## SUPPLEMENTARY MATERIALS

**Supplementary Table 1.** Maternal exposure during pregnancy events

| Event Preferred Term | Patient Age | Neonate Birth Type | Neonate Fetal Outcome | Trimester of Exposure |
|---|---|---|---|---|
| Pregnancy | 28-year-old partner's | Full-term | Normal | 1st trimester |
| Pregnancy of partner | age not provided | Full-term | Normal | 1st trimester |
| Unintended pregnancy | 36-year-old | Elective termination | N/A | 1st trimester |
| Maternal exposure during pregnancy | 42-year-old | Elective termination | N/A | 1st trimester |

N/A, non-applicable; UNK, unknown.

**Supplementary Table 2.** Latent tuberculosis per country

| Event Preferred Term | Study | Country |
|---|---|---|
| Interferon gamma release assay positive | I1F-MC-RHAP | Belgium |
| Interferon gamma release assay positive | I1F-MC-RHAP | Belgium |
| Interferon gamma release assay positive | I1F-MC-RHAP | Estonia |
| Interferon gamma release assay positive | I1F-MC-RHAP | Estonia |
| Interferon gamma release assay positive | I1F-MC-RHAP | Estonia |
| Interferon gamma release assay positive | I1F-MC-RHAP | Poland |
| Interferon gamma release assay positive | I1F-MC-RHAP | Poland |
| Interferon gamma release assay positive | I1F-MC-RHAP | Poland |
| Interferon gamma release assay positive | I1F-MC-RHAP | Poland |
| Interferon gamma release assay positive | I1F-MC-RHAP | Poland |
| Interferon gamma release assay positive | I1F-MC-RHAP | Poland |
| Interferon gamma release assay positive | I1F-MC-RHAP | Russia |
| Interferon gamma release assay positive | I1F-MC-RHAP | Russia |
| Latent tuberculosis | I1F-MC-RHAP | Spain |
| Latent tuberculosis | I1F-MC-RHAP | Poland |
| Latent tuberculosis | I1F-MC-RHAP | Poland |
| Latent tuberculosis | I1F-MC-RHAP | Poland |

| | | |
|---|---|---|
| Latent tuberculosis | I1F-MC-RHAP | Mexico |
| Latent tuberculosis | I1F-MC-RHAP | Mexico |
| Latent tuberculosis | I1F-MC-RHBE | USA |
| Latent tuberculosis | I1F-MC-RHBE | USA |
| Latent tuberculosis | I1F-MC-RHBE | Germany |
| Latent tuberculosis | I1F-MC-RHBF | Czech Republic |
| Latent tuberculosis | I1F-MC-RHBF | Estonia |
| Latent tuberculosis | I1F-MC-RHBF | Slovakia |
| Latent tuberculosis | I1F-MC-RHBF | Ukraine |
| Latent tuberculosis | I1F-MC-RHBF | South Africa |
| Latent tuberculosis | I1F-MC-RHBF | South Africa |
| Mycobacterium tuberculosis complex test positive | I1F-MC-RHAP | Ukraine |
| Mycobacterium tuberculosis complex test positive | I1F-MC-RHBF | Ukraine |
| Tuberculin test positive | I1F-MC-RHAP | United Kingdom |
| Tuberculin test positive | I1F-MC-RHAP | Bulgaria |
| Tuberculin test positive | I1F-MC-RHAP | Russia |
| Tuberculin test positive | I1F-MC-RHBF | Czech Republic |
| Tuberculin test positive | I1F-MC-RHBF | Czech Republic |

