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Three Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Ustekinumab in Axial Spondyloarthritis

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Abstract

Objectives: The efficacy and safety of ustekinumab were evaluated in 3 randomized, placebo-controlled studies in patients with axial spondyloarthritis (axSpA). The first 2 studies included patients with radiographic axSpA (Study 1 [anti-tumor necrosis factor (TNF)-naïve]; Study 2 [anti-TNF refractory]), and Study 3 patients had non-radiographic axSpA.

Methods: In all 3 studies, patients were randomly assigned (1:1:1) to receive subcutaneous ustekinumab 45mg or 90mg or placebo up to 24 weeks, after which placebo-treated patients were rerandomized to receive ustekinumab 45mg or 90mg. The primary endpoint in Studies 1 and 2 was 40% improvement on Assessment of SpondyloArthritis international Society (ASAS40); for Study 3, it was 20% ASAS improvement (ASAS20). Other disease activity and safety measures were also evaluated. A Week 24 analysis of Study 1 was pre-planned to determine continuation of Studies 2 and 3.

Results: For Study 1, primary and major secondary endpoints were not met, and the study was discontinued. As a result, Studies 2 and 3 were prematurely discontinued before they were fully enrolled. For all 3 studies, neither ustekinumab dose group demonstrated clinically meaningful improvement over placebo on key efficacy endpoints. The proportion of patients experiencing adverse events in the ustekinumab groups was consistent with those in previous studies.

Conclusions: In these 3 placebo-controlled trials, efficacy of ustekinumab in the treatment of axSpA was not demonstrated. The safety profile was consistent with that of studies in other indications.

Keywords: axial spondyloarthritis, ankylosing spondylitis, ustekinumab, anti-interleukin 12/23, biologic.

Introduction

Axial spondyloarthritis (axSpA) is an immune-mediated systemic chronic inflammatory arthritis involving the axial skeleton that may involve peripheral joints. It is characterized by chronic inflammatory back pain (IBP; combination of morning stiffness, improvement with exercise and not with rest, and back pain in the second half of the night) and manifests with sacroiliitis, spondylitis, and enthesitis, which may lead to ankylosis (1). Extra-articular manifestations include uveitis, inflammatory bowel disease, and psoriasis. Chronic inflammation in axSpA can lead to bone loss and structural damage, including erosions and ankylosis of the sacroiliac (SI) joints and spine. This damage may lead to postural changes and mobility restriction resulting in functional impairment and decreased health-related quality of life (2, 3). AxSpA includes patients with non-radiographic axSpA (nr-axSpA; before the occurrence of definitive structural damage in the SI joints on X-ray) and radiographic axSpA (r-axSpA). The terms r-axSpA and ankylosing spondylitis (AS) describe the same subgroup of patients, with slight differences in the exact definitions (4, 5) (see also below).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat symptoms of axSpA in many patients; however, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or systemic corticosteroids are ineffective for the axial component. Anti-tumor necrosis factor (anti-TNF) therapies are approved for use in AS globally and for nr-axSpA in many countries. More recently, a monoclonal antibody that inhibits interleukin (IL)-17A was approved to treat adults with AS (6). Although these agents show efficacy in many patients with axSpA, some patients do not respond adequately; thus, there is a need to target other mechanisms of action (7, 8).

AxSpA may be triggered by a combination of genetic and environmental factors. AxSpA is strongly associated with human leukocyte antigen (HLA)-B27; its misfolding and accumulation can activate upregulation of IL-23 production and induction of the T-helper (T_h)17 axis (9). The IL-23/T_h17 axis has gained attention recently as a possible inflammatory pathway for axSpA (10, 11), suggesting that IL-23 is involved in disease pathogenesis (12, 13).

Ustekinumab, a human monoclonal antibody targeting the IL-12/23 p40 subunit, is effective in treating active psoriasis (14, 15), Crohn's disease (16), and psoriatic arthritis (PsA) (17-20), including inhibition of radiographic progression, and has been shown to improve spondylitis symptoms in a subgroup of PsA patients with physician-reported spondylitis (21). A small, open-label study suggested preliminary efficacy of ustekinumab for the treatment of AS (8). Twenty patients with active AS received ustekinumab 90mg at Weeks 0, 4, and 16. Clinically meaningful improvements were noted at Week 24, and significant improvements in inflammation were observed in magnetic resonance imaging (MRI) parameters (8).

In the 3 randomized, placebo-controlled studies reported here, efficacy and safety of ustekinumab were evaluated in patients with active axSpA (radiographic or non-radiographic).

Patients and Methods

Study Design

Two parallel, Phase 3, multicenter, randomized, double-blind, placebo-controlled studies evaluated treatment with ustekinumab 45mg and 90mg in patients with active r-axSpA who were inadequate responders or intolerant to NSAIDs and were naïve to anti-TNF therapy (Study 1) or refractory to a single anti-TNF agent (Study 2). A third study evaluated patients with active nr-axSpA who had inadequate response or were intolerant to NSAIDs and could have had exposure to a single anti-TNF agent (Study 3). These studies were conducted in accordance with the principles of the Declaration of Helsinki. Each patient gave written informed consent. An independent data monitoring committee regularly reviewed unblinded safety data.

In all 3 studies, patients were randomly assigned (1:1:1) to receive subcutaneous (SC) administration of ustekinumab 45mg or 90mg at Weeks 0, 4, and 16 and then every 12 weeks (q12w) or placebo at Weeks 0, 4, and 16. Placebo-treated patients were rerandomized at Week 24 to receive ustekinumab 45mg or 90mg at Weeks 24 and 28 and then q12w. For Studies 1 and 2, at Week 16, patients in all 3 treatment groups who qualified for early escape (EE; <10% improvement from baseline in both total back pain and morning stiffness measures at both Weeks 12 and 16) received open-label golimumab 50mg SC at Week 16 and every 4 weeks thereafter through Week 52. Final safety evaluations were to be performed at Weeks 64 (Study 2) and 112 (Study 1).

