**Protocol Number: 22104**

**Official Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Phase 2b/3 Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Active Psoriatic Arthritis**

**NCT Number: NCT05623345**

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# Title Page

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**A Randomized, Double-blind, Placebo-controlled, Multicenter Phase 2b/3 Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Active Psoriatic Arthritis**

**Protocol Number:** 22104

**Protocol Version:** 7.0

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**Compound:** Izokibep

**Brief Title:** Psoriatic Arthritis Phase 2b/3 Study of Izokibep

**Study Phase: Phase 2b/3**

**Sponsor Name: ACELYRIN, INC.**

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United States of America

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**Sponsor Signatory:** [redacted]

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[redacted]

**Date**

**Medical monitor's name and contact information will be provided separately.**

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# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:**

**A Randomized, Double-blind, Placebo-controlled, Multicenter Phase 2b/3 Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Active Psoriatic Arthritis**

**Brief Title:** Psoriatic Arthritis Phase 2b/3 Study of Izokibep

**Rationale:**

Izokibep is a small protein molecule that acts as a selective, potent inhibitor of interleukin-17A, to which it binds with high affinity. Izokibep has been investigated in nonclinical and clinical studies including healthy subjects, and subjects with psoriasis and psoriatic arthritis (PsA). The clinical development plan also includes axial spondyloarthritis, uveitis, and hidradenitis suppurativa. This study investigates izokibep in subjects with active PsA, including tumor necrosis factor-alpha inhibitor (TNFi) naïve subjects, and those who had an inadequate response or intolerance to TNFi, or for whom TNFi is contraindicated. The study is intended to be 1 of 2 adequate and well-controlled studies to support a claim of efficacy of izokibep in subjects with PsA.

**Objectives and Endpoints:**

| **Objectives** | **Endpoints** |
|---|---|
| **Primary** | |
| To demonstrate that 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo, as measured by the proportion of subjects achieving 50% improvement in ACR core set measurements (ACR50) at Week 16 | • ACR50 at Week 16 |
| **Secondary (Efficacy)** | |
| To demonstrate that 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo, as measured by:<br>• Proportion of subjects achieving 90% or greater reduction in PASI score from baseline (PASI90) at Week 16 in subjects with ≥ 3% BSA psoriasis at baseline | • PASI90 at Week 16 |

| Objectives | Endpoints |
|---|---|
| • Proportion of subjects with resolution of enthesitis at Week 16 as assessed by LEI in subpopulation that had enthesitis (LEI > 0) at baseline | • Resolution of enthesitis (LEI = 0) at Week 16 |
| • Proportion of subjects achieving minimal disease activity (MDA) at Week 16 | • MDA at Week16 |
| • Proportion of subjects achieving 20% improvement in ACR core set measurements (ACR20) at Week 16 | • ACR20 at Week 16 |
| • Proportion of subjects achieving an improvement in PsAID of at least 3 units at Week 16 compared to baseline in subjects with PsAID ≥ 3 at baseline | • PsAID at Week 16 |
| • Change in physical function as assessed by HAQ-DI change from baseline to Week 16 | • HAQ-DI change from baseline to Week 16 |
| **Secondary (Other)** | |
| To assess the safety and tolerability of izokibep as measured by the incidence of TEAEs, events of interest, SAEs, and clinically significant laboratory values and vital signs | • TEAEs, events of interest, and SAEs<br>• Laboratory values and vital signs at collected timepoints |
| To assess the immunogenicity of izokibep as measured by the presence of ADAs | • Treatment-emergent ADAs |
| **Exploratory** | |
| To demonstrate that 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo up to Week 16 | |

| Objectives | Endpoints |
|---|---|
| and to estimate the efficacy of each regimen after week 16, as measured by: | |
| • Proportion of subjects achieving 70% improvement in ACR core set measurements (ACR70) at Weeks 16, 24, and 52 | • ACR70 at Weeks 16, 24, and 52 |
| • Change in DAS28-CRP at Weeks 16, 24, and 52 as compared to baseline | • Change in DAS28-CRP at Weeks 16, 24, and 52 |
| • Change in DAPSA score at Weeks 16, 24, and 52 as compared to baseline | • Change in DAPSA at Weeks 16, 24, and 52 |
| • Change in clinical DAPSA (cDAPSA) score at Weeks 16, 24, and 52, as compared to baseline | • Change in cDAPSA at Weeks 16, 24, and 52 |
| • Proportion of subjects achieving DAPSA and proportion of subjects achieving cDAPSA low disease activity or remission at Weeks 16, 24, and 52 | • DAPSA/cDAPSA ≤ 14 at Weeks 16, 24, and 52 |
| • Proportion of subjects achieving DAPSA and proportion of subjects achieving cDAPSA remission at Weeks 16, 24, and 52 | • DAPSA/cDAPSA ≤ 4 at Weeks 16, 24, and 52 |
| • Change in PASDAS at Weeks 16, 24, and 52 as compared to baseline | • Change in PASDAS at Weeks 16, 24, and 52 |
| • Proportion of subjects achieving 75% or greater reduction in PASI score from baseline (PASI75) at Weeks 16, 24, and 52 in subjects with ≥ 3% BSA psoriasis at baseline | • PASI75 at Weeks 16, 24, and 52 with ≥3% BSA psoriasis at baseline |
| • Proportion of subjects achieving PASI90 at Weeks 24 and 52 in subjects with ≥3% BSA psoriasis at baseline | • PASI90 at Weeks 24 and 52 in subjects with ≥3% BSA psoriasis at baseline |
| • Proportion of subjects achieving 100% reduction in PASI score from baseline (PASI100) at Weeks 16, 24, and 52 in subjects with ≥3% BSA psoriasis at baseline | • PASI100 at Weeks 16, 24, and 52 in subjects with ≥3% BSA psoriasis at baseline |

| Objectives | Endpoints |
|---|---|
| • Proportion of subjects achieving 75% or greater reduction in PASI score from baseline (PASI75) at Weeks 16, 24, and 52 in subjects with ≥ 10% BSA psoriasis at baseline | • PASI75 at Weeks 16, 24, and 52 in subjects with ≥10% BSA psoriasis at baseline |
| • Proportion of subjects achieving PASI90 at Weeks 16, 24 and 52 in subjects with ≥10% BSA psoriasis at baseline | • PASI90 at Weeks 16, 24 and 52 in subjects with ≥10% BSA psoriasis at baseline |
| • Proportion of subjects achieving 100% reduction in PASI score from baseline (PASI100) at Weeks 16, 24, and 52 in subjects with ≥ 10% BSA psoriasis at baseline | • PASI100 at Weeks 16, 24, and 52 in subjects with ≥10% BSA psoriasis at baseline |
| • Proportion of subjects achieving PASI90 at weeks 16, 24, and 52 in subjects with baseline PASI score ≥10 | • PASI90 at Weeks 16, 24 and 52 in subjects with baseline PASI score ≥10 |
| • Proportion of subjects achieving PASI100 at weeks 16, 24, and 52 in subjects with baseline PASI score ≥10 | • PASI100 at Weeks 16, 24, and 52 in subjects with baseline PASI score ≥10 |
| • Proportion of subjects achieving MDA at Weeks 24 and 52 | • MDA at Weeks 24 and 52 |
| • Proportion of subjects achieving VLDA response at Weeks 16, 24, and 52 | • VLDA at Weeks 16, 24, and 52 |
| • Proportion of subjects with resolution of dactylitis at Weeks 16, 24, and 52 in subpopulation that had dactylitis at baseline (pooled izokibep doses), as assessed with LDI | • Resolution of dactylitis at Weeks 16, 24, and 52 in subjects with LDI >0 at baseline |
| • Change from baseline in mNAPSI at Weeks 16, 24, and 52 in subpopulation with nail psoriasis at baseline (pooled izokibep doses) | • Change in mNAPSI at Weeks 16, 24, and 52 in subjects with mNAPSI >0 at baseline |
| • Progression of structural damage assessed radiographically and expressed as the change in mTSS at Weeks 16 and 52, compared to baseline | • Change in mTSS at Weeks 16 and 52 |

| Objectives | Endpoints |
|---|---|
| • Change in SPARCC enthesitis score at Weeks 16, 24, and 52, as compared to baseline in subpopulation with enthesitis (SPARCC > 0) at baseline | • Change in SPARCC enthesitis score at Weeks 16, 24, and 52 |
| • Change in spinal pain NRS at Weeks 16, 24, and 52, as compared to baseline in subjects reporting spinal pain at baseline | • Change in spinal pain NRS at Weeks 16, 24, and 52 |
| • Change from baseline in spine pain NRS in those with sacroiliitis on pelvic x-ray at Weeks 16, 24 and 52 | • Change from baseline in spine pain NRS in those with sacroiliitis on pelvic x-ray at Weeks 16, 24 and 52 |
| • Change from baseline in spinal pain NRS in those with investigator assessed spinal involvement at Weeks 16, 24 and 52 | • Change from baseline in spinal pain NRS in those with investigator assessed spinal involvement at Weeks 16, 24 and 52 |
| • Association of investigator assessed sacroiliac involvement with sacroiliitis on x-ray at baseline | • Clinical and radiographic sacroiliitis |
| • Proportion of subjects achieving each MDA component (TJC68, SJC66, PASI, BSA, SAPVAS, SGADA, HAQ-DI, tender entheseal points from LEI) at Weeks 16, 24 and 52 | • Each MDA component (TJC68, SJC66, PASI, BSA, SAPVAS, SGADA, HAQ-DI, tender entheseal points from LEI) at Weeks 16, 24 and 52 |
| • Change in quality of life as assessed by SF-36 total score, physical component summary (PCS), and mental component summary (MCS) change from baseline to Weeks 16, 24, and 52 | • Change in SF-36 total score, PCS, and MCS at Weeks 16, 24, and 52 |
| • Fatigue as assessed by FACIT-F change from baseline to Weeks 16, 24, and 52 | • Change in FACIT-F at Weeks 16, 24 and 52 |
| • Proportion of subjects achieving ACR50 at Weeks 24 and 52 | • ACR50 at Weeks 24 and 52 |
| • Proportion of subjects with resolution of enthesitis at Weeks 24 and 52 as | • Resolution of enthesitis (LEI = 0) at Weeks 24 and 52 |

| Objectives | Endpoints |
|---|---|
| assessed by LEI in subpopulation that had enthesitis (LEI >0) at baseline | |
| • Proportion of subjects achieving an improvement in PsAID of at least 3 units at Weeks 24 and 52 compared to baseline in subjects with PsAID ≥3 at baseline | • PsAID response at Weeks 24 and 52 |
| • Proportion of subjects achieving ACR20 at Weeks 24 and 52 | • ACR20 at Weeks 24 and 52 |
| • Mean (median) ACR-N at Week 16, 24, and 52, where ACR-N is defined as the largest number N such that ACR-N is met (analogous to the primary endpoint definition of ACR 50) | • ACR-N at Weeks 16, 24 and 52 |
| • Change in enthesitis at Weeks 16, 24 and 52 as assessed by change from baseline in LEI | • LEI change from baseline to Weeks 16, 24 and 52 |
| • Time to resolution of enthesitis at weeks 4, 12, 16, 24 and 52 among subjects with enthesitis (LEI > 0) at baseline | • Time to resolution of enthesitis at weeks 4, 12 16, 24 and 52 among subjects with enthesitis (LEI > 0) at baseline |
| • Occurrence of enthesitis (LEI > 0) at weeks 4, 12, 16, 24 and 52 among subjects without enthesitis (LEI = 0) at baseline | • Occurrence of enthesitis (LEI > 0) at week 4, 12, 16, 24 and 52 among subjects without enthesitis (LEI = 0) at baseline |
| • Depression and anxiety as assessed by change in HADS score from baseline to Weeks 16 and 52 | • HADS change from baseline to Weeks 16 and 52 |
| • Change in physical function as assessed by HAQ-DI change from baseline to Weeks 24 and 52 | • HAQ-DI change from baseline to Weeks 24 and 52 |
| • Proportion of subjects with a decrease of at least 2 from baseline in LEI, among subjects with baseline LEI of at least 2, at weeks 4, 12 16, 24 and 52 | • LEI decrease of at least 2 from baseline at Weeks 4, 12 16, 24 and 52 |

| Objectives | Endpoints |
|---|---|
| • Subject's Global Impression of Change Questionnaire at weeks 16 and 52<br>• Mean (median) Area under the curve (AUC) for ACR-N through weeks 16, 24 and 52<br>• Change from baseline in LEI at Weeks 16, 24 and 52<br>• Time to first achievement of ACR50<br>• Time to first achievement of PASI90 among subjects with at least 3% BSA at baseline<br>• Time to first achievement of MDA<br>• Time to first achievement of ACR20<br>• Time to first achievement of PsAID improvement of at least 3 among subjects with PsAID at least 3 at baseline<br>• Time to first achievement of PASI100 among subjects with at least 3% BSA at baseline | • Subject's Global Impression of Change Questionnaire at Weeks 16 and 52<br>• AUC for ACR-N through week 16, 24 and 52<br>• LEI change from baseline to Weeks 16, 24 and 52<br>• Time to first achievement of ACR50<br>• Time to first achievement of PASI90 among subjects with at least 3% BSA at baseline<br>• Time to first achievement of MDA<br>• Time to first achievement of ACR20<br>• Time to first achievement of PsAID improvement of at least 3 among subjects with PsAID at least 3 at baseline<br>• Time to first achievement of PASI100 among subjects with at least 3% BSA at baseline |
| To investigate whether 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo up to Week 16 and to estimate the efficacy of each regimen after week 16 in the subpopulation with enthesitis as baseline, as measured by:<br>• Proportion of subjects achieving an improvement in PsAID of at least 3 units at Weeks 16, 24 and 52 compared to baseline in subjects with PsAID ≥3 at baseline<br>• Change from baseline in PsAID at Weeks 16, 24 and 52 | • PsAID response at Weeks 16, 24 and 52<br>• PsAID change from baseline to Week 16, 24 and 52 |

