or weighing ≤100 kg (table 2, figure 2B,C).




†For patients who qualified for early escape, data at or prior to week 16 were carried forward through week 24. After week 24, observed data were used.
*p<0.001 vs placebo.

**Figure 1** Proportions of patients achieving ACR20 response over time through week 52 for all patients (A), patients with MTX use (B), patients without MTX use (C), anti-TNF-naïve patients (D) and anti-TNF-experienced patients (E), with the vertical dotted lines indicating the time after which data-handling rules changed as noted in the footnote to the figure. ACR20, at least 20% improvement in the American College of Rheumatology response criteria; MTX, methotrexate; TNF, tumour necrosis factor-α; UST, ustekinumab.

### Physical function and quality of life

Improvements in HAQ-DI scores at week 24 were significantly greater among ustekinumab-treated than placebo-treated patients ($p \leq 0.001$; table 2). See supplementary tables S2 and S3 for further details of physical function and quality-of-life measures.

### Efficacy by prior anti-TNF exposure

A majority of the 180 anti-TNF-experienced patients had received ≥2 such agents and >70% had discontinued prior agent(s) due to lack of efficacy/intolerance (table S1). At week 24, ustekinumab efficacy was also observed in the 180 anti-TNF-experienced patients, among whom week 24 ACR20 and PASI75 response rates were 35.6% and 47.1%, respectively, for combined ustekinumab-treated vs 14.5% and 2.0%, respectively, for placebo-treated patients (both $p<0.01$; table 2, figures 1D,E and 2D,E; online supplementary figure S4). Also among anti-TNF-experienced patients, median changes in HAQ-DI scores at week 24 were –0.13 for combined ustekinumab-treated vs 0.0 for placebo-treated patients ($p<0.05$). Response to ustekinumab through 1 year appeared more pronounced in patients with only 1 vs ≥2 prior anti-TNF agents, although assessments are limited by small sample sizes (table 3). Based on posthoc regression analyses performed, no consistent predictors were identified for ACR20 and ACR50 responses (data not shown).