In Study 3, patients in the placebo group who met EE criteria were to be rerandomized at Week 16 in a blinded fashion to SC ustekinumab 45mg or 90mg and dosed at Weeks 16, 20, 28, and q12w thereafter through Week 52. At Week 24, all remaining placebo-treated patients crossed over to either ustekinumab 45mg or 90mg at Weeks 24 and 28, then q12w. All patients who achieved inactive disease at both Weeks 40 and 52 were to be rerandomized at Week 52 to either remain on ustekinumab or switch to placebo. The study was to continue to Week 100.

Inclusion/Exclusion Criteria

A central reader assessed the presence or absence of modified New York (mNY) criteria for radiographic sacroiliitis for all 3 studies and the Assessment of SpondyloArthritis international Society (ASAS) definition for MRI of the SI joints for Study 3. In Studies 1 and 2, eligible adult patients (≥18 years of age) fulfilled mNY criteria for AS (4). They also had active disease, defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (22) ≥4 and a Visual Analog Scale (VAS) for total back pain ≥4, at screening and baseline, a high-sensitivity C-reactive protein (hsCRP) level ≥0.3 mg/dL at screening, and inadequate response or intolerance to a single anti-TNF agent (Study 2) but were otherwise biologic-naïve. Concomitant NSAIDs, glucocorticoids (≤10mg prednisone equivalent per day), or the csDMARDs methotrexate, sulfasalazine, or hydroxychloroquine were permitted; however, NSAIDs and glucocorticoids required stable doses for ≥2 weeks, and csDMARDs were to be stable for ≥4 weeks prior to baseline. Patients with complete ankylosis of the spine (assessed locally) were limited to 10% of the study population. Key exclusion criteria included other inflammatory diseases, active infection, uncontrolled concomitant diseases, and pregnancy.

For Study 3, adults (18 to 50 years of age) were eligible if they had active nr-axSpA, fulfilling the ASAS criteria (5) for axSpA (back pain ≥3 months and age at onset by 45 years of age as well as evidence of active acute inflammation on MRI and ≥1 SpA feature **or** HLA-B27-positive and ≥2 SpA features)

without radiographic sacroiliitis according to mNY criteria (4). Patients without a positive MRI of the SI joints according to the ASAS definition required an elevated hsCRP ≥0.6 mg/dL at screening. All patients had active disease as defined in Studies 1 and 2; patients could have been exposed to 1 anti-TNF agent.

Outcome Assessments

Primary and Major Secondary Endpoints

The primary endpoint was the proportion of patients who achieved an ASAS40 response at Week 24 in Studies 1 and 2 and an ASAS20 response at Week 24 in Study 3 (23-25). Major secondary endpoints were the proportions of patients who achieved an ASAS20 response (Studies 1 and 2) and ASAS40 response (Study 3), 50% improvement in BASDAI (BASDAI50), change from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) (26), and the proportion of patients with Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP inactive disease (score <1.3) (27).

Additional Secondary Endpoints

Additional secondary endpoints included changes from baseline in hsCRP and ASDAS-CRP. A subset of patients from Study 1 underwent MRI for spinal inflammation assessment using the Berlin MRI scoring method (28) (baseline and Week 24, averaged scores of 2 central readers). During the double-blind period of Studies 1, 2, and 3, serum samples were collected to evaluate ustekinumab pharmacokinetics, antibodies to ustekinumab, and/or biomarkers. Evaluation of the presence of antibodies to ustekinumab utilized a drug-tolerant enzyme chemiluminescent immunoassay (ECLIA) in patients who received ≥1 administration of ustekinumab and had ≥1 post-administration sample available.

Serum biomarkers were assayed using the Singulex system (IL-17A, IL-17F, IL-22, and IL-23), Meso Scale Discovery Platform (matrix metalloproteinase [MMP]-1, MMP-3, MMP-9, interferon-gamma [IFN-γ], IL-12p70, IL-6, IL-8, TNF-alpha [TNF-α], CRP, serum amyloid A [SAA], soluble intercellular adhesion molecule 1 [sICAM-1], and soluble vascular cell adhesion molecule 1 [sVCAM-1]), R&D Quantikine human enzyme-linked immunosorbent assay (ELISA) (chemokine [C-X-C motif] ligand 13 protein [CXCL13]), and Cisbio human kit (S100 calcium-binding protein A12 [S100A12]). Biomarkers were evaluated in a subset of patients from Studies 1 and 2, and clinical responders were oversampled versus the overall study population to increase statistical power for testing clinical response associations.

Due to the study discontinuation, most secondary endpoints were only summarized for samples from Study 1.

Safety outcomes included the proportions of patients experiencing treatment-emergent adverse events (AEs) and serious AEs (SAEs) from baseline to the end of study, along with clinical laboratory testing.

Statistical Methods

Sample sizes of all 3 studies were chosen to achieve 90% power to detect treatment differences between ustekinumab and placebo for the primary endpoint at a 2-sided significance level of 0.05. Sample size calculations were based on results from a ustekinumab investigator-initiated study and a

certolizumab pegol axSpA study (29). For Study 1, the planned sample size calculation was based on anticipating an ASAS40 response of 40% in the ustekinumab group and 20% in the placebo group with n=109 for each group. For Study 2, the planned sample size calculation was based on an ASAS40 response of 30% in the ustekinumab group and 15% in the placebo group with n=161 for each group. For Study 3, the planned sample size calculation was based on the ASAS20 responses in the ustekinumab groups versus the placebo groups: 50% versus 35% in the anti-TNF inadequate responder group and 60% versus 40% in the other group (anti-TNF-naïve and anti-TNF experienced patients) with n=130 for each group. It was pre-planned to determine continuation of Studies 2 and 3 based on the Study 1 results at Week 24.

For Study 1, efficacy analyses were performed using the modified intent-to-treat (mITT) population, which included all patients who received ≥1 dose of study medication. Primary and major secondary endpoints were analyzed sequentially to control for multiplicity and were contingent on the success of the primary analysis.

Because Studies 2 and 3 were terminated early based on Study 1 results, a modified full analysis set was defined that included patients who were anticipated to have reached the Week 24 visit. Additionally, only selected efficacy analyses through Week 24, including primary and major secondary endpoints, were performed.