| Objectives | Endpoints |
|---|---|
| • Proportion of subjects with a HAQ-DI decrease of at least 0.35 at Weeks 16, 24 and 52 compared to baseline in subjects with HAQ-DI >0.35 at baseline | • HAQ-DI response at Weeks 16, 24 and 52 |
| • Change in physical function as assessed by HAQ-DI change from baseline to Weeks 16, 24 and 52 | • HAQ-DI change from baseline to Week 16, 24 and 52 |
| • Proportion of subjects achieving MDA at Weeks 16, 24 and 52 | • MDA at Weeks 16, 24 and 52 |
| • Change in DAPSA and cDAPSA at Weeks 16, 24 and 52 as compared to baseline | • DAPSA/cDAPSA change from baseline to Week 16, 24 and 52 |
| • Proportion of subjects achieving VLDA at Weeks 16, 24 and 52 | • VLDA at Weeks 16, 24 and 52 |
| • Change in quality of life as assessed by SF-36 total score, physical component summary (PCS), and mental component summary (MCS) change from baseline to Weeks 16, 24 and 52 | • Change in SF-36 total score, PCS, and MCS at Weeks 16, 24 and 52 |
| To investigate the durability of response after Weeks 16 in subjects on izokibep 160mg QW and Q2W who achieved the primary and secondary endpoints at W16 | ACR50, PASI 90, LEI, MDA, ACR20, and PsAID responses at Weeks 24 and 52 |
| To investigate the incremental response after Week 16 in subjects in all treatment groups (izokibep 160mg QW, izokibep Q2W and placebo/izokibep cross-over) who did not achieve the primary and secondary endpoints at Week 16 | ACR50, PASI 90, LEI, MDA, ACR20, and PsAID responses at Weeks 24 and 52 |
| To investigate the relationship between ACR50 response and other factors<br>• Association of baseline WPI positive WPI >=7 with ACR50 response | • Baseline positive WPI >=7 and ACR50 response |

| Objectives | Endpoints |
|---|---|
| To investigate that the 80 mg Q4W regimen is efficacious compared to placebo, as measured by the same primary, secondary and exploratory endpoints<br>To compare the three regimens of izokibep for assessment of dose-response relationships, as measured by the primary and secondary endpoints | |
| To evaluate the pharmacokinetics of izokibep in subjects with psoriatic arthritis<br>To evaluate the immunogenicity of izokibep in subjects with PsA | • Trough plasma concentrations of izokibep at collected timepoints<br>• Presence of anti-drug antibodies (positive or negative) |

Abbreviations: ACR = American College of Rheumatology; ADAs = anti-drug antibodies; BSA = body surface area; cDAPSA = Change in Clinical Disease Activity in Psoriatic Arthritis; CRP = C-reactive protein; DAPSA = Disease Activity in Psoriatic Arthritis; DAS28 = Disease Activity Score in 28 joints; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MCS=Mental Component Summary; MDA = Minimal Disease Activity; mNAPSI = modified Nail Psoriasis Severity Index; mTSS = modified total Sharp score; NRS = numeric rating scale; PASDAS = Psoriatic Disease Activity Score; PASI = Psoriasis Area and Severity Index; PCS=Physical Component Summary; PsAID = Psoriatic Arthritis Impact of Disease; SAE = serious adverse event; SF-36 = 36-Item Short Form Survey; SPARCC = Spondyloarthritis Research Consortium of Canada; TEAE = treatment-emergent adverse event; VLDA = very low disease activity.

**Overall Design:**

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 2b/3 Study to evaluate the efficacy and safety of izokibep in subjects with active PsA who are TNFi naïve, who have had an inadequate response or intolerance to TNFi, or for whom TNFi is contraindicated. This study will be conducted at study sites in North America and Europe.

**Brief Summary:**

Approximately 325 subjects with active PsA will be enrolled.

Subjects will be screened within 28 days of study drug administration. Subjects meeting eligibility criteria will be randomized 4:4:4:1 to 1 of 4 treatment groups on Day 1, and will receive via subcutaneous injection:

- Group 1 (n = 100): placebo every week (QW) from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Week 16 to Week 51.

- Group 2 (n = 100): izokibep 160 mg QW from Day 1/Week 0 to Week 51.
- Group 3 (n = 100): izokibep 160 mg every 2 weeks (Q2W) from Day 1/Week 0 to Week 50, with matching placebo Q2W until Week 51 for the weeks in between izokibep doses to maintain the blind.
- Group 4 (n = 25): izokibep 80 mg every 4 weeks (Q4W) from Day 1/Week 0 to Week 48, with matching placebo QW until Week 51 for the weeks in between izokibep doses to maintain the blind.

Randomization will be stratified by prior TNFi use (Yes/No) and enthesitis (Leeds Enthesitis Index [LEI] > 0/LEI = 0). Anticipated enrollment of subjects previously treated with TNFi is 20% to 30%. The number of subjects without enthesitis entering into the study (LEI = 0 at baseline) will be capped at 70%.

Subjects will complete study assessments according to the study visits outlined in the Schedule of Activities below. The primary endpoint will be assessed at Week 16. The last dose of study drug will be administered on Week 51.

Starting at Week 24, subjects who do not meet clinical Disease Activity for PsA (cDAPSA) low disease activity (cDAPSA ≤ 14) at 2 consecutive visits (e.g. at Week 20 and Week 24) will be discontinued from study drug and can receive SOC as deemed appropriate by the investigator.

An End of Treatment (EOT) visit will be conducted at Week 52. A Safety Follow-up visit will be conducted at Week 59. A pharmacokinetic/anti-drug antibody (PK/ADA) Follow-up and End of Study Visit will be conducted at Week 65. For subjects that prematurely discontinue study drug for any reason, the EOT visit should be completed within 14 days of withdrawal. Safety follow-up visit should be completed at 8 weeks and PK/ADA follow-up visit should be completed 14 weeks after the last dose of study drug, respectively, where possible. Subjects should continue to complete study assessments as outlined in the SoA (Section 1.3) where possible, with the exception of study drug administration and anti-drug antibody sample and PK sample collection.

The final analysis of primary and secondary endpoints will be conducted after the last subject has had the opportunity to complete Week 16 assessments or prematurely discontinues the study drug and/or study.

**Number of Subjects:**

Approximately 325 subjects will be enrolled into this study.

**Intervention Groups and Duration:**

- Group 1 (n = 100): placebo QW from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Week 16 to Week 51.
- Group 2 (n = 100): izokibep 160 mg QW from Day 1/Week 0 to Week 51.

- Group 3 (n = 100): izokibep 160 mg Q2W from Day 1/Week 0 to Week 50, with matching placebo Q2W until Week 51 for the weeks in between izokibep doses to maintain the blind.
- Group 4 (n = 25): izokibep 80 mg Q4W from Day 1/Week 0 to Week 48, with matching placebo QW until Week 51 for the weeks in between izokibep doses to maintain the blind.

Izokibep and matching placebo (collectively referred to as study drug) will be visually indistinguishable to prevent unblinding during preparation or administration of study material.

Study drug doses are fixed and will not be adjusted for individual subjects during the study.

**Eligibility Criteria:**

Refer to Section 5 in Protocol.

**Data Monitoring/ Other Committee:**

An independent data monitoring committee (DMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to make recommendations on further development activities for izokibep.

The DMC will consist of at least 1 medical expert with expertise in the relevant therapeutic area and at least 1 statistician and will have a minimum of 3 members, 1 of whom will serve as the Chair. The DMC responsibilities, members (including their qualifications and possible conflicts of interest), authorities, meeting frequency to review unblinded interim data, and procedures will be documented in the DMC charter. The committee will meet as needed to review significant safety findings.. After each review, the DMC will make recommendations regarding the continuation of the study based on safety. The DMC will review unblinded efficacy data when approximately 120 subjects have had the opportunity to complete the Week 12 visit. Data from the first 105 subjects randomly assigned to receive izokibep 160 mg QW, izokibep 160 mg Q2W or placebo will be used for these DMC summaries. The DMC may make a recommendation on further development activities for izokibep based on this data review. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The study team operationalizing the day-to-day of the study, the subjects, and the investigators will remain blinded to these interim results until after the study is completed.

**Statistical Considerations:**

Summaries of continuous variables will include mean, median, standard deviation, minimum, and maximum; change from baseline will additionally include standard error. Summaries of dichotomous, categorical, and ordinal variables will include counts and percentages.

Baseline characteristics and demographics will be summarized by randomized treatment group using the last value obtained before randomization. Efficacy and safety data will be summarized

by randomized treatment group during the first 16 weeks of treatment; these data will also be summarized by randomized treatment group over 52 weeks for subjects randomized to receive a dose of izokibep during the first 16 weeks, and separately over the last 36 weeks for subjects randomized to receive placebo during the first 16 weeks. Efficacy variables (primary, secondary, and exploratory) will be summarized at each planned collection timepoint. Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs; percent of subjects reporting each TEAE and each SAE) will be summarized. Anti-drug antibodies will be summarized at each planned collection timepoint.

Comparisons of efficacy between doses will test each dose group of izokibep versus placebo in a single analysis. Response rates will be compared with a stratified test for differences: the strata used for randomization (prior TNFi use and enthesitis), using Cochran-Mantel-Haenszel weights. *P*-values for each pairwise comparison of a dose of izokibep versus placebo will be reported, with a 2-sided 95% confidence interval on the difference in response rates. Continuous endpoints will be analyzed with a longitudinal model using values at each post-randomization timepoint.

The primary efficacy comparison will be of American College of Rheumatology 50% (ACR50) response rates at Week 16. The statistical comparisons for the primary efficacy endpoint and the secondary endpoints, all at Week 16, will be carried out in sequential order. The primary endpoint, comparing izokibep dosed QW to placebo, will be tested first, with significance concluded if $p < 0.05$. Testing of secondary endpoints, comparing izokibep dosed QW to placebo, will only be carried out if all prior tests, including the tests of the primary endpoint, first show significance with $p < 0.05$. If all primary and secondary endpoints, comparing izokibep doses QW to placebo, are significant, testing of izokibep doses Q2W to placebo will begin and follow the same order. As long as all prior tests showed statistically significant differences compared to placebo, testing will proceed using $\alpha = 0.05$. If any comparison (primary or secondary) results in $p > 0.05$, *p*-values for subsequent comparisons will be reported but not considered conclusive.

Exploratory endpoints will be compared analogously, with the exception of a prespecified alpha-controlling testing strategy. *P*-values for exploratory endpoints will be considered descriptive and not considered conclusive.

The primary efficacy analyses will use the treatment policy estimands, using all available data from all randomized subjects regardless of treatment compliance. Subjects will be analyzed in the group to which they are randomized. Subjects who do not have an evaluation for a dichotomous endpoint at a given timepoint will be imputed as nonresponders. Subjects who do not have a continuous measure at a given timepoint will have available data at other timepoints included in the longitudinal model, resulting in an analysis that is robust to data that are missing at random or missing completely at random. Sensitivity and supplementary analyses will be used to assess the impact of missing data assumptions.

Incidence of TEAEs over the first 16 weeks will be summarized by randomized treatment group. No *p*-values will be reported. Incidence will also be summarized over all 52 weeks for subjects randomized to receive izokibep, and summarized over the last 36 weeks for subjects randomized to receive placebo for the first 16 weeks. Serious adverse events will be summarized analogously. Subjects will be summarized for safety according to treatment actually received.