**Table 2** Summary of primary and major secondary efficacy endpoints at week 24 among randomised patients

| | Placebo (N=104) | UST 45 mg (N=103) | UST 90 mg (N=105) | Combined UST (N=208) |
|---|---|---|---|---|
| ACR20 response (1° endpoint) | 21 (20.2) | 45 (43.7)*** | 46 (43.8)*** | 91 (43.8)*** |
| Difference (CI) | | 23.5 (11.2 to 35.8) | 23.6 (11.4 to 35.8) | |
| ACR20 by MTX use | | | | |
| Yes | 14/49 (28.6) | 27/54 (50.0) | 21/52 (40.4) | 48/106 (45.3) |
| No | 7/55 (12.7) | 18/49 (36.7) | 25/53 (47.2) | 43/102 (42.2) |
| ACR20 by body weight | | | | |
| ≤100 kg | 17/74 (23.0) | 32/74 (43.2) | 34/73 (46.6) | 66/147 (44.9) |
| >100 kg | 4/30 (13.3) | 13/29 (44.8) | 12/31 (38.7) | 25/60 (41.7) |
| ACR20 by anti-TNF use | | | | |
| Anti-TNF-naïve | 12/42 (28.6) | 23/43 (53.5) | 26/47 (55.3) | 49/90 (54.4) |
| Anti-TNF-experienced | 9/62 (14.5) | 22/60 (36.7) | 20/58 (34.5) | 42/118 (35.6) |
| ACR50 response (major 2° endpoint) | 7 (6.7) | 18 (17.5)* | 24 (22.9)** | 42 (20.2)** |
| Difference (CI) | | 10.7 (2.0 to 19.5) | 16.1 (6.8 to 25.5) | |
| ACR70 response (major 2° endpoint) | 3 (2.9) | 7 (6.8) | 9 (8.6) | 16 (7.7) |
| Difference (CI) | | 3.9 (−1.9 to 9.7) | 5.7 (−0.6 to 11.9) | |
| PASI75 response† (major 2° endpoint) | 4/80 (5.0) | 41/80 (51.3)*** | 45/81 (55.6)*** | 86/161 (53.4)*** |
| Difference (CI) | | 46.3 (34.3 to 58.2) | 50.6 (38.7 to 62.4) | |
| PASI75 by MTX use | | | | |
| Yes | 3/29 (10.3) | 19/39 (48.7) | 22/39 (56.4) | 41/78 (52.6) |
| No | 1/51 (2.0) | 22/41 (53.7) | 23/42 (54.8) | 45/83 (54.2) |
| PASI75 by body weight | | | | |
| ≤100 kg | 4/54 (7.4) | 31/58 (53.4) | 32/57 (56.1) | 63/115 (54.8) |
| >100 kg | 0/26 (0.0) | 10/22 (45.5) | 13/24 (54.2) | 23/46 (50.0) |
| PASI75 by anti-TNF use | | | | |
| Anti-TNF-naïve | 3/30 (10.0) | 21/36 (58.3) | 25/40 (62.5) | 46/76 (60.5) |
| Anti-TNF-experienced | 1/50 (2.0) | 20/44 (45.5) | 20/41 (48.8) | 40/85 (47.1) |
| HAQ-DI score | | | | |
| Change from baseline (major 2° endpoint) | 0.00 (−0.13 to 0.13) | −0.13 (−0.38 to 0.00)** | −0.25 (−0.50 to 0.00)*** | −0.25 (−0.38 to 0.00)*** |
| Difference (CI) | | 0.13 (0.00 to 0.30) | 0.25 (0.10 to 0.30) | |
| HAQ-DI change from baseline | | | | |
| Anti-TNF-naïve, N | 42 | 43 | 47 | 90 |
| | 0.00 (−0.25 to 0.25) | −0.25 (−0.50 to 0.00) | −0.25 (−0.50 to 0.00) | −0.25 (−0.50 to 0.00) |
| Anti-TNF-experienced, N | 62 | 60 | 58 | 118 |
| | 0.00 (−0.13 to 0.13) | −0.13 (−0.38 to 0.00) | −0.19 (−0.38 to 0.00) | −0.13 (−0.38 to 0.00) |

Data are reported as n (%), n/N (%) or median (IQR).
*, ** and *** indicate p<0.05, 0.01 and 0.001, respectively, versus placebo.
†Among patient with ≥3% BSA psoriasis involvement at baseline.
ACR, American College of Rheumatology; BSA, body surface area; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; TNF, tumour necrosis factor-α; UST, ustekinumab.

## Immunogenicity

See online supplement.