The following analysis rules were applied to all 3 studies. For dichotomous responder-type endpoints, patients with missing post-baseline responses or those who met treatment failure criteria (initiating new therapies or increasing concomitant medication doses for axSpA or discontinuing study treatment due to lack of efficacy) were classified as non-responders. Patients who entered EE at Week 16 were considered non-responders for dichotomous endpoints at Weeks 20 and 24; measurement values at those weeks were set as missing for continuous endpoints. The Cochran-Mantel-Haenszel chi-square test was used to compare categorical variables. Generally, continuous parameters were compared using a Mixed Model Repeated Measurements with treatment group, strata, baseline value, visit week, and an interaction of treatment and visit week as independent variables. All statistical testing was performed at a 2-sided α-level of 0.05.

Patients who received ≥1 dose of study medication were included in safety analyses.

Serum proteins for biomarker analysis were assayed at Weeks 0, 4, and 16 from a subset of patients from Study 1 (n=105 ustekinumab arms [pooled dose groups], n=45 placebo, n=40 demographically matched healthy controls) and Study 2 (n=41 ustekinumab arms [pooled dose groups], n=29 demographically matched healthy controls), with the exception of T_h17 analytes, which were measured only at baseline in a small subset of patients (n=29 ustekinumab randomized, n=29 healthy controls). Significance was defined by $p<0.05$ and absolute value of fold change >1.2 or $p<0.05$ and Pearson correlation coefficient $r>0.25$.

Results

Patient Disposition

Data were collected from July 2015 to September 2017. Patients were randomized at 58 sites in 7 countries for Study 1, 114 sites in 19 countries for Study 2, and 93 sites in 14 countries for Study 3. The scheduled Week 24 database lock and review of results for Study 1 showed that the primary and

major secondary endpoints were not met for either ustekinumab dose. As a result, the sponsor discontinued all 3 studies in May 2017.

A total of 2062 patients were screened, of whom 1018 were randomized and 1017 were treated (Figure 1, Supplemental Figure 1, and Supplemental Figure 2). Safety data were evaluated for treated patients, and all 346 treated patients were evaluable for efficacy in Study 1. Efficacy was evaluated in a subset of the mITT population for Study 2 (n=213, 44.1% of planned sample size) and Study 3 (n=250, 64.1% of planned sample size) as a result of sponsor-initiated early study termination.

Overall, in Studies 1 and 2, 85% and 83% of patients were male, 73% and 79% were white, mean age was 39.0 and 41.2 years, and mean duration of IBP was 10.8 and 14.3 years, respectively. In Study 3 overall, 51% of patients were male, 85% were white, mean age was 34.3 years, and mean duration of IBP was 4.5 years. Approximately 12% of patients in Study 3 were anti-TNF-experienced. Baseline demographics and disease characteristics are shown in Table 1. All patients in Study 1 and Study 2 met the mNY criteria for AS, as specified in the protocol, and 92.8% and 93.7% met the ASAS classification criteria for r-axSpA, respectively (7.2% and 6.3% had IBP that started at or after age 45 in Study 1 and Study 2, respectively, and therefore, did not formally fulfill the ASAS axSpA criteria).

The subset of patients included in the Study 1 MRI analysis (n=104) were primarily male (78%) and white (98%) and had a mean ± standard deviation (SD) age of 38.2 ± 11.2 years, a mean ± SD duration of IBP of 10.0 ± 8.4 years, and a mean ± SD hsCRP level of 2.7 ± 2.6 mg/dL. Mean baseline ASAS20/40 response component scores for this subset of patients ranged from 7.2 to 7.9.

Efficacy Outcomes

Results for primary and major secondary endpoints for Studies 1 (Figure 2), 2, and 3 are shown in Table 2.

In Study 1 (naïve to anti-TNF therapy), primary (ASAS40) and major secondary endpoints were not achieved. At Week 16, EE criteria were met by patients in the placebo (22%), ustekinumab 45mg (18%), and 90mg (12%) groups. No patient met treatment failure criteria. The proportions of patients who achieved ASAS40 response in the ustekinumab 45mg (31%) and 90mg (28%) groups and placebo (28%) were not significantly different (Figure 2). Neither ustekinumab dose group demonstrated improvement over placebo in achieving ASAS20, BASDAI50, ASDAS-CRP inactive disease (<1.3), or mean change from baseline for BASFI (Figure 2). In general, secondary efficacy and health-related quality of life endpoints did not show meaningful differences between treatment groups. However, modest improvement was noted for the change in hsCRP from baseline, which was generally greater in both ustekinumab groups over placebo as early as Week 4 through Week 24. At Week 24, mean changes from baseline in hsCRP were numerically higher in the ustekinumab-treated groups versus the placebo group (Table 2). Additionally, in the MRI sub-study, the mean change from baseline Berlin MRI spine score of patients evaluated at Week 24 was -0.6 for the ustekinumab 45mg group, -1.2 for the 90mg group, and -0.5 for the placebo group.

In Study 2 (anti-TNF-refractory), early study discontinuation prohibited valid statistical testing and formulating subsequent clinical conclusions. The proportion of patients with ASAS40 response (primary endpoint) in the ustekinumab 45mg and 90mg groups was 19% and 27%, respectively, and

12% in the placebo group. Similar patterns were noted for major secondary endpoints (Table 2). At Week 24, mean changes from baseline in hsCRP were not numerically larger in the ustekinumab-treated groups versus the placebo group (Table 2).

In Study 3 (nr-axSpA), 55% and 49% of patients in the ustekinumab 45mg and 90mg groups, respectively, achieved ASAS20 response (primary endpoint) versus 48% in the placebo group. Similar patterns were noted in major secondary endpoints (Table 2). At Week 24, mean changes from baseline in hsCRP were numerically higher in the ustekinumab-treated groups versus the placebo group (Table 2).