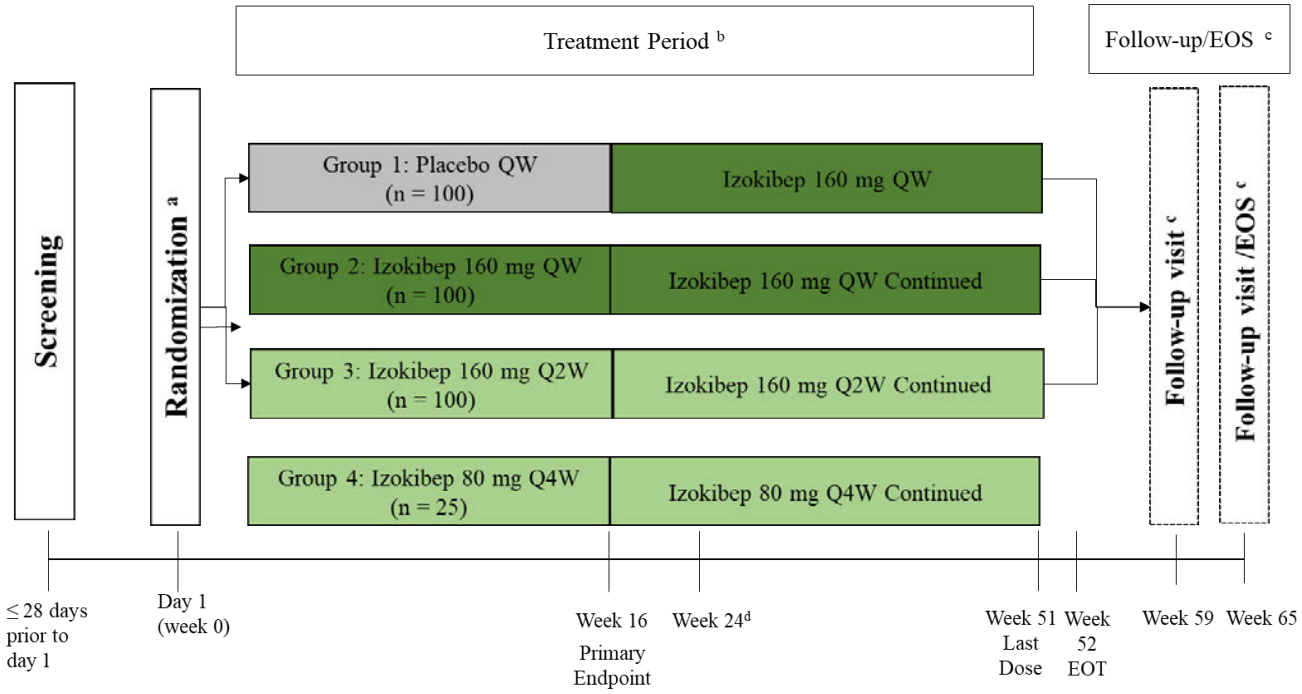
Available PK data will be summarized by dose group of izokibep.

Incidence of ADAs at any time will be summarized by treatment group and overall.

At Week 16 response rates for ACR50 are expected to be 20% for placebo and 45% for a dose regimen of 160 mg izokibep (QW or Q2W or both). With 100 subjects receiving placebo and 100 subjects receiving a dose regimen of izokibep, there will be 97% power to show a difference in the primary endpoint of ACR50 response rate. If a 45% response rate is observed with a dose regimen of izokibep, the 2-sided 95% confidence interval for the true response rate will have a half-width of approximately 10 percentage points.

Up to 60% of subjects are expected to have enthesitis at baseline, based on the LEI. Response rates, proportion of subjects who have LEI = 0 at Week 16, are expected to be 25% for placebo and 60% for subjects receiving izokibep, with on treatment groups combined. With 50 subjects with enthesitis at baseline receiving placebo and 50 subjects receiving a dose regimen of izokibep, there will be 95% power to show a difference in the secondary endpoint of resolution of enthesitis.

## 1.2. Schema




Abbreviations: EOS = End of Study; EOT = End of Treatment; Q2W = every 2 weeks; QW = every week; TNFi = tumor necrosis factor-alpha inhibitor; LEI = Leeds Enthesitis Index

[a] Randomization will be stratified by prior TNFi use (Yes/No) and enthesitis (LEI > 0/LEI = 0). Anticipated enrollment of subjects previously treated with TNFi is 20% to 30%. The number of subjects without enthesitis entering into the study (LEI = 0 at baseline) will be capped at 70%.
[b] Subjects in Group 1 (placebo QW) will receive placebo weekly until Week 15, then izokibep weekly until Week 51. Subjects in Group 2 (izokibep QW) will receive izokibep weekly. Subjects in Group 3 (izokibep Q2W) will receive izokibep every other week, with matching placebo in between izokibep doses to

maintain the blind. Subjects in Group 4 (izokibep Q4W) will receive izokibep every 4 weeks, with matching placebo between izokibep doses to maintain the blind.

[c] Two follow-up visits will be completed by all subjects at Weeks 59 and 65. For subjects that early terminate the follow-up visits should be completed at 8 weeks and 14 weeks after the last dose of study drug.

[d] Starting at Week 24, subjects who do not meet clinical Disease Activity for PsA (cDAPSA) low disease activity (cDAPSA ≤ 14) at 2 consecutive visits (e.g. at Week 20 and Week 24) will be discontinued from study drug.

## 1.3. Schedule of Activities

| **Procedure** | **Screening (≤ 28 days before Day 1)** | **Day 1 / W0** | **Study Week (± 3 days) [a]** | | | | | | | | | | | | | | **EOT [b] (±3 days)** | **Safety FU [b] (±5 days)** | **PK &ADA FU/ End of Study [b] (±5 days)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **1** | **2** | **3** | **4** | **8** | **12** | **16 [c]** | **17** | **18** | **20 [c]** | **24 [c]** | **32 [c]** | **36** | **40** | **52 [b]** | **59** | **65** |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | X | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | | | | | | X | | |
| Weight | X | X | | | | | | | | | | | | | | | X | X | |
| Height | X | | | | | | | | | | | | | | | | | | |
| Medical and medication history | X | X | | | | | | | | | | | | | | | | | |
| Alcohol and nicotine use | X | | | | | | | | | | | | | | | | | | |
| Vital signs[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| 12-lead ECG [e] | X | | | | | | | | X | | | | | | | | X | X | |
| Chest x-ray [f] | X | | | | | | | | | | | | | | | | | | |

| Procedure | Screening (≤ 28 days before Day 1) | Day 1 / W0 | Study Week (± 3 days) [a] | | | | | | | | | | | | | | EOT [b] (±3 days) | Safety FU [b] (±5 days) | PK &ADA FU/ End of Study [b] (±5 days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 8 | 12 | 16 [c] | 17 | 18 | 20 [c] | 24 [c] | 32 [c] | 36 | 40 | 52 [b] | 59 | 65 |
| HADS | | X | | | | | | | X | | | | | | | | X | | |
| AE reporting[g] | | X | — | — | — | — | — | — | — | — | — | — | — | — | — | — | → | | |
| SAE reporting[g] | X | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | → | X | |
| Concomitant medication | | X | — | — | — | — | — | — | — | — | — | — | — | — | — | — | → | X | |
| Efficacy Assessments | | | | | | | | | | | | | | | | | | | |
| Subject's Global Impression of Change | | | | | | | | | X | | | | | | | | X | | |
| Subject's Global Assessment of Disease Activity | | X | | X | | X | | X | X | | | X | X | X | X | X | X | | |
| Subject's Assessment of Pain (VAS) | | X | | X | | X | | X | X | | | X | X | X | X | X | X | | |
| Subject's Assessment of Spinal Pain (NRS) | | X | | | | | | | X | | | | X | | | | X | | |
| Widespread Pain Index | | X | | | | | | | | | | | | | | | | | |
| HAQ-DI | | X | | X | | X | | X | X | | | | X | X | X | | X | | |
| PsAID-9 | | X | | X | | X | | X | X | | | | X | X | X | | X | | |
| SF-36 | | X | | | | | | X | X | | | | X | X | | | X | | |
| FACIT-F | | X | | | | | | | X | | | | X | | | | X | | |
| Joint Assessments [h] | X | X | | X | | X | | X | X | | | X | X | X | X | X | X | | |
| Investigator's Global Assessment of Disease Activity | | X | | X | | X | | X | X | | | X | X | X | X | | X | | |
| PASI/affected BSA | | X | | X | | X | | X | X | | | | X | X | | | X | | |
| mNAPSI | | X | | | | | | X | X | | | | X | X | | | X | | |

| Procedure | Screening (≤ 28 days before Day 1) | Day 1 / W0 | Study Week (± 3 days) [a] | | | | | | | | | | | | | | EOT [b] (±3 days) | Safety FU [b] (±5 days) | PK &ADA FU/ End of Study [b] (±5 days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 8 | 12 | 16 [c] | 17 | 18 | 20 [c] | 24 [c] | 32 [c] | 36 | 40 | 52 [b] | 59 | 65 |
| Leeds Enthesitis Index | | X | | | | X | | X | X | | | | X | X | X | | X | | |
| SPARCC Enthesitis Index | | X | | | | X | | X | X | | | | X | X | X | | X | | |
| Leeds Dactylitis Index | | X | | | | X | | X | X | | | | X | X | X | | X | | |
| Investigator Question on Presence of Axial Involvement | | X | | | | | | | | | | | | | | | | | |
| Radiographs for PsA (x-ray) – Hands, Wrists, and Feet | | X | | | | | | | X [i] | | | | | | | | X [i] | | |
| Radiograph - Pelvis | | X | | | | | | | | | | | | | | | | | |
| Laboratory Assessments | | | | | | | | | | | | | | | | | | | |
| Serology (HBV [j], HCV, HIV) | X | | | | | | | | | | | | | | | | | | |
| TB test [k] | X | | | | | | | | | | | | | | | | | | |
| Hematology/ Chemistry | X | X | | | | X | X | X | X | | | X | X | X | X | X | X | X | |
| Urinalysis | X | X | | | | X | | X | X | | | | X | X | | | | X | |
| Fasting lipid (total cholesterol, triglycerides & HDL) | | X | | | | | | | X | | | | | | | | | | X |
| A1C | | X | | | | | | | X | | | | | | | | X | | |
| Rheumatoid factor/anti-CCP | X | | | | | | | | | | | | | | | | | | |
| C-reactive protein | X | X | | X | | X | | X | X | | | X | X | X | X | X | X | | |
| Pregnancy test (WOCBP only) [l] | X | X | | | | X | X | X | X | | | X | X | X | X | X | X | X | |
| Fecal Calprotectin[m] | X | | | | | | | | | | | | | | | | | | |
| Pharmacokinetic sampling [n] | | X | | X | | X | | X | X | | | | X | | X | | X | X | X |

| Procedure | Screening (≤ 28 days before Day 1) | Day 1 / W0 | Study Week (± 3 days) [a] | | | | | | | | | | | | | | EOT [b] (±3 days) | Safety FU [b] (±5 days) | PK &ADA FU/ End of Study [b] (±5 days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 8 | 12 | 16 [c] | 17 | 18 | 20 [c] | 24 [c] | 32 [c] | 36 | 40 | 52 [b] | 59 | 65 |
| Anti-drug antibody sampling [n] | | X | | X | | X | | X | X | | | | X | | X | | X | X | X |
| Study drug Administration | | | | | | | | | | | | | | | | | | | |
| Treatment assignment/randomization | | X | | | | | | | | | | | | | | | | | |
| Study drug dosing (at site) [q] | | X[o] | X[o] | X[o] | X | X [p] | X | X | X [o] | X[o] | X[o] | X | X | X | X | X | | | |
| Dosing diary [r] | | | | | | | | | | | | | | | | | → | | |

Abbreviations: ACR = American College of Rheumatology; ADA = anti-drug antibodies; AE = adverse event; anti-CCP = anti-cyclic citrullinated peptide; BSA = body surface area; DAS28 = Disease Activity Score in 28 joints; ECG = electrocardiogram; EOT = end of treatment; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FU = follow-up; HADS = Hospital Anxiety and Depression Scale; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; mNAPSI = modified Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic; PsA = psoriatic arthritis; PsAID = Psoriatic Arthritis Impact of Disease; SAE = serious adverse event; SF-36 = Short Form-36; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; W = week; WOCBP = women of childbearing potential.

[a] Visit/dosing windows of ±3 days on either side of the scheduled visits/dosing are permitted. In case of a delayed or missed dose, the investigator should return subjects on the original visit/dosing schedule in relation to Day 1 for subsequent doses. The window of ±3 days is relative to Day 1 and applicable for all subsequent visits/dosing. The minimum of time between doses should be no less than 4 days and no more than 10 days. Subjects do not need to return to the clinical site for dosing on weeks without study visits noted above if subject/caregiver completes study drug administration at home. See footnote "r" below.
[b] Visit window of ±5 days. For subjects who prematurely discontinue study drug , the End of Treatment (EOT) visit should be completed within 14 days of withdrawal and follow-up visits should be completed at 8 weeks (Safety FU) and 14 weeks (PK & ADA FU) after the last dose of study drug, where possible. Subjects should continue to complete study assessments as outlined above where possible, with the exception of study drug administration. Anti-drug antibody sample and PK sample collection will not need to be completed if study drug is prematurely discontinued other than at the PK & ADA FU visit.
[c]

All subjects who do not achieve cDAPSA low disease activity (cDAPSA ≤14) for 2 consecutive visits starting at Week 24 (e.g. at Week 20 and Week 24) will be required to discontinue study drug as described in Section 7.1. Participation in the study should be continued, with EOT visit and assessments as described in Section 4.1 and in footnote b and n.

[d] Vital signs include measurements of temperature, respiratory rate, systolic and diastolic blood pressure, and pulse. Measurements should be taken in a sitting position after 5 minutes' rest.

[e] Electrocardiograms in triplicate will be recorded (one minute apart) after subject has been supine for at least 5 minutes.

[f]Chest x-ray (posterior/anterior or anterior/posterior) will be performed at screening in subjects who do not have a chest x-ray available within 3 months of screening. Women of childbearing potential must have a negative pregnancy test before an x-ray is performed.