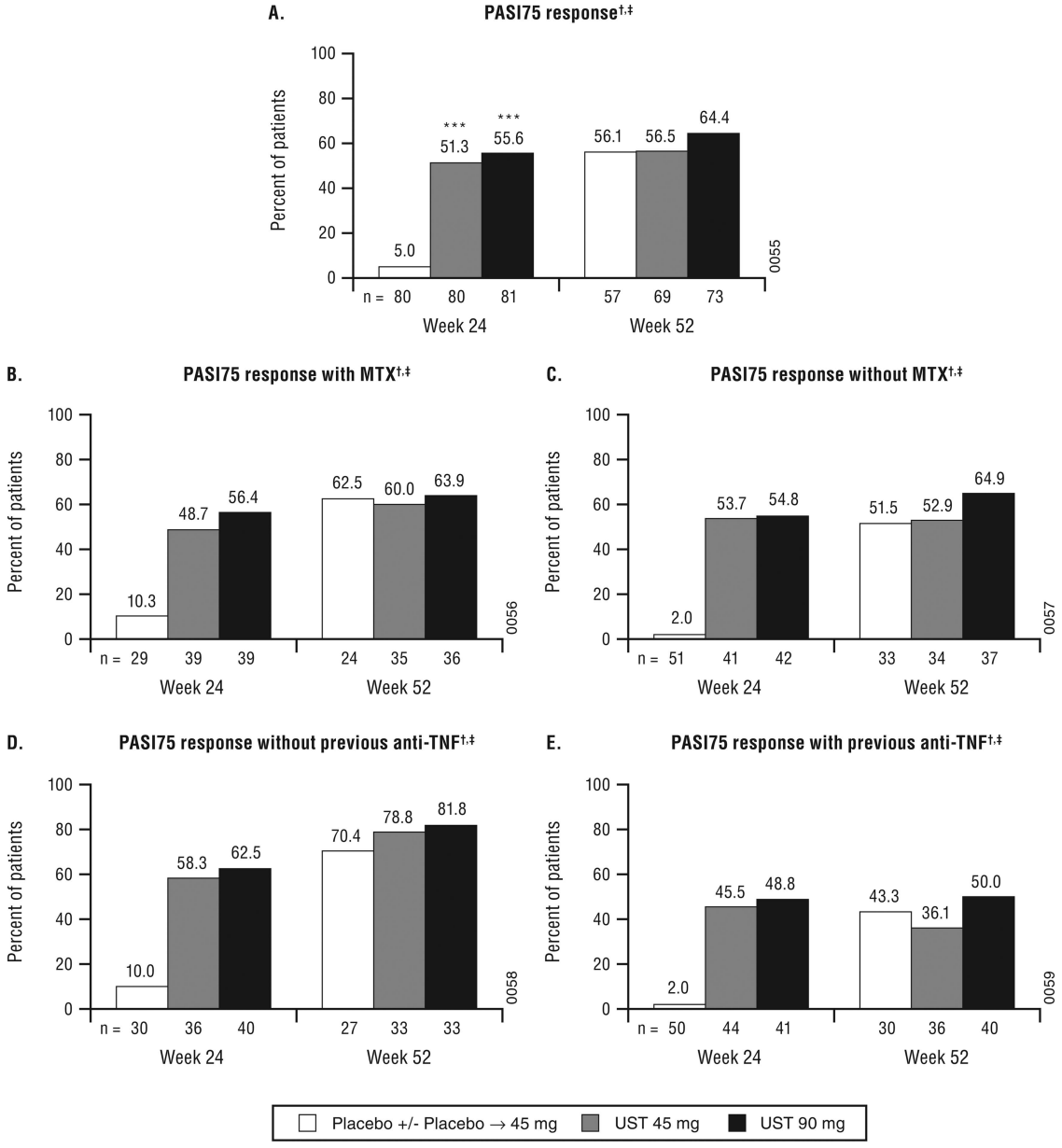
## Safety

Safety findings are provided through week 16 (placebo-controlled period) and week 24 in table 4 and through week 60 in online supplementary table S4.

Among ustekinumab-treated and placebo-treated patients, 61.8% and 54.8% reported AEs, 27.1% and 24.0% had investigator-reported infections, 1.9% and 7.7% discontinued study agent because of an AE, and 0.5% and 4.8% had serious AEs, respectively, through week 16. Increases in the occurrence of AEs through week 60 were consistent with the additional ustekinumab exposure accrued from week 16 forward without obvious dose trend. Serious AEs (table 4; online supplementary table S4) occurred in 5.2% (15/287) of all ustekinumab-treated patients through week 60 (rate=11.82/100 patient-years). Serious AE rates in ustekinumab-treated patients receiving and not receiving MTX were 3.4% and 7.1%, respectively.

No patients died, and no cases of TB were reported through week 60. Through week 16, one placebo-treated and no ustekinumab-treated patients reported serious infections. Through week 60, two ustekinumab-treated patients reported serious infections (rate=0.74/100 patient-years). One patient (90 mg) had septic shock/severe dehydration, with *Candida* spp. in her stool; systemic candidiasis was not identified. Another patient (90 mg) had a serious infection through week 60 (bacteraemia in a 50-year-old man (per AMA guidelines) (methicillin-sensitive *Staphylococcus aureus*) believed to result from psoriatic plaque infection and subsequent knee arthritis). Both patients recovered without sequelae following appropriate therapy. Two patients had malignancies reported through week 60 (placebo→45 mg breast cancer, 90 mg squamous cell carcinoma in situ in an area of cleared plaque psoriasis); both were anti-TNF-experienced patients.