Safety

Through the end of Week 24, the proportions of patients experiencing AEs in the ustekinumab groups were consistent across treatment groups in all 3 studies (Table 3 and Table 4) and similar between the active and placebo groups. No patient died, experienced a serious or opportunistic infection, or presented with malignancy or active tuberculosis. In all 3 studies, <2.0% of ustekinumab-treated patients had an injection-site reaction; all were mild in severity.

In Study 1, through Week 24, 43% of patients in the placebo group and 40% in the combined ustekinumab groups had ≥1 AE. No patient in Study 1 discontinued due to AEs through Week 24 (Table 3). During this period, 2 placebo-treated patients reported an SAE (ischemic stroke and vertebrobasilar insufficiency). In the combined ustekinumab group, 3 patients reported an SAE (subdural hematoma, osteoarthritis, and facial paralysis).

The proportion of patients reporting AEs through Week 24 for Studies 2 (Table 3) and 3 (Table 4) was similar to Study 1 (Table 3). In Study 2, discontinuation due to an AE through Week 24 occurred for 1 placebo-treated patient (back and musculoskeletal pain) and 3 ustekinumab-treated patients (worsening of AS, arthralgia, and back pain). During this period, 3 SAEs were reported in 3 placebo patients (uterine prolapse, back pain, and myocardial ischemia), and 10 SAEs were reported in 7 ustekinumab patients (upper abdominal pain, nausea, vomiting, obesity, uterine polyp, gastrointestinal hemorrhage, cholelithiasis, worsening of AS, rotator cuff syndrome, and cerebrovascular accident). In Study 3, 1 ustekinumab-treated patient discontinued due to an AE (pustular psoriasis) through Week 24 (Table 4). During this period, SAEs were reported for 2 placebo patients (uveitis and worsening of axSpA) and 3 ustekinumab patients (inguinal hernia, chronic sinusitis, and ankle fracture).

For all 3 studies, through end of study (Supplemental Table 1 and Supplemental Table 2), the safety profile was consistent with what was reported through Week 24 (Table 3 and Table 4). In Study 1, after Week 24, an additional 6 ustekinumab-treated patients reported 9 SAEs. In Study 2, after Week 24, an additional 3 ustekinumab-treated patients reported SAEs. In Study 3, after Week 24, an additional 7 ustekinumab-treated patients reported SAEs. Serious infections were reported for 2 patients in Study 1 and 1 patient in Study 3. No patient presented with malignancy or active tuberculosis. In Study 1 after Week 52, 1 patient (randomized to 45mg ustekinumab then early escaped to golimumab) reported a fatal SAE of blunt trauma. No deaths were reported for Studies 2 or 3.

Pharmacokinetics and Immunogenicity

After administration of ustekinumab at Week 0 and Week 4, then q12w in Study 1, serum ustekinumab concentrations were dose proportional without evidence of accumulation in ustekinumab concentrations over time, which was similar to prior studies with ustekinumab in PsA. Ustekinumab concentrations were reviewed to confirm that patients received ustekinumab versus placebo. Given the fixed dosing of ustekinumab, median ustekinumab concentrations were generally higher in the lower body weight quartiles than in the higher body weight quartiles. Patients with lower baseline hsCRP had higher median ustekinumab concentrations than those with higher baseline hsCRP. Through Week 24, median ustekinumab concentrations were lower for ASAS40 non-responders than responders after receiving ustekinumab 45mg; however, median ustekinumab concentrations were similar between ASAS40 responders and non-responders for those who received ustekinumab 90mg. ASAS20 and ASAS40 response rates were consistent across the 4 trough ustekinumab concentration quartiles.

Antibodies to ustekinumab were detected in 18% of 230 patients through Week 24 using a validated drug-tolerant ECLIA. Antibody peak titers were generally low, with 11% (26/230) of patients positive for neutralizing antibodies. Patients positive for antibodies to ustekinumab had similar ASAS20 and higher ASAS40 responses than patients negative for antibodies to ustekinumab. No antibody-positive patients and 1 antibody-negative patient had an injection-site reaction through Week 24. Due to the early discontinuation, these analyses were not performed for Studies 2 and 3.

Biomarker Analysis

In Study 1, 10 of 18 analytes tested at baseline were either correlated with disease activity (ASDAS) or were elevated compared with matched healthy controls. However, neither T_h17 (IL-17A, IL-17F, IL-22, and IL-23) nor T_h1 (IFN-γ and IL-12p70) cytokines were dysregulated at baseline in AS compared with healthy controls (Supplemental Table 3). In Study 2, overall, there was greater elevation of inflammatory cytokines compared with Study 1, including the statistically significant dysregulation of IL-17A, MMP-3, and MMP-9 (but not IL-17F, IFN-γ, or IL-12p70), which did not reach statistical significance in Study 1. Additionally, a higher fold change of SAA, CRP, and TNF-α was observed in the cohort from Study 2. Although overall baseline levels of IL-17A were slightly higher in Study 2 compared with healthy controls, there was no association with clinical response in this small sample.

In Study 1, ustekinumab treatment had only a relatively minor impact on analytes at Weeks 4 and 16, with only MMP-3, SAA, and IL-8 being significantly decreased. The decreases in these 3 analytes were independent of Week 16 ASAS20 clinical response. In summary, in these cohorts, upregulation of acute inflammatory proteins (and MMPs) was seen, but very modest to no elevation of T_h17/T_h1 cytokines in the periphery was observed.

Discussion

The patients in these 3 randomized, placebo-controlled, Phase 3 studies demonstrated significant systemic inflammatory burden, as evidenced by mean disease activity scores and elevated hsCRP levels at baseline. Patients in Study 3 (nr-axSpA) required a positive MRI or hsCRP ≥0.6 mg/dL at screening. Results from the Week 24 database lock of Study 1 showed no treatment effect between

ustekinumab and placebo groups across primary and major secondary endpoints. Based on these results, the sponsor discontinued all 3 studies early. Not all patients in Studies 2 and 3 reached the Week 24 time point when the studies were discontinued, limiting the extent of those efficacy analyses. The efficacy data available through Week 24 of Studies 2 and 3 were inconclusive; however, no consistent trends of clinically relevant response were observed among primary and major secondary endpoints.

