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OP0228

EFFICACY AND SAFETY OF IXEKIZUMAB VERSUS ADALIMUMAB (SPIRIT-H2H) WITH AND WITHOUT CONCOMITANT CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARD) IN BIOLOGIC DMARD-NAÏVE PATIENTS WITH PSORIATIC ARTHRITIS: 52-WEEK RESULTS

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Background: Ixekizumab (IXE), a high-affinity monoclonal antibody selectively targeting IL-17A, was superior to adalimumab (ADA) at Week (Wk) 24 for simultaneous achievement of ACR50 and 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI 100) (primary endpoint) in patients (pts) with active PsA from SPIRIT-H2H¹. SPIRIT-H2H had two major secondary endpoints and achieved both: noninferiority of IXE to ADA for ACR50 at Wk 24, and superiority of IXE to ADA for PASI 100 at Wk 24.

Objectives: To determine how concomitant conventional synthetic DMARD (csDMARD) use affects safety and efficacy of IXE and ADA in prespecified

subgroups defined by biologic monotherapy, concomitant MTX use, and concomitant csDMARD use through Wk 52 in SPIRIT-H2H.

Methods: SPIRIT-H2H (NCT03151551) was a 52-week, multicentre, randomised, open-label, assessor-blinded, parallel-group study evaluating the efficacy and safety of IXE versus ADA in adults with PsA and naïve to biologic DMARDs. Patients were required to have active PsA fulfilling Classification for Psoriatic Arthritis (CASPAR) criteria and ≥3/68 tender and ≥3/66 swollen joints, ≥3% plaque psoriasis BSA involvement, no prior treatment with bDMARDs, and with prior inadequate response to ≥1 csDMARD (but not necessarily current treatment with csDMARDs). Randomization (1:1) was stratified by concomitant use of csDMARD and the presence/absence of moderate to severe PsO (baseline: BSA≥10% + PASI≥12, + static Physician's Global Assessment≥3). Patients (N=566) received IXE/ADA through 52 wks according to the labelled dose dependent on presence/absence of moderate-to-severe PsO. In this prespecified subgroup analysis by presence or absence of csDMARD, efficacy outcomes through wk 52 were compared between IXE and ADA using logistic regression models and Fisher's exact tests. Missing data were imputed using non-responder imputation.

Results: At baseline, 167 of 283 IXE-treated patients and 169 of 283 ADA-treated patients had concomitant MTX use. Of these, 9.0% (15/167) and 7.1% (12/169) treated with IXE and ADA, respectively, were taking an additional csDMARD (sulfasalazine, cyclosporine, or leflunomide). A significantly greater proportion of patients on IXE versus ADA achieved the primary endpoint or PASI 100 when used as monotherapy or in combination with csDMARD (Figure 1A and 1C). At Wk 52, the proportion of patients achieving ACR50 was not statistically different between IXE and ADA, regardless of monotherapy or concomitant csDMARD use (Figure 1B). A significantly higher proportion of patients achieved MDA on IXE compared to ADA in the monotherapy subgroup (49% vs 33%), while the response rates were similar in both combination subgroups (Figure 1D). These data support consistent ACR50, PASI 100, and MDA response for IXE across all three subgroups. Frequencies of adverse events were similar across the three subgroups for IXE and ADA (Figure 2).

Conclusion: As with prior studies,^{2,3} consistent efficacy across multiple PsA disease-specific endpoints was observed with IXE in SPIRIT-H2H, regardless of whether IXE was taken as monotherapy or in combination with MTX or another csDMARD. No unexpected safety signals were found for either agent.

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Figure 1. Proportion patients through 52 weeks with simultaneous achievement of ACR50 + PASI 100, ACR50, and MDA-18 Enthesal Points. Nine patients with active PsO and BSA≥3% were assessed as PASI=0 at baseline, a medical inconsistency that was resolved using medical judgement. These patients were considered PASI 100 responders if PASI=0 and BSA=0 at post baseline visit. *p<.05 vs. ADA; †p<.01 vs. ADA; ‡p<.001 vs. ADA.

Abbreviations: ACR, American College of Rheumatology criteria; ADA, adalimumab; csDMARD, conventional synthetic DMARD; IXE, ixekizumab; MTX, methotrexate; MDA, minimal disease activity – PsA; PASI, Psoriasis Area Severity Index score.

Safety data for patients through 52 weeks. 2 events of IBD were reported in the ixekizumab treatment arm but only 1 case met the adjudication criteria of confirmed inflammatory bowel disease.