[g]Serious adverse events should be recorded from the signing of informed consent through the Safety Follow-up visit (ie, 8 weeks after the last dose of study drug); adverse events will be recorded from Day 1 (ie, administration of study drug) until 4 weeks after the last dose of study drug.

[h] Joint assessment will be performed for ACR66/68 and DAS28 joints for swollen and tender joint counts.

[i] Radiographs of hands/wrists/feet will be done on all subjects who discontinue from the study drug or the study at Week 16 or later and it has been at least 12 weeks from the time the last radiographs were obtained. Radiographs should be obtained as close as possible to the EOT date.

[j]Hepatitis B surface antigen will be conducted. A positive result for the HBsAg will be exclusionary. Samples negative for HBsAg will be tested for HBsAb and HBcAb. If test results are positive for HBcAb or HBsAb, then HBV DNA polymerase chain reaction will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

[k] QuantiFERON test (or equivalent) for TB will be performed. Note: T-SPOT testing may be allowed after consultation with medical monitor.

[l] Serum pregnancy test required for screening and urine pregnancy test required at all other times for WOCBP. Local authorities may require more frequent pregnancy testing.

[m] Fecal calprotectin at screening only required if subject has: a) Prolonged or recurrent diarrhea b) Prolonged or recurrent abdominal pain c) blood in stool or d) any other symptoms in the opinion of the Investigator that may be suggestive of IBD

[n] Pharmacokinetic and anti-drug antibody blood sampling will be taken prior to administration of study drug (predose) on dosing days. For subjects who prematurely discontinue study treatment for any reason, follow-up sampling should be taken at a PK & ADA FU visit 14 weeks after the last dose of study drug where possible, but do not need to be completed at other timepoints.

[o] Subjects will be monitored at the study site for at least 1 hour after study drug administrations for the following visits: Day 1/Week 0, Week 1, Week 2, Week 16, Week 17, and Week 18.

[p] After Week 4, subjects may perform home dosing of study drug at weeks without study visits (see footnote "a") and do not need to return to the clinical site on those weeks. Subjects may begin self-administration of study drug from Week 5. Subjects will be trained on study drug handling and self-administration of study drug at the study visits prior to beginning self-administration. Subject's caregiver or designee can also be trained on home dosing based on subject's preference.

[q] Last dose of study drug will be administered on Week 51.

[r]A dosing diary will be completed for every home dosing administration.

# 2. Introduction

Izokibep has been investigated in nonclinical and clinical studies including healthy subjects, and subjects with psoriasis and psoriatic arthritis (PsA). The clinical development plan also includes axial spondyloarthritis, uveitis, and hidradenitis suppurativa.

## 2.1. Study Rationale

Izokibep is a small protein molecule that acts as a selective, potent inhibitor of interleukin (IL)-17A, to which it binds with high affinity. Izokibep has been investigated in nonclinical and clinical studies including healthy subjects, and subjects with psoriasis and PsA. The clinical development plan also includes axial spondyloarthritis, uveitis, and hidradenitis suppurativa. The study investigates izokibep in subjects with active PsA, including tumor necrosis factor-alpha (TNF) inhibitor (TNFi) naïve subjects, and those who had an inadequate response or intolerance to TNFi, or for whom TNFi is contraindicated. The study is intended to be 1 of 2 adequate and well-controlled studies to support a claim of efficacy of izokibep in subjects with PsA.

## 2.2. Background

### 2.2.1. Disease Background

Psoriasis and PsA are types of psoriatic disease. Psoriasis is a chronic relapsing/remitting, immune-mediated systemic disease characterized by skin lesions including red scaly plaques, resulting from an abnormally excessive and rapid growth of the epidermal layer of the skin. The most common form is plaque psoriasis, and other disease types include pustular, guttate, and erythrodermic psoriasis (Merola et al, 2016; Raharja et al, 2021).

Psoriatic arthritis is a chronic, immune-mediated, inflammatory musculoskeletal disease associated with psoriasis, manifesting most commonly with peripheral arthritis, dactylitis, enthesitis, and spondylitis (Singh et al, 2019; Veale and Fearon, 2018). Nail lesions, including pitting and onycholysis, occur in about 80% to 90% of patients with PsA (Sobolewski et al, 2017; Colunga-Pedraza et al, 2021).

The incidence of PsA in the general population ranges from 3.6 to 7.2 per 100,000 person years. Prevalence estimates in the US range from 0.06% to 0.25%, and in Europe range from 0.05% (Turkey, Czech Republic) to 0.21% (Sweden; Ogdie and Weiss, 2015). The annual incidence of PsA in patients with psoriasis is 2.7% (Singh et al, 2019; Ritchlin et al, 2017), and the reported prevalence of PsA among patients with psoriasis varies between 6% and 41% (Singh et al, 2019; Gladman et al, 2005; Ogdie and Weiss, 2015). In the majority of patients, the skin symptoms develop first, followed by the arthritis; however, in some patients the skin and joint symptoms appear at the same time, and in 10% to 15% the arthritis presents first (Singh et al, 2019; Ritchlin et al, 2017). The common scenario is that psoriasis has its onset approximately 10 years before PsA (Gladman et al, 2005).

Psoriatic arthritis affects men and women equally (Gladman et al, 1998) and can start at any age. It occurs most often in adults between the ages of 45 and 55 (American College of Rheumatology, 2019; Augustin and Radtke, 2017). Psoriatic arthritis is associated with an

adverse impact on health-related quality of life (Adams et al, 2010; American College of Rheumatology, 2019; Husted et al, 2001; Singh and Strand, 2009a) and high health care costs and utilization (American College of Rheumatology, 2019; Javitz et al, 2002; Singh and Strand, 2009b).

Psoriatic arthritis-specific clinical features include the common involvement of distal joints. The condition is also associated with periosteal reaction, enthesitis (observed in 30% to 50% of patients [Kehl et al, 2016]), dactylitis (reported in 40% to 50% of patients [Gladman et al, 2013]), and spinal involvement (Gladman et al, 2005). Most frequent extra-articular manifestations of PsA found in 26% to 33% of the patients are inflammatory bowel disease (IBD; eg, Crohn's disease, ulcerative colitis), cardiovascular (eg, aortic insufficiency, conduction disturbances, major cardiac events), ocular (uveitis and conjunctivitis), and urogenital (eg, urethritis, prostatitis, vaginitis; Peluso et al, 2015).

Greater disease activity is associated with progressive joint damage and higher mortality (American College of Rheumatology, 2019; Bond et al, 2007; Cresswell et al, 2011; Gladman et al, 1998; Gladman, 2008), being early identification of PsA and early initiation of therapy important for improving long-term outcomes (Gladman, 2012).

The "treat to target" is disease remission or at least minimal disease activity (MDA) in order to maximize clinical improvement and minimize long-term damage (Mease, 2011). The quality of life and comorbidities of the patients must be taken into account when selecting the therapy. Depending on the predominant involvement (peripheral, axial, dactylitis, enthesitis, skin, nails) the therapy is different (Augustin and Radtke, 2017). There is currently a wide variety of pharmacologic therapies for PsA including symptomatic treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular (IA) injections, as well as immunomodulatory therapies (American College of Rheumatology, 2019).

### 2.2.2. Interleukin-17

Interleukin-17A, which is produced by T-helper (Th)17 and other immune cells, is one of the major proinflammatory cytokines that contributes to the pathogenesis of several inflammatory disorders (Miossec and Kolls, 2012). Dysfunction of the Th17/IL-17 axis is a source of inflammation in the pathogenesis of psoriasis and PsA, and IL-17A is considered to be involved as a key driver cytokine (Gooderham et al, 2015; Raychaudhuri et al, 2015).

Interleukin-17A inhibiting agents have demonstrated to be efficacious in the treatment of PsA.

The clinical development program for secukinumab in PsA included patients with active disease despite current or previous NSAIDs, conventional-synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and/or previous anti-TNF therapy (biological disease-modifying antirheumatic drug [DMARD]). In 2 pivotal secukinumab studies in 1003 patients with PsA (FUTURE-1 and FUTURE-2), approximately 50% of patients on 150 mg or 300 mg secukinumab (the approved doses) achieved ≥ 20% improvement from baseline in tender and swollen joint counts (and American College of Rheumatology [ACR] 20% [ACR20] response score) after 24 weeks. This was in comparison to approximately 15% ACR20 responders in patients on placebo. Sustained inhibition of radiographic progression and improved quality of life measures were also achieved (Patel et al, 2017). Ixekizumab has been shown to be similarly

effective in treating PsA in pivotal studies. In SPIRIT-P1 (biologic-naïve patients), 62.1%, 57.9%, and 30.2% of patients treated with ixekizumab 80 mg every 2 weeks (Q2W), every 4 weeks (Q4W), or placebo achieved ACR20 response, respectively. In SPIRIT-P2 (patients who failed anti-TNF therapy), 48.0%, 53.3%, and 19.5% of patients treated with ixekizumab 80 mg Q2W, Q4W, or placebo achieved ACR20 response, respectively (Canadian Agency for Drugs and Technologies in Health 2018).

### 2.2.3. Izokibep Background

Izokibep is a biologic drug that binds IL-17A with high affinity and with a potency corresponding to clinically tested monoclonal antibodies in terms of blocking the biological activity of IL-17A. Izokibep has the potential to be an efficacious treatment for a variety of IL-17A-related diseases. The smaller size of izokibep compared to monoclonal antibodies offers advantages in terms of required dosing volumes and potential for alternative pharmacological formulations.

Izokibep is based on a small protein binding to and blocking the biological effect of the cytokine IL-17A. The izokibep protein molecule also contains an albumin-binding domain that confers specific binding to a single site on endogenous serum albumin and thereby prolonging half-life ($t_{½}$) in the circulation and in tissues after parenteral administration.

IL-17 inhibitors have already demonstrated efficacy and a favorable safety profile in different inflammatory diseases, including psoriasis, PsA, and axial spondyloarthritis. These include secukinumab (Cosentyx) and ixekizumab (Taltz) in the US, Canada, and the European Union.

Doses up to 160 mg Q2W have been tested and were well tolerated. A detailed description of the chemistry, pharmacology, pharmacokinetics (PK), efficacy, and safety of izokibep is provided in the Investigator's Brochure.

#### 2.2.3.1. Nonclinical Studies

Assessments of target-binding specificity have demonstrated high specificity and affinity of izokibep to IL-17A and to albumin. The in vitro and in vivo pharmacodynamic evaluations show that izokibep has a 3-to 5-fold higher potency than the anti-IL-17A monoclonal antibody secukinumab on a molar basis and appears to be approximately equipotent to ixekizumab on a molar basis.

Pharmacokinetic data for intravenous (IV)- and subcutaneous (SC)-administered izokibep have been obtained in rat and monkey. Pharmacokinetic assessments in rat and monkey indicate that the time course of izokibep concentrations after a bolus IV injection and SC injection is well described by a 2- or 3-compartment model. Pharmacokinetic assessments indicate that the elimination rate of izokibep is similar to that of albumin in the respective species.

Repeated (10 days to 3 months) SC or IV administration of izokibep to cynomolgus monkeys was well tolerated, with no observed adverse effect levels (NOAELs) of 40 mg/kg/dose administered every third day (IV, 28-day study), 20 mg/dose administered every third day (SC, 28-day study), and 20 mg/kg/week (SC, 3-month study), being the highest dose levels tested in the respective studies.

In the 26-week repeated dose toxicity study in cynomolgus monkeys, weekly SC injection of 10, 20, or 40 mg/kg/week izokibep to monkeys for 26 weeks was generally well tolerated. However, due to the presence of local abscessation and systemic sequelae in 1 female administered 40 mg/kg/week, which was considered adverse, the NOAEL for SC administration is considered to be 20 mg/kg/week.

In the enhanced pre and postnatal developmental toxicity study in cynomolgus monkeys, SC izokibep administration of up to 40 mg/kg/week to pregnant monkeys for approximately 21 weeks was well tolerated. The NOAEL was 40 mg/kg/week.

The results from the immunotoxicity screening assays do not suggest that izokibep has an intrinsic capacity for immune system activation.

Metabolism and genotoxicity have not been investigated, since izokibep is a protein molecule and contains only naturally occurring amino acids.

For additional information please refer to the Investigator's Brochure.

#### 2.2.3.2. Clinical Overview

A first-in-human multipart clinical study (Study ABY-035-001, EudraCT number 2015-004531-13, NCT02690142) has been conducted with the parenteral formulation of izokibep. Izokibep was administered IV and SC to healthy subjects and plaque psoriasis patients, in doses ranging from 2 mg to 40 mg in a single- or multiple-dose regimen.

A Phase 2 dose-finding study in subjects with moderate to severe plaque psoriasis was recently completed with up to 3 years of exposure (Study ABY-035-002, EudraCT number 2017-001615-36, NCT03591887). One hundred eight subjects were randomized into 5 dose groups: 2 mg, 20 mg, 80 mg, and 160 mg izokibep or placebo. The treatment period consisted of an induction period (12 weeks), an optimization period (12 weeks), and an individualization period including 4 weeks follow-up (28 weeks), and 2 further years of extension. The induction period was double blind and placebo controlled.