Because no formal Phase 2 dose-ranging study was performed, it may be questioned whether the ustekinumab doses studied were too low to achieve clinical response in axSpA. Median serum ustekinumab concentrations were lower for ASAS40 non-responders compared with responders receiving the 45-mg dose but were similar for those receiving the 90-mg dose. However, no difference was seen in ASAS20 or ASAS40 response rates across the trough concentration quartiles. Also, Studies 1 and 3 showed little difference between doses in the proportions of patients achieving primary and major secondary endpoints with the lower dose (45mg) having a slightly numerical advantage in Study 3. In Study 2, there appeared to be a dose response, but the separation from placebo was limited, and it was not consistent across endpoints. The hsCRP was modestly improved at most time points compared with placebo in Studies 1 and 3, but not in Study 2, which is in direct contrast to the hint of efficacy in clinical endpoints seen in Study 2. The MRI differences from Study 1 favored 90mg slightly, while 45mg and placebo were almost equivalent, which contrasts with the lack of clinical benefit demonstrated. Overall, these differences may represent chance variation over the program.

Blocking IL-12/23 p40 with ustekinumab has been shown to be efficacious in plaque psoriasis, PsA, and Crohn's disease (14-20), where elevation of the IL-23/IL-17 pathway has been reported (30-32). Despite both scientific and clinical rationale, including an open-label study of patients with AS (8) and improvement in PsA patients with physician-reported spondylitis (21), to support initiation of these Phase 3 studies of ustekinumab in axSpA, questions remain as to why ustekinumab was not effective. A recent review highlighted differences in axial disease in AS and PsA, suggesting that spondylitis may be driven by different mechanisms in those 2 diseases (33). While the immunopathogenesis of axSpA remains unknown, the interplay of genetics, (HLA-B27), exposure to microbial triggers originating from the gut or skin, as well as dysregulated innate and adaptive immune responses (T_h17 pathway) have been implicated (34). Although reports have been published demonstrating upregulation of the T_h17 pathway in the spine and joints (35, 36), there is conflicting evidence regarding dysregulation of the IL-23/IL-17 axis in the serum of AS patients (37-39). In the biomarker subpopulation that was assayed, upregulation of serum IL-17A was modestly increased only in Study 2, but there was no baseline elevation in serum IL-12p70, IL-23, IFN-γ, and IL-17A/F compared with healthy controls in either study. How these findings relate to the lack of clinically relevant efficacy of ustekinumab observed in these studies is unclear. It should be noted that serum cytokine levels may not fully represent disease mechanisms present locally in the joints or spine.

The therapeutic success of TNF and IL-17 blockers in controlling axSpA disease activity suggests that the etiology of axSpA may involve both inflammatory and immune mechanisms. IL-23^+ and IL-17^+ cells, more so than IL-12^+ cells, have been observed in the spine of patients with AS (35). Blockade of IL-12/23 p40 with ustekinumab did not show efficacy in AS, but neutralization of IL-17A is clinically effective (40), suggesting that the interplay between IL-12, IL-23, and IL-17 is complex in axSpA and warrants further studies to understand the results. There may be synergistic or opposing effects of

inhibiting IL-12 and IL-23 or sources of IL-17 secreted independently of T_h17 cells. For example, there is evidence to suggest that innate γδ T cells secrete IL-17 independently of IL-23 to protectively maintain the integrity of the epithelial barrier and prevent excessive permeability after injury (41, 42). Imbalances in immunopathogenic mechanisms driven by innate lymphoid cell populations may help explain the ineffectiveness of ustekinumab in axSpA.

AEs reported in these studies were consistent with the known safety profile of ustekinumab (15, 16, 19, 20). Through Week 24, AE rates in the combined ustekinumab group were similar to those in the placebo group in each study. Infections were the most common type of AE in all 3 studies. Through end of study, SAEs were reported by 3.2% of ustekinumab-treated patients, including 3 (0.3%) patients with serious infections. There were no opportunistic infections or malignancies during these studies.

Ustekinumab does not appear to be effective in the treatment of axSpA. Additional research is needed to better understand the pathogenic mechanisms and the cytokine pathways that manifest as axSpA. No new safety signals were identified, and the safety profile of ustekinumab in these populations was consistent with that observed in other indications.

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Figures

Figure 1

Patient Disposition Through Week 24 for Study 1 (anti-TNF-naïve AS). AE, adverse event; AS, ankylosing spondylitis; EE, early escape; EOS, end of study; FU, follow-up; TNF, tumor necrosis factor.

Figure 2

Primary and Major Secondary Endpoints at Week 24 for Study 1 (anti-TNF-naïve AS). A. Primary endpoint, proportion of patients who achieved an ASAS40 response at Week 24 (NS for both dose groups versus placebo). B. Major secondary endpoints of proportion of patients who achieved ASAS20 at Week 24 (NS for both dose groups versus placebo), who achieved BASDAI50 at Week 24 (NS for both dose groups versus placebo), and who had ASDAS-CRP inactive disease (<1.3) at Week 24 (NS for both dose groups versus placebo). C. BASFI mean change from baseline to Week 24 (NS for both dose groups versus placebo). AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; NS, not significant; TNF, tumor necrosis factor.

Tables

Table 1. Baseline Demographic and Disease Characteristics of Patients in Studies 1, 2, and 3. Data are presented as mean ± SD unless otherwise noted.