No major cardiovascular AEs (MACE) were observed through week 16. Through week 60, three patients (2–45 mg, 1–90 mg, all anti-TNF-experienced patients) had myocardial infarctions




†Among randomized patients with ≥3% body surface area with psoriasis skin involvement at baseline.
‡For patients who qualified for early escape, data at or prior to week 16 were carried forward through week 24. After week 24, observed data were used.
***p<0.001 vs placebo.

**Figure 2** Proportions of patients achieving PASI75 response over time through week 52 for all patients (A), patients with MTX use (B), patients without MTX use (C), anti-TNF-naïve patients (D) and anti-TNF-experienced patients (E), with data handling rule changes as noted in the footnote to the figure. MTX, methotrexate; PASI75, at least 75% improvement in the Psoriasis Area and Severity Index response criteria; TNF, tumour necrosis factor-α; UST, ustekinumab.

reported; only two events were adjudicated as a myocardial infarction (rate=0.74/100 patient-years). These patients had cardiovascular risk factors independent of PsA identified (history of stroke, hypertension, smoking and/or symptoms of metabolic syndrome).

## DISCUSSION

In this multicentre, phase 3, double-blind, placebo-controlled trial, subcutaneous ustekinumab was effective and demonstrated an acceptable safety profile among patients with active PsA, more than half of whom had previously received ≥1 anti-TNF agent. The study's primary endpoint was met, with significantly higher week 24 ACR20 response rates among ustekinumab-treated than placebo-treated patients. Although efficacy was observed as early as week 4, maximal efficacy was not reached until week 24 through week 28. Ustekinumab also demonstrated superiority to placebo when clinical response was assessed using the DAS28-CRP score and when improvements in skin disease and physical function were evaluated. There was also numerical superiority in BASDAI measurements in patients with spondylitis, indicating that ustekinumab may improve spinal disease, although this effect was not studied systematically and the BASDAI has not been validated for use in patients with PsA. Thus, PSUMMIT 2 efficacy findings are consistent with those

**Table 3** Summary of efficacy at week 24 and week 52 among randomised patients by number of prior biological anti-TNF exposure (1 vs >1)

| | Placebo→UST 45 mg | UST 45 mg | UST 90 mg | Combined UST |
|---|---|---|---|---|
| *Week 24* (N) | 62 | 60 | 58 | 118 |
| ACR20 response by number of prior biological anti-TNF agents | | | | |
| 1 prior agent | 3/30 (10.0) | 8/23 (34.8) | 10/28 (35.7) | 18/51 (35.3) |
| >1 prior agent | 6/32 (18.8) | 14/37 (37.8) | 10/30 (33.3) | 24/67 (35.8) |
| PASI75 response by number of prior biological anti-TNF agents* | | | | |
| 1 prior agent | 0/27 (0.0) | 7/15 (46.7) | 12/21 (57.1) | 19/36 (52.8) |
| >1 prior agent | 1/23 (4.3) | 13/29 (44.8) | 8/20 (40.0) | 21/49 (42.9) |
| HAQ-DI change from baseline by number of prior biological anti-TNF agents | | | | |
| 1 prior agent (n) | 30<br>0.00 (0.00 to 0.25) | 23<br>−0.13 (−0.38 to 0.00) | 28<br>−0.25 (−0.50 to 0.00) | 51<br>−0.25 (−0.50 to 0.00) |
| >1 prior agent (n) | 32<br>0.00 (−0.13 to 0.00) | 37<br>−0.13 (−0.38 to 0.00) | 30<br>0.00 (−0.38 to 0.00) | 67<br>−0.13 (−0.38 to 0.00) |
| *Week 52* (N) | 43† | 60 | 58 | 118 |
| ACR20 response by number of prior biological anti-TNF agents | | | | |
| 1 prior agent | 12/22 (54.5) | 11/21 (52.4) | 14/28 (50.0) | 25/49 (51.0) |
| >1 prior agent | 4/18 (22.2) | 9/33 (27.3) | 8/26 (30.8) | 17/59 (28.8) |
| PASI75 response by number of prior biological anti-TNF agents* | | | | |
| 1 prior agent | 8/20 (40.0) | 5/13 (38.5) | 12/21 (57.1) | 17/34 (50.0) |
| >1 prior agent | 5/10 (50.0) | 8/23 (34.8) | 8/19 (42.1) | 16/42 (38.1) |
| HAQ-DI change from baseline by number of prior biological anti-TNF agents | | | | |
| 1 prior agent (n) | 22<br>0.00 (−0.13 to 0.13) | 21<br>−0.25 (−0.50 to 0.00) | 28<br>−0.19 (−0.50 to 0.00) | 49<br>−0.25 (−0.50 to 0.00) |
| >1 prior agent (n) | 18<br>0.00 (−0.13 to 0.13) | 33<br>−0.13 (−0.38 to 0.00) | 26<br>0.00 (−0.50 to 0.00) | 59<br>0.00 (−0.50 to 0.00) |