The primary endpoint of the study was the proportion of patients that achieved a Psoriasis Area and Severity Index (PASI) response of 90% (PASI90) after 12 weeks of treatment. The PASI90 at 12 weeks was 71.4% and 59.1% in subjects treated with 80 mg and 160 mg Q2W of izokibep, respectively. In the lower dose groups, 2 mg and 20 mg izokibep, only 5.0% and 19.0% of subjects, respectively, reached the primary endpoint. None of the subjects receiving placebo reached PASI90 response at Week 12. At Week 24, PASI90 responses were comparable between the initial 80 mg and 160 mg treatment groups. The safety and efficacy data obtained from the 52-week core period of the study with izokibep suggest a favorable benefit-risk profile in plaque psoriasis (Investigator's Brochure).

A Phase 2 clinical trial in subjects with active PsA has recently been completed (Study ABY-035-202). Study ABY-035-202 is a dose-finding trial of 40 mg or 80 mg izokibep or placebo SC Q2W. The primary endpoint is the ACR 50% (ACR50) response at Week 16; further key secondary endpoints comprise other ACR responses, PASI scores, enthesitis endpoints, proportion of subjects achieving MDA, adverse events (AEs; safety), and izokibep blood levels (PK), and ADA assessments.

The primary endpoint of ACR50 at 16 weeks was met with 52% response rate in subjects receiving 80 mg Q2W of izokibep versus 13% for placebo ($p$-value = 0.0006). Subjects receiving 40 mg Q2W had an ACR50 response rate of 48%. The PASI response of 75%, in subjects with a minimum psoriasis body surface area (BSA) ≥ 3% at baseline, at 16 weeks was 85% and 83% in subjects treated with 80 mg and 40 mg Q2W, respectively versus 14% for those receiving placebo. In subjects with enthesitis at baseline utilizing the Leeds Enthesitis Index (LEI), resolution of enthesitis was achieved by 88% of subjects receiving 80 mg Q2W, 63% of subjects receiving 40 mg Q2W of izokibep and 10% receiving placebo.

#### 2.2.3.3. Safety Overview

In the first-in-human study in healthy subjects and subjects with psoriasis (Study ABY-035-001), doses of up to 40 mg IV and SC of izokibep (n = 62) were well tolerated, with no deaths or treatment-related serious AEs (SAEs).

Intravenous administration (single doses up to 40 mg in 46 subjects in total) resulted in the following treatment-emergent AEs (TEAEs) by preferred term: oropharyngeal pain (10.9%), nasopharyngitis (6.5%), diarrhea (4.3%), and headache (4.3%). A further 9 TEAEs were reported, which affected 1 subject each (2.2% each). Subcutaneous administration (single and multiple doses up to 40 mg in 21 subjects in total) resulted in the following TEAEs by preferred term: injection site reaction (61.9%) and injection site pain (28.6%). A further 11 TEAEs were reported, which affected 1 subject each (5.2% each). The majority of the injection site reactions were of mild intensity and required no treatment or limited therapy.

In the Phase 2, 52-week core period in subjects with plaque psoriasis (ABY-035-002), multiple doses of up to 160 mg Q2W SC of izokibep (n = 108) were well tolerated with no deaths or treatment-related SAEs. A total of 65 subjects (60.2%) experienced at least 1 izokibep-related TEAE. The most common izokibep-related TEAEs (n/%) were injection site reaction (42/38.9%), nasopharyngitis (13/12.0%), diarrhea (7/6.5%) and fatigue (6/5.6%) consistent with the first-in-human study.

In the Phase 2, randomized, double-blind, placebo-controlled clinical trial in subjects with active PsA (ABY-035-202), doses of 40 mg and 80 mg Q2W were well tolerated. Safety evaluation showed no serious or severe AEs up to Week 16. Treatment-emergent AE rate overall was 52.3% for placebo, 65.9% for 40 mg Q2W and 55.3% for 80 mg Q2W. The most common AEs (≥ 5% in either arm with active treatment) were injection site reaction or erythema, headache, hyperkalemia, and upper respiratory tract infection. Three patients had AEs of special interest: 2 subjects experienced injection site reaction and 1 subject experienced vulvovaginal candidiasis.

For more details on the safety and tolerability of izokibep, refer to the Investigator's Brochure.

#### 2.2.3.4. Pharmacokinetics

Following SC administration of single izokibep doses in the first–in-human study (Study ABY-035-001), median time to maximum observed concentration ($t_{max}$) was 60 hours postdose. After reaching maximum observed plasma concentration ($C_{max}$), plasma levels of izokibep declined in an apparent mono or biphasic manner with the geometric mean $t_{½}$ being 278 hours which was similar to that after IV administration (288 hours). Individual $t_{½}$ estimates

ranged from 199 to 464 hours and 220 to 340 hours for SC and IV treatments, respectively. The absolute SC bioavailability after a 40-mg dose of izokibep was estimated to 77%. In general, as assessed by the geometric percent coefficient of variation (CV%) low between-subject variability was noted for area under the concentration-time curve (AUC) extrapolated to infinity ($AUC_{0-\infty}$) and $C_{max}$ for both dose routes, with values ranging from 20% to 22% and 14% to 15%, respectively.

Following 40 mg repeated SC doses, maximum plasma concentrations occurred at a median $t_{max}$ of 48.0 hours postdose on Days 1 and 29 (individual range: 24.0 to 71.0 hours postdose). On Day 85, median $t_{max}$ was slightly later at 71.6 hours postdose (individual range: 66.6 to 73.1 hours postdose). After reaching $C_{max}$ on Day 85, plasma concentrations of izokibep declined in an apparent mono or biphasic manner with a geometric mean $t_{½}$ of 279 hours with individual patients ranging from 229 to 423 hours. Predose trough izokibep plasma concentrations showed that steady state was achieved by Day 71, following 5 doses of izokibep administered Q2W. There was evidence of accumulation following repeated dosing by Day 85 with geometric mean accumulation ratio, based on AUC over the dose interval ($AUC_{0-\tau}$) of 1.95, and individual patients ranging from 1.35 to 5.09. Between-patient variability, based on geometric CV%, was moderate on the monitored study days for $AUC_{0-\tau}$ with values ranging from 29.4% to 36.0%, and low-to-moderate for $C_{max}$ with values ranging from 20.4% to 28.8%.

For more details on the PK of izokibep, refer to the Investigator's Brochure.

## 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of izokibep may be found in the Investigator's Brochure.

### 2.3.1. Risk Assessment

Izokibep is a biologic drug that binds IL-17A with high affinity and with a potency corresponding to clinically tested monoclonal antibodies in terms of blocking the biological activity of IL-17A.

- IL-17A inhibitors, including secukinumab at 10 mg/kg and 30 mg/kg and ixekizumab as well as izokibep at doses up to 160 mg SC, do not appear to have dose-limiting AEs.
- Class effects and potential risks seen with other IL-17 inhibitors have not been identified with izokibep. Given the small numbers of subjects treated to date, class effects and potential risks of IL-17 inhibitors will be explicitly monitored (ie, events of special interest) and have been taken into consideration in the development of inclusion and exclusion criteria. These events include Candida infections and IBD.
- Non-serious, mild-to-moderate injection site reactions are the most common adverse event reported in association with SC administration of izokibep. These are typically self-resolving; however, additional measures to mitigate/manage injection site reactions include the following:
    - Allow study drug to warm to room temperature prior to administration, about 15 to 20 minutes

- Administer study drug slowly
- Use ice/ice packs to the area prior to and following study drug administration
- Rotate sites of administration; avoid injecting the same site twice during any visit
- Use of oral antihistamines
- Use of acetaminophen or ibuprofen for pain or discomfort
- Topical corticosteroids may be used on area affected by the injection site reaction for localized erythema, edema, or pruritis.

- No genotoxicity or carcinogenicity is foreseen as izokibep is a protein consisting of natural amino acids. However, since no data are available at this stage of clinical development on possible effects on the reproductive system, the following precautionary measure will be taken:
    - Females of childbearing potential as well as reproductive female partners of male subjects must use an adequate method of contraception while participating in the clinical study until 8 weeks after the last dose of study drug. Pregnancy testing will be performed at regular intervals prior to, during treatment and after the end of treatment (ie, 8 weeks after last investigational medicinal product dosing).

### 2.3.2. Benefit Assessment

The safety, efficacy, and PK data obtained in clinical trials with izokibep in healthy volunteers and in patients with psoriasis and PsA suggest a favorable benefit-risk profile. Based on results from the izokibep Phase 2 randomized, double-blind, placebo-controlled clinical trial in subjects with active PsA and published data showing efficacy and safety for other IL-17 inhibitors in patients with PsA, the benefit-risk relationship in these patients appears favorable and justifies clinical development of izokibep in PsA as well.

The investigator is referred to the current Investigator's Brochure where additional and more detailed information (including nonclinical toxicology, metabolism, pharmacology, and safety experience) regarding potential risks and benefits of izokibep can be found.

### 2.3.3. Overall Benefit: Risk Conclusion

The following considerations are important for the benefit-risk assessment:

- Only subjects with active PsA will be enrolled. Subjects must have had an inadequate response to NSAIDs or a DMARD, demonstrated intolerance to, or have a contraindication to NSAIDs or a DMARD for treatment of their PsA. Subjects previously treated with TNFi, or TNFi naïve, are eligible.
- The inclusion and exclusion criteria will ensure that subjects who might be predisposed to a higher risk of drug-related TEAEs are either excluded or identified and treated with caution. Class effects seen with other IL-17 inhibitors have been taken into account when designing the eligibility criteria. Subjects with active infections will be excluded from participating in the study.

- Subjects will be monitored at the study site for at least 1 hour after administration of izokibep at designated visits.
- Placebo treatment will be limited to 16 weeks. After Week 16, subjects randomized to placebo will begin blinded active treatment (izokibep 160 mg QW) in order to potentially derive benefit from the disease-relevant effect of IL-17 inhibition.
- Starting at Week 24, subjects who do not meet clinical Disease Activity for PsA (cDAPSA) low disease activity (cDAPSA ≤ 14) at 2 consecutive visits (e.g. at Week 20 and Week 24) will be discontinued from study drug and can receive SOC as deemed appropriate by the investigator.
- Given the known possibility of disease progression if PsA goes untreated, subjects across all treatment arms of this study will be allowed to continue methotrexate, leflunomide, sulfasalazine, apremilast, hydroxychloroquine, corticosteroids, or NSAIDS during the study provided the dose has been stable within the time defined in Section 5.1 prior to Day 1 and within the acceptable limits listed in Section 5.1. Additionally, subjects must have had an inadequate response to NSAIDs, DMARDs, or TNFi, or demonstrated intolerance to, or have a contraindication to NSAIDs, DMARDs, or TNFi for treatment of their PsA. Prior treatment failure and the use of concomitant background medications/treatments to mitigate the risk of progression of disease in the placebo group, and a short-term exposure to placebo to 16 weeks all justify a placebo cohort.
- Participation in the study is voluntary. Each subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Taking into account the measures taken to minimize risk to subjects participating in this study, the lack of clear dose-limiting AEs associated with izokibep at the doses under study, and the pre-existing data on the effects of izokibep and other IL-17 inhibitors in PsA, the potential risks identified in association with izokibep in this study are justified by the anticipated benefits that may be afforded to subjects with PsA.

### 2.3.4. COVID-19 Benefit/Risk Assessment

A benefit-risk assessment related to severe acute respiratory syndrome coronavirus (SARS-CoV-2) has been considered for this study and concluded that the coronavirus disease of 2019 (COVID-19) pandemic does not alter the overall benefit-risk for conducting this study. Risk mitigation measures will be implemented based on the prevailing situation during study conduct, at the investigator's discretion and in accordance with local and institutional guidelines as applicable. The benefit-risk of the study in relation to the COVID-19 pandemic will continue to be assessed during the study and additional or revised measures may be implemented based on any updates to the benefit-risk assessment.