STUDY 1 (anti-TNF-naïve AS)	Placebo (N=116)	Ustekinumab 45 mg (N=116)	Ustekinumab 90 mg (N=114)	Ustekinumab Combined (N=230)	Total (N=346)
Age, years	38.3 ± 11.4	39.2 ± 10.5	39.5 ± 11.3	39.3 ± 10.9	39.0 ± 11.0
Male sex, n (%)	101 (87.1)	93 (80.2)	100 (87.7)	193 (83.9)	294 (85.0)
White, n (%)	86 (74.1)	84 (72.4)	82 (71.9)	166 (72.2)	252 (72.8)
Inflammatory back pain duration, years[a]	10.6 ± 7.8	11.2 ± 8.2	10.5 ± 8.3	10.9 ± 8.2	10.8 ± 8.1
Years since AS diagnosis	6.6 ± 7.0	6.3 ± 7.1	6.3 ± 6.5	6.3 ± 6.8	6.4 ± 6.8
HLA-B27 positive, n (%)	113 (97.4)	111 (95.7)	110 (96.5)	221 (96.1)	334 (96.5)
BASDAI (0-10)	7.4 ± 1.4	7.4 ± 1.3	7.3 ± 1.3	7.3 ± 1.3	7.4 ± 1.4
ASDAS-CRP[a]	4.3 ± 0.8	4.3 ± 0.7	4.3 ± 0.9	4.3 ± 0.8	4.3 ± 0.8
ASAS20/40 response components					
Patient's Global Assessment of Disease Activity (VAS) (0-10 cm)	7.5 ± 1.6	7.5 ± 1.6	7.6 ± 1.4	7.5 ± 1.5	7.5 ± 1.5
Total Back Pain (VAS) (0-10 cm)	7.6 ± 1.5	7.6 ± 1.4	7.7 ± 1.4	7.6 ± 1.4	7.6 ± 1.4
BASFI (0-10)	6.6 ± 2.2	6.8 ± 1.9	7.0 ± 1.6	6.9 ± 1.8	6.8 ± 1.9
Inflammation score[b]	7.5 ± 1.7	7.7 ± 1.5	7.7 ± 1.5	7.7 ± 1.5	7.6 ± 1.6
hsCRP, mg/dL[c]	2.1 ± 2.1	2.1 ± 2.2	2.5 ± 3.1	2.3 ± 2.7	2.2 ± 2.5

STUDY 2 (anti-TNF-refractory AS)	Placebo (N=104)	Ustekinumab 45 mg (N=106)	Ustekinumab 90 mg (N=105)	Ustekinumab Combined (N=211)	Total (N=315)
Age, years	40.8 ± 11.7	41.4 ± 11.3	41.5 ± 11.0	41.5 ± 11.2	41.2 ± 11.3
Male sex, n (%)	80 (76.9)	88 (83.0)	92 (87.6)	180 (85.3)	260 (82.5)
White, n (%)	82 (78.8)	84 (79.2)	84 (80.0)	168 (79.6)	250 (79.4)
Inflammatory back pain duration, years[a]	13.8 ± 9.6	13.6 ± 8.1	15.3 ± 10.8	14.5 ± 9.6	14.3 ± 9.6
Years since AS diagnosis	7.8 ± 6.7	9.1 ± 7.9	9.6 ± 8.1	9.3 ± 8.0	8.8 ± 7.6
HLA-B27 positive, n (%)	96 (92.3)	95 (89.6)	98 (93.3)	193 (91.5)	289 (91.7)
BASDAI (0-10)	7.5 ± 1.3	7.6 ± 1.4	7.5 ± 1.3	7.6 ± 1.3	7.5 ± 1.3
ASDAS-CRP[a]	4.5 ± 0.8	4.4 ± 0.8	4.4 ± 0.8	4.4 ± 0.8	4.5 ± 0.8
ASAS20/40 response components					
Patient's Global Assessment of Disease Activity (VAS) (0-10 cm)	8.1 ± 1.5	7.9 ± 1.4	7.9 ± 1.4	7.9 ± 1.4	8.0 ± 1.4
Total Back Pain (VAS) (0-10 cm)	7.8 ± 1.6	7.7 ± 1.5	7.8 ± 1.4	7.7 ± 1.4	7.8 ± 1.5
BASFI (0-10)	7.2 ± 1.6	6.9 ± 2.0	6.9 ± 1.7	6.9 ± 1.8	7.0 ± 1.8
Inflammation score[b]	7.8 ± 1.8	7.8 ± 1.9	7.8 ± 1.5	7.8 ± 1.7	7.8 ± 1.7
hsCRP, mg/dL[c]	2.8 ± 3.2	2.6 ± 2.7	2.5 ± 2.5	2.5 ± 2.6	2.6 ± 2.8

STUDY 3 (nr-axSpA)	Placebo (N=116)	Ustekinumab 45 mg (N=118)	Ustekinumab 90 mg (N=122)	Ustekinumab Combined (N=240)	Total (N=356)
Age, years	34.0 ± 8.8	33.9 ± 8.4	34.9 ± 9.1	34.4 ± 8.7	34.3 ± 8.7
Male sex, n (%)	64 (55.2)	53 (44.9)	63 (51.6)	116 (48.3)	180 (50.6)
White, n (%)	98 (84.5)	99 (83.9)	104 (85.2)	203 (84.6)	301 (84.6)
Inflammatory back pain duration, years[a]	4.0 ± 4.6	4.3 ± 4.9	5.2 ± 5.9	4.8 ± 5.5	4.5 ± 5.2

Years since axSpA diagnosis	1.4 ± 1.3	1.6 ± 1.5	1.6 ± 1.5	1.6 ± 1.5	1.5 ± 1.5
HLA-B27 positive, n (%)	89 (76.7)	93 (79.5)	95 (77.9)	188 (78.7)	277 (78.0)
BASDAI (0-10)	7.3 ± 1.4	7.4 ± 1.4	7.4 ± 1.3	7.4 ± 1.3	7.4 ± 1.3
ASDAS-CRP[a]	3.8 ± 0.9	3.7 ± 0.9	3.8 ± 0.9	3.8 ± 0.9	3.8 ± 0.9
ASAS20/40 response components					
Patient's Global Assessment of Disease Activity (VAS) (0-10 cm)	7.6 ± 1.6	7.5 ± 1.5	7.5 ± 1.5	7.5 ± 1.5	7.5 ± 1.5
Total Back Pain (VAS) (0-10 cm)	7.5 ± 1.6	7.5 ± 1.6	7.6 ± 1.4	7.6 ± 1.5	7.6 ± 1.5
BASFI (0-10)	6.1 ± 2.2	6.2 ± 2.0	6.2 ± 2.0	6.2 ± 2.0	6.1 ± 2.0
Inflammation score[b]	7.3 ± 1.9	7.4 ± 1.8	7.4 ± 1.7	7.4 ± 1.7	7.4 ± 1.8
hsCRP, mg/dL[c]	1.3 ± 2.0	1.3 ± 2.4	1.3 ± 2.1	1.3 ± 2.2	1.3 ± 2.1

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HLA, human leukocyte antigen; hsCRP, high-sensitivity C-reactive protein; nr-, non-radiographic; SD, standard deviation; TNF, tumor necrosis factor; VAS, Visual Analog Scale.