Data are reported as n (%), n/N (%) or median (IQR).
*Among patient with ≥3% BSA psoriasis skin involvement at baseline.
†Excludes patients who did not receive ustekinumab.
ACR, American College of Rheumatology; BSA, body surface area; HAQ-DI, Health Assessment Questionnaire-Disability Index; PASI, Psoriasis Area and Severity Index; TNF, tumour necrosis factor-α; UST, ustekinumab.

observed in the larger phase 3, multicentre, placebo-controlled PSUMMIT 1 trial of 615 biologically-naïve patients with active PsA through week 52, in which ustekinumab was shown to significantly improve signs and symptoms of disease and patient physical function.[14] Note that the results of combined radiographic findings across the PSUMMIT 1 and PSUMMIT 2 trials are the subject of a forthcoming publication.[31]

Clinical improvements translated into significantly improved physical function and quality of life among ustekinumab-treated patients. Nearly half of the ustekinumab-treated patients achieved a clinically meaningful improvement from baseline to week 24 in FACIT-Fatigue score compared with approximately one-quarter of placebo-treated patients.

Although the PSUMMIT 2 trial was not designed to compare the efficacy or safety of concomitant MTX versus no concomitant MTX treatment, or of anti-TNF-experienced versus anti-TNF-naïve patient groups, ustekinumab treatment appeared effective regardless of concomitant MTX use and, importantly, also among all combined anti-TNF-experienced patients, although to a lesser degree than was observed in anti-TNF-naïve patients. Lower clinical response rates in anti-TNF-experienced patients who switch to a second biological agent are well documented for rheumatoid arthritis,[32] psoriasis[12 33] and now in the PSUMMIT 2 PsA trial (table 3). In a longitudinal observational study of 95 PsA patients who switched from one to another TNF inhibitor, significantly poorer responses were noted compared with patients who did not switch (n=344) (ACR50 response: 22.5% vs 40.0%, DAS28 remission: 28.2% vs 54.1%).[34] Similarly, among 548 Danish PsA patients who switched from their first TNF inhibitor to a second biological agent, response rates were lower with the second treatment ($p<0.01$ for each agent vs initial TNF inhibitor).[35] Thus, response to ustekinumab may possibly be reduced in anti-TNF-experienced patients, particularly those previously treated with multiple anti-TNF agents, given findings observed through 1 year of ustekinumab therapy in PSUMMIT 2 (table 3) and those observed with other biological agents as noted above. While the reason(s) for the lower response rates remain unclear, it is possible that prior treatment with TNF inhibitors alters the natural history and clinical response to other agents in patients with psoriasis and/or PsA, or that such patients may be recalcitrant to multiple therapies. This is an important area of future research.