# 3. Objectives, Endpoints and Estimands

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To demonstrate that 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo, as measured by the proportion of subjects achieving 50% improvement in ACR core set measurements (ACR50) at Week 16 | • ACR50 at Week 16 |
| **Secondary (Efficacy)** | |
| To demonstrate that 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo, as measured by:<br>• Proportion of subjects achieving 90% or greater reduction in PASI score from baseline (PASI90) at Week 16 in subjects with ≥ 3% BSA psoriasis at baseline<br>• Proportion of subjects with resolution of enthesitis at Week 16 as assessed by LEI in subpopulation that had enthesitis (LEI > 0) at baseline<br>• Proportion of subjects achieving minimal disease activity (MDA) at Week 16<br>• Proportion of subjects achieving 20% improvement in ACR core set measurements (ACR20) at Week 16<br>• Proportion of subjects achieving an improvement in PsAID of at least 3 units at Week 16 compared to baseline in subjects with PsAID ≥ 3 at baseline<br>• Change in physical function as assessed by HAQ-DI change from baseline to Week 16 | • PASI90 at Week 16<br>• Resolution of enthesitis (LEI = 0) at Week 16<br>• MDA at Week16<br>• ACR20 at Week 16<br>• PsAID at Week 16<br>• HAQ-DI change from baseline to Week 16 |

| Objectives | Endpoints |
|---|---|
| **Secondary (Other)** | |
| To assess the safety and tolerability of izokibep as measured by the incidence of TEAEs, events of interest, SAEs, and clinically significant laboratory values and vital signs | • TEAEs, events of interest, and SAEs<br>• Laboratory values and vital signs at collected timepoints |
| To assess the immunogenicity of izokibep as measured by the presence of ADAs | • Treatment-emergent ADAs |
| **Exploratory** | |
| To demonstrate that 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo up to Week 16 and to estimate the efficacy of each regimen after week 16, as measured by:<br>• Proportion of subjects achieving 70% improvement in ACR core set measurements (ACR70) at Weeks 16, 24, and 52<br>• Change in DAS28-CRP at Weeks 16, 24, and 52 as compared to baseline<br>• Change in DAPSA score at Weeks 16, 24, and 52 as compared to baseline<br>• Change in clinical DAPSA (cDAPSA) score at Weeks 16, 24, and 52, as compared to baseline<br>• Proportion of subjects achieving DAPSA and proportion of subjects achieving cDAPSA low disease activity or remission at Weeks 16, 24, and 52<br>• Proportion of subjects achieving DAPSA and proportion of subjects achieving cDAPSA remission at Weeks 16, 24, and 52<br>• Change in PASDAS at Weeks 16, 24, and 52 as compared to baseline<br>• Proportion of subjects achieving 75% or greater reduction in PASI score from | • ACR70 at Weeks 16, 24, and 52<br>• Change in DAS28-CRP at Weeks 16, 24, and 52<br>• Change in DAPSA at Weeks 16, 24, and 52<br>• Change in cDAPSA at Weeks 16, 24, and 52<br>• DAPSA/cDAPSA $\leq$ 14 at Weeks 16, 24, and 52<br>• DAPSA/cDAPSA $\leq$ 4 at Weeks 16, 24, and 52<br>• Change in PASDAS at Weeks 16, 24, and 52<br>• PASI75 at Weeks 16, 24, and 52 with $\geq$3% BSA psoriasis at baseline |

| Objectives | Endpoints |
|---|---|
| baseline (PASI75) at Weeks 16, 24, and 52 in subjects with ≥ 3% BSA psoriasis at baseline | |
| • Proportion of subjects achieving PASI90 at Weeks 24 and 52 in subjects with ≥3% BSA psoriasis at baseline | • PASI90 at Weeks 24 and 52 in subjects with ≥3% BSA psoriasis at baseline |
| • Proportion of subjects achieving 100% reduction in PASI score from baseline (PASI100) at Weeks 16, 24, and 52 in subjects with ≥3% BSA psoriasis at baseline | • PASI100 at Weeks 16, 24, and 52 in subjects with ≥3% BSA psoriasis at baseline |
| • Proportion of subjects achieving 75% or greater reduction in PASI score from baseline (PASI75) at Weeks 16, 24, and 52 in subjects with ≥ 10% BSA psoriasis at baseline | • PASI75 at Weeks 16, 24, and 52 in subjects with ≥10% BSA psoriasis at baseline |
| • Proportion of subjects achieving PASI90 at Weeks 16, 24 and 52 in subjects with ≥10% BSA psoriasis at baseline | • PASI90 at Weeks 16, 24 and 52 in subjects with ≥10% BSA psoriasis at baseline |
| • Proportion of subjects achieving 100% reduction in PASI score from baseline (PASI100) at Weeks 16, 24, and 52 in subjects with ≥ 10% BSA psoriasis at baseline | • PASI100 at Weeks 16, 24, and 52 in subjects with ≥10% BSA psoriasis at baseline |
| • Proportion of subjects achieving PASI90 at weeks 16, 24, and 52 in subjects with baseline PASI score ≥10 | • PASI90 at Weeks 16, 24 and 52 in subjects with baseline PASI score ≥10 |
| • Proportion of subjects achieving PASI100 at weeks 16, 24, and 52 in subjects with baseline PASI score ≥10 | • PASI100 at Weeks 16, 24, and 52 in subjects with baseline PASI score ≥10 |
| • Proportion of subjects achieving MDA at Weeks 24 and 52 | • MDA at Weeks 24 and 52 |
| • Proportion of subjects achieving VLDA response at Weeks 16, 24, and 52 | • VLDA at Weeks 16, 24, and 52 |

| Objectives | Endpoints |
|---|---|
| • Proportion of subjects with resolution of dactylitis at Weeks 16, 24, and 52 in subpopulation that had dactylitis at baseline (pooled izokibep doses), as assessed with LDI | • Resolution of dactylitis at Weeks 16, 24, and 52 in subjects with LDI >0 at baseline |
| • Change from baseline in mNAPSI at Weeks 16, 24, and 52 in subpopulation with nail psoriasis at baseline (pooled izokibep doses) | • Change in mNAPSI at Weeks 16, 24, and 52 in subjects with mNAPSI >0 at baseline |
| • Progression of structural damage assessed radiographically and expressed as the change in mTSS at Weeks 16 and 52, compared to baseline | • Change in mTSS at Weeks 16 and 52 |
| • Change in SPARCC enthesitis score at Weeks 16, 24, and 52, as compared to baseline in subpopulation with enthesitis (SPARCC > 0) at baseline | • Change in SPARCC enthesitis score at Weeks 16, 24, and 52 |
| • Change in spinal pain NRS at Weeks 16, 24, and 52, as compared to baseline in subjects reporting spinal pain at baseline | • Change in spinal pain NRS at Weeks 16, 24, and 52 |
| • Change from baseline in spine pain NRS in those with sacroiliitis on pelvic x-ray at Weeks 16, 24 and 52 | • Change from baseline in spine pain NRS in those with sacroiliitis on pelvic x-ray at Weeks 16, 24 and 52 |
| • Change from baseline in spinal pain NRS in those with investigator assessed spinal involvement at Weeks 16, 24 and 52 | • Change from baseline in spinal pain NRS in those with investigator assessed spinal involvement at Weeks 16, 24 and 52 |
| • Association of investigator assessed sacroiliac involvement with sacroiliitis on x-ray at baseline | • Clinical and radiographic sacroiliitis |
| • Proportion of subjects achieving each MDA component (TJC68, SJC66, PASI, BSA, SAPVAS, SGADA, HAQ-DI, tender entheseal points from LEI) at Weeks 16, 24 and 52 | • Each MDA component (TJC68, SJC66, PASI, BSA, SAPVAS, SGADA, HAQ-DI, tender entheseal points from LEI) at Weeks 16, 24 and 52 |

| Objectives | Endpoints |
|---|---|
| • Change in quality of life as assessed by SF-36 total score, physical component summary (PCS), and mental component summary (MCS) change from baseline to Weeks 16, 24, and 52 | • Change in SF-36 total score, PCS, and MCS at Weeks 16, 24, and 52 |
| • Fatigue as assessed by FACIT-F change from baseline to Weeks 16, 24, and 52 | • Change in FACIT-F at Weeks 16, 24 and 52 |
| • Proportion of subjects achieving ACR50 at Weeks 24 and 52 | • ACR50 at Weeks 24 and 52 |
| • Proportion of subjects with resolution of enthesitis at Weeks 24 and 52 as assessed by LEI in subpopulation that had enthesitis (LEI >0) at baseline | • Resolution of enthesitis (LEI = 0) at Weeks 24 and 52 |
| • Proportion of subjects achieving an improvement in PsAID of at least 3 units at Weeks 24 and 52 compared to baseline in subjects with PsAID ≥3 at baseline | • PsAID response at Weeks 24 and 52 |
| • Proportion of subjects achieving ACR20 at Weeks 24 and 52 | • ACR20 at Weeks 24 and 52 |
| • Mean (median) ACR-N at Week 16, 24, and 52, where ACR-N is defined as the largest number N such that ACR-N is met (analogous to the primary endpoint definition of ACR 50) | • ACR-N at Weeks 16, 24 and 52 |
| • Change in enthesitis at Weeks 16, 24 and 52 as assessed by change from baseline in LEI | • LEI change from baseline to Weeks 16, 24 and 52 |
| • Time to resolution of enthesitis at weeks 4, 12, 16, 24 and 52 among subjects with enthesitis (LEI > 0) at baseline | • Time to resolution of enthesitis at weeks 4, 12 16, 24 and 52 among subjects with enthesitis (LEI > 0) at baseline |
| • Occurrence of enthesitis (LEI > 0) at weeks 4, 12, 16, 24 and 52 among subjects without enthesitis (LEI = 0) at baseline | • Occurrence of enthesitis (LEI > 0) at week 4, 12, 16, 24 and 52 among subjects without enthesitis (LEI = 0) at baseline |

| Objectives | Endpoints |
|---|---|
| • Depression and anxiety as assessed by change in HADS score from baseline to Weeks 16 and 52<br>• Change in physical function as assessed by HAQ-DI change from baseline to Weeks 24 and 52 | • HADS change from baseline to Weeks 16 and 52<br>• HAQ-DI change from baseline to Weeks 24 and 52 |
| • Proportion of subjects with a decrease of at least 2 from baseline in LEI, among subjects with baseline LEI of at least 2, at weeks 4, 12 16, 24 and 52 | • LEI decrease of at least 2 from baseline at Weeks 4, 12 16, 24 and 52 |
| • Subject's Global Impression of Change Questionnaire at weeks 16 and 52<br>• Mean (median) Area under the curve (AUC) for ACR-N through weeks 16, 24 and 52<br>• Change from baseline in LEI at Weeks 16, 24 and 52<br>• Time to first achievement of ACR50<br>• Time to first achievement of PASI90 among subjects with at least 3% BSA at baseline | • Subject's Global Impression of Change Questionnaire at Weeks 16 and 52<br>• AUC for ACR-N through week 16, 24 and 52<br>• LEI change from baseline to Weeks 16, 24 and 52<br>• Time to first achievement of ACR50<br>• Time to first achievement of PASI90 among subjects with at least 3% BSA at baseline |
| • Time to first achievement of MDA<br>• Time to first achievement of ACR20<br>• Time to first achievement of PsAID improvement of at least 3 among subjects with PsAID at least 3 at baseline<br>• Time to first achievement of PASI100 among subjects with at least 3% BSA at baseline | • Time to first achievement of MDA<br>• Time to first achievement of ACR20<br>• Time to first achievement of PsAID improvement of at least 3 among subjects with PsAID at least 3 at baseline<br>• Time to first achievement of PASI100 among subjects with at least 3% BSA at baseline |

| Objectives | Endpoints |
|---|---|
| To investigate whether 1 or both regimens of izokibep (160 mg QW and 160 mg Q2W) are efficacious compared to placebo up to Week 16 and to estimate the efficacy of each regimen after week 16 in the subpopulation with enthesitis as baseline, as measured by:<br>• Proportion of subjects achieving an improvement in PsAID of at least 3 units at Weeks 16, 24 and 52 compared to baseline in subjects with PsAID ≥3 at baseline<br>• Change from baseline in PsAID at Weeks 16, 24 and 52<br>• Proportion of subjects with a HAQ-DI decrease of at least 0.35 at Weeks 16, 24 and 52 compared to baseline in subjects with HAQ-DI >0.35 at baseline<br>• Change in physical function as assessed by HAQ-DI change from baseline to Weeks 16, 24 and 52<br>• Proportion of subjects achieving MDA at Weeks 16, 24 and 52<br>• Change in DAPSA and cDAPSA at Weeks 16, 24 and 52 as compared to baseline<br>• Proportion of subjects achieving VLDA at Weeks 16, 24 and 52<br>• Change in quality of life as assessed by SF-36 total score, physical component summary (PCS), and mental component summary (MCS) change from baseline to Weeks 16, 24 and 52 | • PsAID response at Weeks 16, 24 and 52<br>• PsAID change from baseline to Week 16, 24 and 52<br>• HAQ-DI response at Weeks 16, 24 and 52<br>• HAQ-DI change from baseline to Week 16, 24 and 52<br>• MDA at Weeks 16, 24 and 52<br>• DAPSA/cDAPSA change from baseline to Week 16, 24 and 52<br>• VLDA at Weeks 16, 24 and 52<br>• Change in SF-36 total score, PCS, and MCS at Weeks 16, 24 and 52<br>ACR50, PASI 90, LEI, MDA, ACR20, and PsAID responses at Weeks 24 and 52 |
| • To investigate the durability of response after Weeks 16 in subjects on izokibep 160mg QW and Q2W who achieved the primary and secondary endpoints at W16 | ACR50, PASI 90, LEI, MDA, ACR20, and PsAID responses at Weeks 24 and 52 |

| **Objectives** | **Endpoints** |
|---|---|
| To investigate the incremental response after Week 16 in subjects in all treatment groups (izokibep 160mg QW, izokibep Q2W and placebo/izokibep cross-over) who did not achieve the primary and secondary endpoints at Week 16<br><br>To investigate the relationship between ACR50 response and other factors<br>• Association of baseline WPI positive WPI >=7 with ACR50 response<br><br>To investigate that the 80 mg Q4W regimen is efficacious compared to placebo, as measured by the same primary, secondary and exploratory endpoints<br>To compare the three regimens of izokibep for assessment of dose-response relationships, as measured by the primary and secondary endpoints | • Baseline positive WPI >=7 and ACR50 response |
| To evaluate the pharmacokinetics of izokibep in subjects with psoriatic arthritis<br>To evaluate the immunogenicity of izokibep in subjects with PsA | • Trough plasma concentrations of izokibep at collected timepoints<br>• Presence of anti-drug antibodies (positive or negative) |

Abbreviations: ACR = American College of Rheumatology; ADAs = anti-drug antibodies; BSA = body surface area; cDAPSA = Change in Clinical Disease Activity in Psoriatic Arthritis; CRP = C-reactive protein; DAPSA = Disease Activity in Psoriatic Arthritis; DAS28 = Disease Activity Score in 28 joints; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MCS=Mental Component Summary; MDA = Minimal Disease Activity; mNAPSI = modified Nail Psoriasis Severity Index; mTSS = modified total Sharp score; NRS = numeric rating scale; PASDAS = Psoriatic Disease Activity Score; PASI = Psoriasis Area and Severity Index; PCS=Physical Component Summary PsAID = Psoriatic Arthritis Impact of Disease; SAE = serious adverse event; SF-36 = 36-Item Short Form Survey; SPARCC = Spondyloarthritis Research Consortium of Canada; TEAE = treatment-emergent adverse event; VLDA = very low disease activity.