[a] Data missing at baseline for ≤2 patients.

[b] Average of the last 2 questions of the BASDAI concerning morning stiffness (0-10).

[c] Normal level for hsCRP is ≤0.287 mg/ dL.

Table 2. Primary, Major Secondary, and Other Selected Endpoints at Week 24 in Studies 1, 2, and 3. Data are presented as mean ± SD unless otherwise noted.

	Study 1 (anti-TNF-naïve AS)			Study 2 (anti-TNF-refractory AS)			Study 3 (nr-axSpA)		
	Placebo (N=116)	Ustekinumab 45 mg (N=116)	Ustekinumab 90 mg (N=114)	Placebo (N=73)	Ustekinumab 45 mg (N=73)	Ustekinumab 90 mg (N=67)	Placebo (N=82)	Ustekinumab 45 mg (N=83)	Ustekinumab 90 mg (N=85)
ASAS40[a], n (%)	33 (28.4)	36 (31.0)	32 (28.1)	9 (12.3)	14 (19.2)	18 (26.9)	21 (25.6)	28 (33.7)	24 (28.2)
ASAS20[a], n (%)	52 (44.8)	64 (55.2)	57 (50.0)	20 (27.4)	23 (31.5)	25 (37.3)	39 (47.6)	46 (55.4)	42 (49.4)
BASDAI50, n (%)	32 (27.6)	29 (25.0)	29 (25.4)	8 (11.0)	11 (15.1)	19 (28.4)	19 (23.2)	27 (32.5)	22 (25.9)
ASDAS-CRP inactive disease, n (%)	4 (3.4)	2 (1.7)	3 (2.6)	0	2 (2.7)	2 (3.0)	6 (7.3)	12 (14.5)	11 (12.9)
ASDAS-CRP change from baseline	-1.1 ± 1.1 (n=85)	-1.2 ± 1.0 (n=95)	-1.1 ± 1.0 (n=98)	0.8 ± 1.0 (n=43)	-1.0 ± 1.1 (n=44)	-1.1 ± 1.1 (n=42)	-1.2 ± 1.1 (n=61)	-1.4 ± 1.4 (n=71)	-1.4 ± 1.2 (n=62)
hsCRP (mg/dL) change from baseline	-0.4 ± 1.7 (n=87)	-0.7 ± 1.6 (n=95)	-0.9 ± 2.3 (n=98)	-0.4 ± 2.1 (n=43)	-0.1 ± 2.0 (n=44)	-0.3 ± 1.9 (n=43)	-0.4 ± 2.2 (n=61)	-0.6 ± 2.5 (n=71)	-1.0 ± 2.7 (n=62)
BASFI change from baseline	-1.9 ± 2.1 (n=88)	-2.1 ± 2.3 (n=95)	-2.1 ± 2.5 (n=99)	-1.3 ± 2.2 (n=44)	-1.7 ± 2.7 (n=44)	-2.2 ± 2.4 (n=42)	-2.1 ± 2.4 (n=61)	-2.3 ± 2.6 (n=72)	-1.9 ± 2.7 (n=63)

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; nr-, non-radiographic; SD, standard deviation; TNF, tumor necrosis factor.

[a] For Studies 1 and 2, ASAS40 was the primary endpoint and ASAS20 was a major secondary endpoint. For Study 3, ASAS20 was the primary endpoint and ASAS40 was a major secondary endpoint.

Table 3. Summary of Adverse Events Through Week 24 in Studies 1 and 2

	Placebo/Early Escape		Ustekinumab 45 mg/ Early Escape		Ustekinumab 90 mg/ Early Escape		Ustekinumab Only Combined[a]
	Placebo[a]	Placebo→ Golimumab[b]	45 mg only[a]	45 mg→ Golimumab[b]	90 mg only[a]	90 mg→ Golimumab[b]	
STUDY 1 (anti-TNF-naïve AS)	N=116	N=26	N=116	N=21	N=114	N=14	N=230
Duration of follow-up, weeks	22.1	8.0	22.6	8.0	23.0	7.9	22.8
Exposure, number of administrations	2.8	2.0	2.8	2.0	2.9	2.0	2.8
Patients with ≥1 AE, n (%)	50 (43.1)	1 (3.8)	46 (39.7)	4 (19.0)	46 (40.4)	2 (14.3)	92 (40.0)
Patients with ≥1 SAE, n (%)	2 (1.7)	0	2 (1.7)	0	1 (0.9)	0	3 (1.3)
Patients with AE leading to discontinuation, n (%)	0	0	0	0	0	0	0
Patients with ≥1 infections, n (%)	19 (16.4)	0	18 (15.5)	2 (9.5)	24 (21.1)	1 (7.1)	42 (18.3)
Patients with ≥1 serious infections, n (%)	0	0	0	0	0	0	0
STUDY 2 (anti-TNF-refractory AS)	N=104	N=21	N=106	N=21	N=105	N=20	N=211
Duration of follow-up, weeks	19.4	7.9	19.5	8.1	19.9	8.1	19.7
Exposure, number of administrations	2.6	2.0	2.5	2.0	2.6	2.0	2.5
Patients with ≥1 AE, n (%)	47 (45.2)	2 (9.5)	44 (41.5)	8 (38.1)	42 (40.0)	4 (20.0)	86 (40.8)
Patients with ≥1 SAE, n (%)	1 (1.0)	2 (9.5)	2 (1.9)	0	5 (4.8)	0	7 (3.3)
Patients with AE leading to discontinuation, n (%)	1 (1.0)	0	1 (0.9)	0	2 (1.9)	0	3 (1.4)
Patients with ≥1 infections, n (%)	17 (16.3)	0	16 (15.1)	3 (14.3)	17 (16.2)	1 (5.0)	33 (15.6)
Patients with ≥1 serious infections, n (%)	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; SAE, serious adverse event; TNF, tumor necrosis factor.