Abbreviations: ADA, adalimumab; csDMARD, conventional synthetic DMARD; IBD, inflammatory bowel disease; IXE, ixekizumab; MTX, methotrexate; TEAE, treatment emergent adverse event.

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OP0229

GUSELKUMAB INDUCES SUSTAINED REDUCTION IN ACUTE PHASE PROTEINS AND TH17 EFFECTOR CYTOKINES IN ACTIVE PSORIATIC ARTHRITIS IN TWO PHASE-3 CLINICAL TRIALS (DISCOVER-1 AND DISCOVER-2)

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Background: Guselkumab (GUS), an IL-23 inhibitor monoclonal antibody (Mab) that specifically binds to the IL-23p19 subunit, demonstrated efficacy compared to placebo (PBO) in reducing skin and musculoskeletal signs and symptoms in patients (pts) with active psoriatic arthritis (PsA) in two phase-3 studies, DISCOVER 1 & 2.^{1,2} Previous results from a GUS PsA Phase-2 trial³ and Ustekinumab (UST, anti-IL12/23p40 Mab) PsA Phase-3 trials (PSUMMIT 1 & 2)⁴ showed associations of baseline IL-17A, IL-17F, and CRP with baseline disease characteristics, and associations of GUS-induced cytokine reductions with clinical responses.

Objectives: To investigate plausible cytokine expression in PsA and alterations after exposure to GUS therapy.

Methods: In DISCOVER 1 & 2, pts were treated with GUS 100mg at Wk 0, 4, then every 8Wks (q8w); GUS 100mg q4w; or matching PBO. 21 serum biomarkers were measured in a random subset of 300 PsA pts from the DISCOVER program at Weeks (Wks) 0, 4, & 24 and in 34 healthy controls matched for age, sex, and ethnicity. Serum proteins measured were acute phase reactants CRP & SAA (Meso Scale Discovery (MSD) Platform) and inflammatory cytokines/chemokines: Th17 effector cytokines IL-17A, IL-17F, & IL-22 (Single Molecule Counting Erenna® Immunoassay Platform) and soluble ICAM-1, soluble VCAM-1, IL-6, CXCL-8, IL-10, IL-13, IL-12p70, CCL22, IFN-γ, CCL2, CCL4, TNFα, IL-1β, IL-2, IL-4 (MSD), & YKL-40 (Quantikine Immunoassay). Serum IL-17A, IL-17B, & CRP measured in the Phase-3 PSUMMIT trials of UST for PsA⁴ were included for comparison with GUS.

Results: At baseline, serum levels of acute phase proteins CRP, SAA, & IL-6, and Th17-effector cytokines IL-17A & IL-17F were elevated in pts with PsA compared with healthy controls ($p < 0.05$, geometric mean $\geq 40\%$ higher, FIG 1). There was no significant dysregulation in the other cytokines measured in PsA pts compared to healthy controls. Baseline IL-17A, IL-17F, IL-22, & CCL22 were significantly associated with baseline psoriasis disease activity (Body Surface Area & Psoriatic Area and Severity Index, Spearman Signed Rank $p < 0.05$, $r > 0.25$). Baseline CRP, SAA, IL-6, & YKL40 were significantly associated with baseline joint disease (Disease Activity Score 28-CRP, Spearman $p < 0.05$, $r > 0.25$). Baseline SAA, IL-6, IL-17A, & IL-17F were higher in pts with prior TNF inhibitor exposure than without ($p < 0.05$, geometric mean $\geq 40\%$ higher), although pts with PsA both with and without prior TNF inhibitor had higher levels than the healthy control set.

GUS treatment resulted in decreases in serum CRP, SAA, IL-6, IL-17A, IL-17F, & IL-22 that were significantly greater than PBO as early as Week 4 (FIG 1). These protein levels continued to decrease through Wk 24 in GUS-treated pts with both dosing regimens ($p < 0.05$, geometric mean decrease from baseline $\geq 33\%$). Further, Wk 24 IL-17A & IL-17F levels for pts treated with either dose of GUS were not significantly different from healthy controls, suggesting a normalization of peripheral effector cytokines associated with the IL-23/Th17 axis following treatment with GUS. Effects on IL-17A/IL-17F were greater in GUS treated pts than UST treated pts, while CRP levels were similar in both programs (FIG 2).

Conclusion: Comprising a strong pharmacodynamic effect, GUS treatment reduced serum protein levels of acute phase and Th17-effector cytokines (whose elevations at baseline were associated with PsA disease characteristics) and achieved comparable levels to those in healthy controls. In pts with PsA, reductions of IL-17A and IL-17F by GUS were of greater magnitude than those by UST.

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