**Primary Estimand**

Estimands are discussed in Section 9.3.2.

The 5 components of the estimand to address the primary objective:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with PsA who meet all inclusion/exclusion criteria.
- Variable of interest: achievement of ACR50 after 16 weeks of treatment.
- Summary measure: response rate, achievement of ACR50 (Yes/No).
- Intercurrent event handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions.

**Secondary Estimand(s)**

Estimands are discussed in Section 9.3.3.

The 5 components of the estimand to address each secondary objective are as follows.

First secondary objective:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with PsA who meet all inclusion/exclusion criteria who have at least 3% BSA affected at baseline.
- Variable of interest: achievement of PASI90 after 16 weeks of treatment.
- Summary measure: response rate, achievement of PASI90 (Yes/No).
- Intercurrent event handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions.

Second secondary objective:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with PsA who meet all inclusion/exclusion criteria who have enthesitis at baseline (LEI > 0).
- Variable of interest: resolution of enthesitis after 16 weeks of treatment.
- Summary measure: response rate, achievement of LEI = 0 (Yes/No).
- Intercurrent event handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions.

Third secondary objective:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with PsA who meet all inclusion/exclusion criteria.
- Variable of interest: achievement of MDA after 16 weeks of treatment.
- Summary measure: response rate, achievement of MDA (Yes/No).
- Intercurrent event handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions.

Fourth secondary objective:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with PsA who meet all inclusion/exclusion criteria.
- Variable of interest: achievement of ACR20 after 16 weeks of treatment.
- Summary measure: response rate, achievement of ACR20 (Yes/No).
- Intercurrent event handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions.

Fifth secondary objective:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with PsA who meet all inclusion/exclusion criteria who have a Psoriatic Arthritis Impact of Disease (PsAID) score of at least 3 at baseline.
- Variable of interest: change in PsAID after 16 weeks of treatment.
- Summary measure: response rate, improvement in PsAID of at least 3 units (Yes/No).
- Intercurrent event handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions.

Sixth secondary objective:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with PsA who meet all inclusion/exclusion criteria.
- Variable of interest: Health Assessment Questionnaire – Disability Index (HAQ-DI) change from baseline.
- Summary measure: mean change from baseline in HAQ-DI.

- Intercurrent event handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions.

# 4. Study Design

## 4.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 2b/3 study. The plan is to evaluate the efficacy and safety of izokibep in subjects with active PsA who are TNFi naïve, who have had an inadequate response or intolerance to TNFi, or for whom TNFi is contraindicated.

Approximately 325 subjects with active PsA will be enrolled. The study consists of up to a 28-day (4-week) screening period, a 51-week treatment period, and a follow-up period with visits at 8 weeks and 14 weeks after the last dose of study drug to assess safety and immunogenicity.

Subjects meeting eligibility criteria will be randomized into 1 of 4 treatment groups in a 4:4:4:1 ratio as follows:

- Group 1 (n = 100): placebo QW from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Week 16 to Week 51.
- Group 2 (n = 100): izokibep 160 mg QW from Day 1/Week 0 to Week 51.
- Group 3 (n = 100): izokibep 160 mg Q2W from Day 1/Week 0 to Week 50, with matching placebo Q2W until Week 51 for the weeks in between izokibep doses to maintain the blind.
- Group 4 (n = 25): izokibep 80 mg Q4W from Day 1/Week 0 to Week 48, with matching placebo QW until Week 51 for the weeks in between izokibep doses to maintain the blind.

The first dose of study drug (ie, izokibep or placebo) will be administered on Day 1 (Week 0).

Randomization will be stratified by any prior treatment with a systemic TNFi (Yes/No) and enthesitis (LEI > 0/LEI = 0). Anticipated enrollment of subjects previously treated with TNFi is 20% to 30%. The number of subjects without enthesitis entering into the study (LEI = 0 at baseline) will be capped at 70%.

Subjects will complete study assessments according to the study visits outlined in the Schedule of Activities (SoA; Section 1.3). The primary endpoint will be assessed at Week 16. The last dose of study drug will be administered on Week 51.

Starting at Week 24, subjects who do not meet clinical Disease Activity for PsA (cDAPSA) low disease activity (cDAPSA ≤ 14) at 2 consecutive visits (e.g. at Week 20 and Week 24) will be discontinued from study drug and can receive SOC as deemed appropriate by the Investigator.

An End of Treatment visit will be conducted at Week 52. A Safety Follow-up visit will be conducted at Week 59. A PK/anti-drug antibody (ADA) Follow-up and End of Study Visit will be conducted at Week 65.

For subjects that prematurely discontinue study drug for any reason, the End of Treatment (EOT) visit should be completed within 14 days of withdrawal and follow-up visits should be completed at 8 weeks (Safety FU) and 14 weeks (PK & ADA FU) after the last dose of study drug, where

possible. Refer to Section 7.1 for discontinuation of study drug. Afterwards, subjects should continue to complete study assessments as outlined in the SoA (Section 1.3) where possible, with the exception of study drug administration, anti-drug antibody sample and PK sample collection, and calculation for cDAPSA if discontinuation occurs prior to Week 24.The final analysis of primary and secondary endpoints will be conducted after the last subject has had the opportunity to complete Week 16 assessments or early terminates from the study. Analysis of data at later timepoints may occur after all subjects have had the opportunity to complete that timepoint.

#### 4.1.1. Independent Data Monitoring Committee

An independent data monitoring committee (DMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to make recommendations on further development activities for izokibep.

The DMC will consist of at least 1 medical expert with expertise in the relevant therapeutic area and at least 1 statistician and will have a minimum of 3 members, 1 of whom will serve as the Chair. The DMC responsibilities, members (including their qualifications and possible conflicts of interest), authorities, and procedures will be documented in the DMC charter. The committee will meet approximately every 12 months to review unblinded interim data and will meet as needed to review significant safety findings. After each review, the DMC will make recommendations regarding the continuation of the study based on safety.

The DMC will review unblinded efficacy data when approximately 120 subjects have had the opportunity to complete the Week 12 visit. Data from the first 105 subjects randomly assigned to receive izokibep 160 mg QW, izokibep 160 mg Q2W or placebo will be used for these DMC summaries. The DMC may make a recommendation on further development activities for izokibep based on this data review. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The study team operationalizing the day-to-day of the study, the subjects, and the investigators will remain blinded to these interim results until after the study is completed.

#### 4.1.2. Number of Sites

Approximately 100 sites across North America and Europe will participate in this study. Additional sites and regions may be added. Sites that do not screen subjects within 2 months of site initiation may be closed.

#### 4.1.3. Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 325 subjects will be randomized. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

#### 4.1.4. Study Duration for Subjects

The maximum planned length of participation in the study for an individual subject is up to 69 weeks, which includes the following:

- screening period of up to 28 days (4 weeks)

- treatment period of 51 weeks
- follow-up visits at 8 weeks and 14 weeks after the last dose of study drug.

## 4.2. Scientific Rationale for Study Design

The design of this clinical study was chosen to evaluate izokibep in subjects with active PsA previously treated with TNFi, or TNFi naïve. The primary aim of the study is to evaluate the safety and efficacy of izokibep administered SC at a dose of 160 mg QW and 160 mg Q2W for the treatment of active PsA. The primary endpoint of ACR50 response will be evaluated after all subjects have the opportunity to complete the 16-week placebo-controlled study period. At Week 16, subjects randomized to placebo will receive blinded active treatment (izokibep 160 mg QW) until Week 51. Long-term efficacy beyond Week 16 will be explored up to Week 52 and safety will be explored up to the End of Study visit at Week 65.

Standard statistical procedures will be utilized in this study. Efficacy measurements in this study have been selected or designed to assess disease activity in subjects with active PsA. All clinical and laboratory procedures in this study are standard and generally accepted.

Males and females ≥ 18 years and ≤ 75 years with active PsA who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study. The population being studied represents a population normally seen in clinical practice. This ensures the activity of izokibep can be evaluated across a distribution of disease severity in the study.

## 4.3. Justification for Dose

The doses of izokibep are: 80 mg SC Q4W, 160 mg SC QW and 160 mg SC Q2W administered from Day 1 (Week 0) through Week 51 in subjects randomized to izokibep. Subjects randomized to placebo will switch to active treatment at Week 16 and will receive izokibep 160 mg QW until Week 51.

The selection of the dosing regimen is informed by the following facts. The 80 mg Q4W and 160 mg dose groups will support dose-response analyses along with the 40 mg Q2W dosing in the prior phase 2 study. A dose of 160 mg QW has 10-fold margin for $C_{max}$ and 9-fold margin for $AUC_{0-\tau}$ based on NOAEL from nonclinical cynomolgus monkey toxicity studies (Table 1).

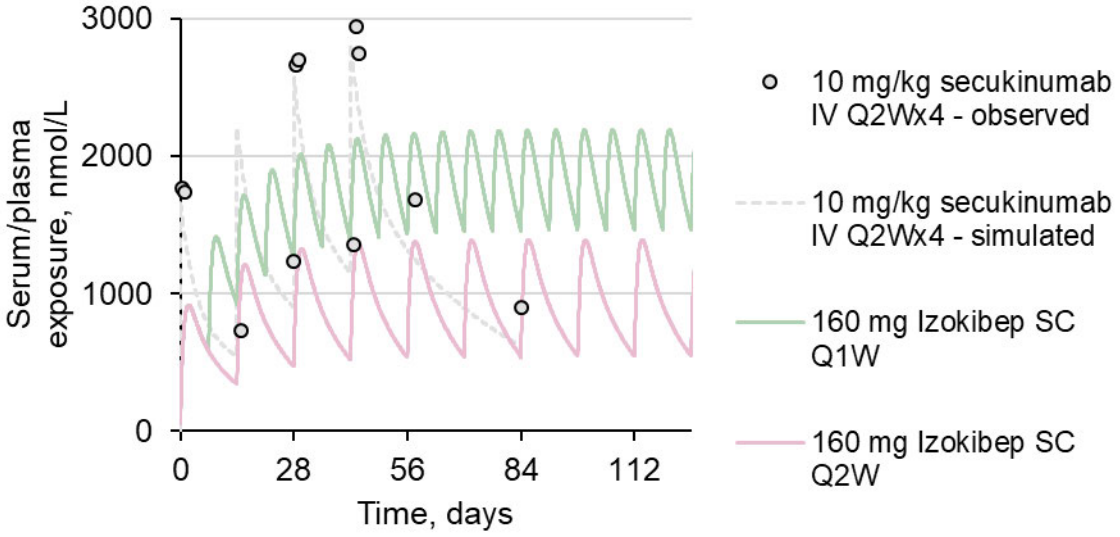
Finally, based on PK modeling of the izokibep and secukinumab plaque psoriasis data and the available data with secukinumab in uveitis, the sponsor aimed to approximate the observed exposure of 10 mg/kg secukinumab IV Q2W (administered on 4 occasions) with the 160 mg QW SC dose of izokibep as shown in Figure 1 and Table 2 (internal data to ACELYRIN Inc).

**Table 1. $C_{max}$ and $AUC_{0-\tau}$ at NOAEL in Cynomolgus Monkey Versus Predicted Exposure Levels in Man and Respective Margins**

| Parameter | NOAEL (20 mg/kg/week) in Cynomolgus Monkey | Predicted in Subjects at Steady State (160 mg QW) | Margin |
|---|---|---|---|
| $C_{max}$ | 409 µg/mL | 40.8 µg/mL | 10 |
| $AUC_{0-\tau}$ | 52500 h·µg/mL | 5850 h·µg/mL | 9.0 |

Abbreviations: $AUC_{0-\tau}$ = area under the concentration-time curve over a dosing interval; $C_{max}$= maximum observed plasma concentration; h = hour; NOAEL = no observed adverse effect level; QW = once a week.

**Figure 1. Observed and Simulated PK Profiles for 10 mg/kg IV Q2W×4 Secukinumab Versus Simulated Profiles for 160 mg Izokibep SC QW and Q2W**




Abbreviations: IV = intravenous; PK = pharmacokinetic; QW/Q1W = once a week; Q2W = every 2 weeks; SC = subcutaneous.