[a] Includes all patients, but AEs for patients who early escaped at Week 16 are only counted up to Week 16.

[b] Only includes patients who early escaped at Week 16. AEs are counted from early escape onward.

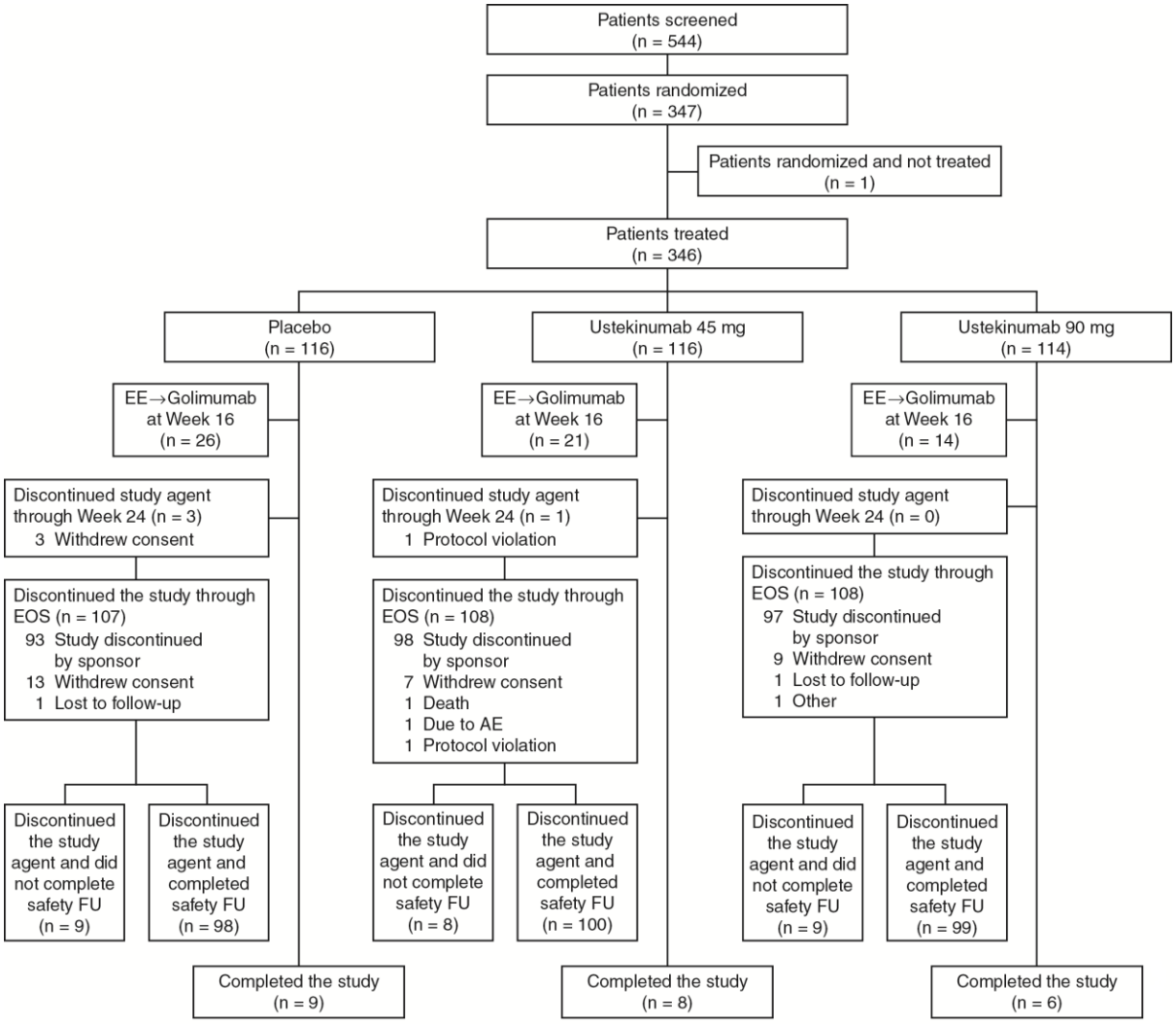
Table 4. Summary of Adverse Events Through Week 24 in Study 3

	Placebo[a]	Ustekinumab				
		Placebo→ 45 mg[b]	Placebo→ 90 mg[b]	45 mg only	90 mg only	Ustekinumab Only Combined
STUDY 3 (nr-axSpA)	N=116	N=10	N=10	N=118	N=122	N=260
Duration of follow-up, weeks	21.7	7.9	8.1	22.3	22.0	21.0
Exposure, number of administrations	3.3	1.9	1.9	2.8	2.7	2.7
Patients with ≥1 AE, n (%)	52 (44.8)	1 (10.0)	3 (30.0)	57 (48.3)	58 (47.5)	119 (45.8)
Patients with ≥1 SAE, n (%)	2 (1.7)	0	0	2 (1.7)	1 (0.8)	3 (1.2)
Patients with AE leading to discontinuation, n (%)	0	0	0	0	1 (0.8)	1 (0.4)
Patients with ≥1 infections, n (%)	26 (22.4)	1 (10.0)	1 (10.0)	22 (18.6)	30 (24.6)	54 (20.8)
Patients with ≥1 serious infections, n (%)	0	0	0	0	0	0

Abbreviations: AE, adverse event; axSpA, axial spondyloarthritis; nr-, non-radiographic; SAE, serious adverse event.

[a] Includes all patients, but AEs for patients who early escaped at Week 16 are only counted up to Week 16.

[b] Only includes patients who early escaped at Week 16. AEs are counted from early escape onward.



AE = Adverse event, EE = Early escape, EOS = End of study, FU = Follow-up