Patient discontinuation rates were 29.4% and 15.9% among anti-TNF-experienced and anti-TNF-naïve patients, respectively; this difference was particularly notable in placebo patients (that is, 42% vs 12% of patients) and could have been related to the longer duration and greater activity of disease that specifically characterised anti-TNF-experienced patients. These cofactors may also have contributed to the lower response rates in anti-TNF-experienced patients.

We observed an apparent diminution of response at week 16 (prior to the third dose of study agent), but also noted a peak effect at weeks 24–28. These observations could be related to the 12-week dosing interval and potential achievement of steady-state pharmacokinetics at weeks 24–28 and/or a low serum drug level in some patients at week 16. In psoriasis, partial loss of response to ustekinumab has been observed in some patients during the 2-week period preceding the next ustekinumab injection in observational studies and in clinical trials.[10 11 33] Thus, as with many drugs, shorter or longer dosing intervals may prove optimal for some patients. Results of

**Table 4** Summary of safety through week 16 and week 24 among all patients who received at least one study agent injection

| | Week 16 (placebo-controlled period)* | | | | Week 24* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo (N=104) | UST 45 mg (N=103) | UST 90 mg (N=104) | Combined UST (N=207) | Placebo (N=104) | Placebo→UST 45 mg (N=31) | UST 45 mg (N=103) | UST 90 mg (N=104) | All UST (N=238) |
| Average weeks of follow-up | 15.1 | 16.0 | 15.9 | 16.0 | 19.4 | 8.2 | 23.8 | 23.3 | 21.6 |
| AEs, n (%) | 57 (54.8) | 65 (63.1) | 63 (60.6) | 128 (61.8) | 66 (63.5) | 13 (41.9) | 73 (70.9) | 72 (69.2) | 158 (66.4) |
| Common AEs† | | | | | | | | | |
| Nasopharyngitis | 5 (4.8) | 8 (7.8) | 10 (9.6) | 18 (8.7) | 8 (7.7) | 0 (0.0) | 10 (9.7) | 13 (12.5) | 23 (9.7) |
| Headache | 4 (3.8) | 5 (4.9) | 5 (4.8) | 10 (4.8) | 5 (4.8) | 2 (6.5) | 7 (6.8) | 6 (5.8) | 15 (6.3) |
| Arthralgia | 1 (1.0) | 5 (4.9) | 4 (3.8) | 9 (4.3) | –‡ | – | – | – | – |
| Upper respiratory tract infection | 4 (3.8) | 5 (4.9) | 3 (2.9) | 8 (3.9) | 4 (3.8) | 3 (9.7) | 10 (9.7) | 6 (5.8) | 19 (8.0) |
| Fatigue | 0 (0.0) | 5 (4.9) | 2 (1.9) | 7 (3.4) | – | – | – | – | – |
| Nausea | 2 (1.9) | 4 (3.9) | 3 (2.9) | 7 (3.4) | – | – | – | – | – |
| Back pain | 0 (0.0) | 1 (1.0) | 4 (3.8) | 5 (2.4) | – | – | – | – | – |
| Diarrhoea | 3 (2.9) | 4 (3.9) | 1 (1.0) | 5 (2.4) | – | – | – | – | – |
| Oropharyngeal pain | 0 (0.0) | 4 (3.9) | 1 (1.0) | 5 (2.4) | – | – | – | – | – |
| Psoriasis | 3 (2.9) | 4 (3.9) | 1 (1.0) | 5 (2.4) | – | – | – | – | – |
| Psoriatic arthropathy | 5 (4.8) | 4 (3.9) | 1 (1.0) | 5 (2.4) | – | – | – | – | – |
| Discontinued study agent due to AEs, n (%) | 8 (7.7) | 2 (1.9) | 2 (1.9) | 4 (1.9) | 11 (10.6) | 0 (0.0) | 2 (1.9) | 3 (2.9) | 5 (2.1) |
| Serious AEs, n (%)§ | 5 (4.8) | 0 (0.0) | 1 (1.0) | 1 (0.5) | 5 (4.8) | 1 (3.2) | 0 (0.0) | 2 (1.9) | 3 (1.3) |
| Investigator-reported infection, n (%) | 25 (24.0) | 30 (29.1) | 26 (25.0) | 56 (27.1) | 30 (29.7) | 4 (12.9) | 42 (40.8) | 36 (34.6) | 82 (34.5) |