**Supplementary Table 3.** Summary of safety of IXE80Q4W and IXE80Q2W

| | **Integrated IXE80Q4W PsA N=648** | **Integrated IXE80Q2W PsA N=752** |
|---|---|---|
| **Total patient-years of exposure** | 1035.6 | 1370.0 |
| | **n (EAIR)** | **n (EAIR)** |
| **Death** | 2 (0.2) | 4 (0.3) |
| **AE leading to discontinuation (including death)** | 47 (4.5) | 67 (4.9) |
| **SAE[a]** | 67 (6.5) | 74 (5.4) |
| **≥1 TEAE[b]** | 521 (50.3) | 637 (46.5) |
| Mild | 194 (18.7) | 276 (20.1) |
| Moderate | 285 (27.5) | 287 (20.9) |
| Severe | 42 (4.1) | 74 (5.4) |
| **Most common TEAEs[c]** | | |
| Upper respiratory tract infection | 80 (7.7) | 119 (8.7) |
| Nasopharyngitis | 72 (7.0) | 99 (7.2) |
| Injection site reaction | 41 (4.0) | 109 (8.0) |
| **TEAEs of special interest** | | |
| Infections | 341 (32.9) | 453 (33.1) |
| Injection site reactions (broad term) | 97 (9.4) | 168 (12.3) |
| Allergic reactions/hypersensitivity | 39 (3.8) | 61 (4.5) |
| Malignancies | 10 (1.0) | 6 (0.4) |
| Depression[d] | 15 (1.4) | 23 (1.7) |
| MACE[e] | 3 (0.3) | 8 (0.6) |
| Cytopenia[f] | 24 (2.3) | 39 (2.8) |

Patients with moderate to severe plaque psoriasis in SPIRIT-H2H received IXEQ2W from week 2 to week 12 then continue with IXEQ4W, the first 12 weeks of exposure was grouped into IXEQ4W for this analysis.

[a]The data collection for the clinical trial database does not specify when events become serious, therefore, the numbers show may represent more serious events than actually occurred during the treatment period.

[b]Patients with multiple occurrences of the same event are counted under the highest severity.

[c]Defined as frequency of TEAEs ≥5%.

[d]Broad, according to SMQ or sub-SMQ classification.

[e]The data represents adjudicated cases.

[f]Broad, according to SMQ classification.

AE, adverse event; EAIR, exposure-adjusted incidence rate per 100 patient-year, IXE80Q4W, ixekizumab 80 mg Q4W; IXE80Q2W, ixekizumab 80 mg Q2W; IXE = ixekizumab; MACE, major adverse cerebro-cardiovascular event; N, number of patients in analysis population; n, number of patients in each category; PsA, psoriatic arthritis; SAE, serious adverse event; SMQ, Standardized MedDRA queries; TEAE, treatment-emergent adverse event.

**Supplementary Protocol –**

**Study design**

SPIRIT-P1 and SPIRIT-P2 were 156-week, phase 3, randomized, double-blind, placebo-controlled trials in patients with active PsA. In SPIRIT-P1, patients were bDMARD-naïve. In SPIRIT-P2, patients had an inadequate response or intolerance to 1 or 2 tumor necrosis factor inhibitors in SPIRIT-P2 and must have been treated with at least 1 csDMARDs.

SPIRIT-P3 was a phase 3, 104-week study with a 36-week open-label period followed by a double-blind randomized withdrawal period which evaluated the effect of ixekizumab twice weekly in patients with active PsA. Patients were bDMARD-naïve and must have had an inadequate response or intolerance to at least 1 csDMARD.

SPIRIT-H2H was a phase 4 randomized, open-label, head-to-head 52-week study of ixekizumab. Patients were bDMARD-naïve and must have had an inadequate response or

intolerance to at least 1 csDMARD. In SPIRIT-H2H, patients must have had at least 3% of their body surface area affected by psoriasis.

**Supplementary Table 4.** Summary of eligibility Criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| **SPIRIT-P1** | |
| • Presents with established diagnosis of active psoriatic arthritis for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria<br>• Active psoriatic arthritis (PsA) defined as the presence of at least 3 tender and at least 3 swollen joints<br>• Presence of active psoriatic skin lesion or a personal history of plaque psoriasis (Ps)<br>• Men must agree to use a reliable method of birth control or remain abstinent during the study<br>• Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment | • Current or prior use of biologic agents for treatment of Ps or PsA<br>• Inadequate response to greater than or equal to 4 conventional disease-modifying antirheumatic drugs (DMARDs)<br>• Current use of more than one conventional DMARD<br>• Evidence of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA<br>• Have participated in any study with interleukin 17 (IL-17) antagonists, including ixekizumab<br>• Serious disorder or illness other than psoriatic arthritis<br>• Serious infection within the last 3 months<br>• Have active Crohn's disease or active ulcerative colitis<br>• Breastfeeding or nursing (lactating) women |
| **SPIRIT-P2** | |
| • Presents with established diagnosis of active psoriatic arthritis (PsA) for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria<br>• Active PsA defined as the presence of at least 3 tender and at least 3 swollen joints<br>• Presence of active psoriatic skin lesion or a history of plaque psoriasis (Ps)<br>• Men must agree to use a reliable method of birth control or remain abstinent during the study<br>• Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment<br>• Have been treated with 1 or more conventional disease-modifying antirheumatic drugs (cDMARDs) | • Current use of biologic agents for treatment of Ps or PsA<br>• Inadequate response to greater than 2 biologic DMARDs<br>• Current use of more than one cDMARDs<br>• Diagnosis of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA<br>• Have received treatment with interleukin (IL) - 17 or IL12/23 targeted monoclonal antibody (MAb) therapy<br>• Serious disorder or illness other than psoriatic arthritis<br>• Serious infection within the last 3 months<br>• Have active Crohn's disease or active ulcerative colitis<br>• Breastfeeding or nursing (lactating) women |

| | |
|---|---|
| • Have had prior treatment with at least 1 and not more than 2 tumor necrosis factor (TNF) inhibitors. The participant must have discontinued at least 1 TNF inhibitor due to either an inadequate response (based on a minimum of 12 weeks on therapy) or documented intolerance. | |
| **SPIRIT-P3** | |
| • Presents with established diagnosis of active psoriatic arthritis (PsA) for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria<br>• Active PsA defined as the presence of at least 3 tender and at least 3 swollen joints<br>• Presence of active psoriatic skin lesion or a history of plaque psoriasis (Ps)<br>• Men must agree to use a reliable method of birth control or remain abstinent during the study<br>• Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment<br>• Have been treated with 1 or more conventional disease-modifying antirheumatic drugs (cDMARDs) | • Current or prior use of biologic agents for treatment of Ps or PsA<br>• Inadequate response to greater than or equal to 4 conventional disease-modifying antirheumatic drugs (DMARDS)<br>• Current use of more than one cDMARDs<br>• Diagnosis of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA<br>• Have received treatment with interleukin (IL) -17 or IL12/23 targeted monoclonal antibody (MAb) therapy<br>• Serious disorder or illness other than psoriatic arthritis<br>• Serious infection within the last 3 months<br>• Have active Crohn's disease or active ulcerative colitis<br>• Breastfeeding or nursing (lactating) women |
| **SPIRIT-H2H** | |
| • Presence of established diagnosis of active psoriatic arthritis for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria<br>• Active PsA defined as the presence of at least 3 (out of 68) tender and at least 3 (out of 66) swollen joints<br>• Presence of active plaque psoriasis with a BSA ≥3%<br>• Men must agree to use a reliable method of birth control or remain abstinent during the study<br>• Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment<br>• Have had an inadequate response when treated with 1 or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) | • Current or prior use of biologic agents for treatment of Ps or PsA<br>• Evidence of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA<br>• Have participated in any study with interleukin 17 (IL-17) antagonists, including ixekizumab<br>• Serious disorder or illness other than psoriatic arthritis<br>• Serious infection within the last 3 months<br>• Active Crohn's disease or active ulcerative colitis<br>• Active vasculitis or uveitis<br>• Diagnosis of or history of malignant disease <5 years prior to randomization<br>• Women who are breastfeeding |