AEs with '–' did not meet the criteria for a 'common' events at that time point (see footnotes † and ‡).
*At week 16, patients with <5% improvement from baseline in both tender and swollen joint counts entered blinded early escape, such that patients receiving ustekinumab 45 mg increased to 90 mg and patients receiving placebo switched to ustekinumab 45 mg; patients receiving ustekinumab 90 mg continued with their blinded dose regimen. AEs through week 24 are cumulative and include those reported through week 16.
†AEs occurring in >2% of patients in the combined ustekinumab (week 16) or > 5% of patients in the all ustekinumab (week 24) groups; AEs are ordered according to decreasing frequency for the combined ustekinumab group at week 16.
‡AEs did not occur in >5% of patients in the All UST group.
§Serious AEs through week 16 included hyperglycaemia, depression, pyrexia, chronic cholecystitis/hypertension/cerebrovascular insufficiency, and interstitial lung disease in five placebo-treated patients and acute renal injury/syncope in one ustekinumab 90 mg patient. From weeks 16 to 24, an additional placebo patient had a serious event of suicidal ideation after early escape to ustekinumab 45 mg and an additional ustekinumab 90 mg patient had a serious event of arthritis.
AE, adverse event; UST, ustekinumab.

a retrospective case review of 129 ustekinumab-treated patients with psoriasis have demonstrated a reduction in efficacy for individuals weighing 90–100 kg and also receiving 45 mg.[36] Consistently, patients in PSUMMIT 1 and PSUMMIT 2 trials weighing >100 kg demonstrated an overall lower response than those weighing ≤100 kg. Pharmacokinetic factors and differences in the dynamics of cytokine down-regulation, coupled with varied responses of cell targets in joint, entheseal or skin lesions, may contribute to the delayed onset of ustekinumab peak response observed in PsA. This response contrasts with that observed with anti-TNF agents, which typically demonstrate higher proportions of patients with significant ACR20 efficacy at earlier time points,[37] although week 28 and week 52 ACR20, ACR50 and ACR70 response rates in the anti-TNF-naïve patients in PSUMMIT 2, as well as in PSUMMIT 1 trial,[14] appear consistent with those of other biological agents. Importantly, no such comparisons can be made for anti-TNF-experienced patients because no other trials have been conducted in a population this severe.

The safety of ustekinumab therapy in the treatment of patients with psoriasis and PsA has been compared during the placebo-controlled periods,[38] and through 3[39] and 5 years[40] of therapy; safety findings through week 60 in this study of patients with PsA appear to be consistent. Specifically, AEs and serious AEs were similar between ustekinumab-treated and placebo-treated patients through week 16. Through week 60, no deaths or cases of TB were reported, and one case of septic shock with *Candida* spp. identified in the stool was reported. Other serious infections were rare (one patient had bacteraemia), and two malignancies (squamous cell carcinoma in situ, breast cancer, both in anti-TNF-experienced patients) were reported through week 60. The two adjudicated events of myocardial infarction after week 16 occurred in anti-TNF-experienced patients with established cardiovascular risk factors.

Thus, the PSUMMIT 2 trial data through week 60 indicate that ustekinumab, representing an alternate mechanism of action to approved biological PsA therapies, induced significant improvement in the joint, enthesitis/dactylitis and skin symptoms of active PsA in a population including ~58% anti-TNF-experienced patients, with an acceptable safety profile. These data also provide further support for the role of the IL-12/23 p40 cytokines in PsA pathogenesis.

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