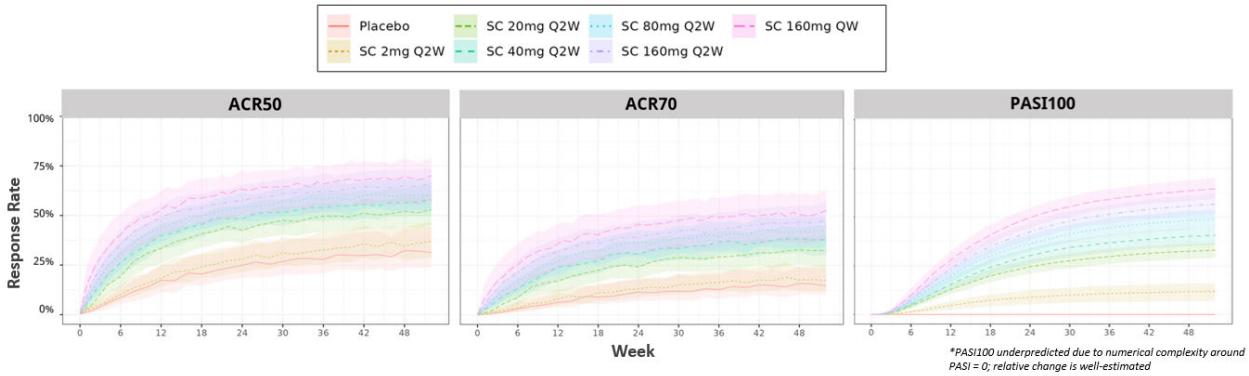
**Table 2. Predicted Exposure at Steady State for 160 mg Izokibep SC QW**

| Parameter | Unit | Value | Unit | Value |
|---|---|---|---|---|
| $C_{max}$ | nmol/L | 2190 | µg/mL | 40.8 |
| $C_{min}$ | nmol/L | 1460 | µg/mL | 27.2 |
| $C_{average}$ | nmol/L | 1870 | µg/mL | 34.8 |
| $AUC_{0-\tau}$ | h·nmol/L | $31.5 \cdot 10^4$ | h·µg/mL | 5850 |

Abbreviations: $AUC_{0-\tau}$ = area under the concentration-time curve over the dose interval; $C_{average}$ = average observed plasma concentration; $C_{max}$= maximum observed plasma concentration; $C_{min}$ = minimum observed plasma concentration; h = hour; QW = once a week; SC = subcutaneous.

Current agents leave considerable room to improve responses, with ACR 50 responses in 35 to 50% of patients at 24 weeks and less than 60% at 52 weeks. Population pharmacokinetic modeling with IV and SC data from Phase 1 and 2 izokibep studies in healthy volunteers, plaque psoriasis, and PsA predict that meaningfully higher ACR50, ACR70, and PASI100 responses may be observed with izokibep 160mg QW and Q2W regimens when compared with 40 mg and 80 mg Q2W regimens in the treatment of PsA, with improvement in responses increasing with longer duration of treatment (Figure 2). Achieving higher levels of response, such as ACR70 for a majority of patients remains an unmet need and modelling from the phase 2 data with 40 mg and 80 mg Q2W suggests higher levels of response are possible. Furthermore, in the clinical setting, izokibep has not demonstrated dose-limiting safety/tolerability up to 160 mg QW with multiple doses across multiple indications, with up to 3 years of exposure, so that safety data available to date suggests the higher doses proposed here are unlikely to lead to additional safety risks.

**Figure 2. Modeling and Simulation of PsA Endpoints by Dose**




- PopulationPK: IV and SC Ph 1, 2 data in healthy volunteers, psoriasis (PsO), and psoriatic arthritis (PsA) subjects
- ACR: individual PK linked to observed ACR in PsA subjects using a categorial model (likelihood of achieving ACRxx based on PK concentration), including a time-dependent placebo effect
- PASI: individual PK linked to observed PASI in PsO and PsA subjects using a continuous model (actual PASI score), with no evidence of a placebo effect
  - PASIxx calculated from change from baseline
  - No effect of disease (PsO vs PsA) on PASI response to izokibep
- Simulated 300 replicates of 1000 subjects

The doses of izokibep used in this study supports the maximum likelihood of demonstrating the potential efficacy for izokibep in subjects with active PsA within an acceptable safety profile. Measures have also been taken to ensure the well-being of subjects by applying appropriate inclusion and exclusion criteria to recruit a broad population that is most likely to benefit from treatment, while excluding subjects with an unacceptable risk to enter the study (Section 5). Further, during the study, measures are in place to monitor the safety of subjects on a regular basis. An independent DMC will also review the data on an ongoing basis.

## 4.4. End of Study Definition

The primary completion for the study is the date all subjects have had the opportunity to complete the Week 16 assessment for the purpose of the primary endpoint. A subject will be considered to have had the opportunity to complete the Week 16 assessment if the subject has the Week 16 assessment, has a visit after Week 16, or permanently discontinues the study before Week 16.

The end of the study is defined as the date of the last scheduled procedure including the last follow-up visit (ie, Week 65) shown in the SoA (Section 1.3) for the last subject in the study globally.

A subject is considered to have completed the study if the subject has completed all periods of the study including the last scheduled procedure shown in the SoA (Section 1.3; ie, Week 65 follow-up visit).

# 5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

**General**

1. Subject has provided signed informed consent including consenting to comply with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Subject must be ≥ 18 (or the legal age of consent in the jurisdiction in which the study is taking place) and ≤ 75 years of age, at the time of signing the informed consent.

**Type of Subject and Disease Characteristics**

3. Clinical diagnosis of PsA with symptom onset at least 6 months prior to first dose of study drug and fulfillment of the ClASsification for Psoriatic ARthritis (CASPAR) criteria at Screening
4. Active PsA as defined by:
   a. ≥ 3 swollen joints out of 66 joints (SJC66) at screening and baseline visits.
   b. ≥ 3 tender joints out of 68 joints (TJC68) at screening and baseline visits.
5. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) negative at screening.
6. Subject must have had an inadequate response, intolerance, or contraindication to at least one of the following:
   a. NSAID
   b. csDMARD (e.g.. methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, cyclosporine A)
   c. TNFi (e.g. adalimumab, infliximab, etanercept, golimumab, certolizumab).
7. For subjects using methotrexate, leflunomide, sulfasalazine, hydroxychloroquine or apremilast, treated for ≥ 3 months and a stable dose (not to exceed 25 mg methotrexate per week, 20 mg leflunomide per day, sulfasalazine 3 g per day, hydroxychloroquine 400 mg per day or apremilast 60 mg per day) for ≥ 4 weeks prior to first dose of study drug.
8. For subjects using corticosteroids, must have been on a stable dose and regimen and not to exceed 7.5 mg per day of prednisone (or other corticosteroid equivalent to 7.5 mg per day of prednisone) for ≥ 4 weeks prior to first dose of study drug.

9. Subjects using NSAIDs or low potency opioid medications (tramadol, paracetamol in combination with hydrocodone or with codeine) must have been on a stable dose and regimen for ≥ 2 weeks prior to first dose of study drug.

**Other Inclusions**

10. No known history of active tuberculosis (TB).
11. Subject has a negative TB test at screening, as defined by[1]:
    - Negative QuantiFERON test
    - Subjects with a positive QuantiFERON test are allowed if all of the following is satisfied:
        - No symptoms of TB as determined by the investigator.
        - Documented history of adequate prophylaxis initiation prior to receiving study drug per local guidelines.
        - No known exposure to a case of active TB after most recent prophylaxis.
        - No evidence of active TB on chest radiograph within 3 months prior to first dose of study drug.
    - Subjects with an indeterminate QuantiFERON test are permitted to retest once. If the retest result is indeterminate, subject may be randomized if all of the following is satisfied:
        - No symptoms of TB as determined by the investigator.
        - Documented history of adequate prophylaxis initiation prior to receiving study drug per local guidelines.
        - No known exposure to a case of active TB. If subject has previously received TB prophylaxis, no known exposure to active TB after most recent prophylaxis.
        - No evidence of active TB on chest radiograph within 3 months prior to first dose of study drug.
        - Deemed to be low risk per risk determination questionnaire and medical monitor review

[1] T-SPOT TB test may be used to establish eligibility if agreed upon with the medical monitor.

**Sex and Contraceptive/Barrier Requirements**

12. Male and female subjects:

    Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    a. Male subjects:

Male subjects are eligible to participate if they agree to the following during the study drug period and for at least 8 weeks after the last dose of study drug:

- Refrain from donating semen, plus either:
  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

    OR
  - Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b. Female subjects:

A female subject is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:

- Is a woman of nonchildbearing potential as defined in Section 10.4 (Contraceptive and Barrier Guidance).

  OR
- Is a WOCBP and uses a contraceptive method that is highly effective, with a failure rate of < 1%, as described in Section 10.4 during the study drug period and for at least 8 weeks after the last dose of study drug. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study drug.

A WOCBP must have a negative highly sensitive serum pregnancy test at screening and a negative urine pregnancy test on Day 1 prior to the first dose of study drug, see Section 8.3.5.

## 5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

**Disease-related Medical Conditions**

1. Any history or current confirmed diagnosis of IBD

   OR

   Any of the following symptoms (of unknown etiology) or any signs or symptoms within the last year that in the opinion of the Investigator may be suggestive of IBD, with fecal calprotectin > 500 µg/g; OR if fecal calprotectin > 150 to 500 µg/g without

confirmed approval from a GI consult that an IBD diagnosis is clinically unlikely (see Section 8.2.11) when the following clinical signs and symptoms are present:

a. prolonged or recurrent diarrhea

b. prolonged or recurrent abdominal pain

c. blood in stool

2. History of fibromyalgia or any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, connective tissue diseases). Prior history of axial spondyloarthritis or fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis was made incorrectly. Prior history of reactive arthritis or axial spondyloarthritis is permitted if an additional diagnosis of PsA is made. Chronic osteoarthritis symptoms that in the Investigator's opinion may interfere with study assessments.
3. Uncontrolled, clinically significant system disease such as:
    a. diabetes mellitus
    b. hypertension
    c. cardiovascular disease including moderate to severe heart failure (New York Heart Association class III/IV)
    d. renal disease
    e. moderate to severe liver disease.
4. Malignancy within 5 years except treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.
5. Severe, uncontrolled, medically unstable mood disorder, such as severe depression.
6. History or evidence of any clinically significant disorder (including psychiatric), condition, or disease that, in the opinion of the investigator, may pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
7. Active infection or history of infection as follows:
    a. Any active infection for which oral anti-infectives (antibiotics, antivirals, antifungals) were used ≤ 14 days prior to first dose of study drug.
    b. A serious infection requiring hospitalization or IV anti-infectives (antibiotics, antivirals, antifungals) ≤ 30 days prior to first dose of study drug.
    c. Recurrent or chronic infections or other active infections that in the opinion of the investigator might cause this study to be detrimental to the subject.
8. *Candida* infection requiring systemic treatment within 3 months prior to first dose of study drug.

9. Tuberculosis or fungal infection seen on available chest x-ray taken within 3 months prior to first dose of study drug or at screening (Exception: documented evidence of completed treatment and clinically resolved).
10. Known history of human immunodeficiency virus (HIV) or positive HIV test at screening.

**Laboratory Abnormalities and Measurements**

11. Positive hepatitis B surface antigen (HBsAg) or detected sensitivity on the hepatitis B virus (HBV) DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HbcAb)/hepatitis B surface antibody (HbsAb) positive subjects OR positive hepatitis C virus antibody test at screening.
12. Laboratory abnormalities at screening:
    a. hemoglobin < 9 g/dL
    b. platelet count < 100 000/$mm^3$
    c. white blood cell count < 3 000 cells/$mm^3$
    d. aspartate aminotransferase and/or alanine aminotransferase ≥ 2.5 times the upper limit of normal
    e. estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$ at screening
    f. any other laboratory abnormality that in the opinion of the investigator, will pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

    Note: Laboratory value(s) out of range due to sampling error or that might be within range after medically appropriate supplementation may be repeated up to 2 times within the screening window before the subject is considered a screen failure.

**Washouts and Nonpermitted Drugs**

13. Previous exposure to izokibep or any other IL-17 inhibitor and IL-17 receptor inhibitors (eg, secukinumab, ixekizumab, bimekizumab, brodalumab).
14. Prior exposure to biologics that had a potential or known association with progressive multifocal leukoencephalopathy (ie, natalizumab [Tysabri], rituximab [Rituxan], or efalizumab [Raptiva]).
15. Exposure to the following within 24 weeks prior to first dose of study drug:
    a. intramuscular (IM) or oral gold
    b. cytotoxic agents such as cyclophosphamide, D-penicillamine.
16. Exposure to the following within 12 weeks prior to first dose of study drug:
    a. TNFi (except etanercept within 4 weeks)
    b. other experimental or commercially available biologic or biosimilar therapies (within 12 weeks or 5 half-lives, whichever is longer)

c. cyclosporine, azathioprine, tacrolimus

d. IV gamma-globulin or Prosorba column therapy.

17. Exposure to the following within 4 weeks prior to first dose of study drug:
    a. janus kinase (JAK) inhibitor (eg, tofacitinib, upadacitinib)
    b. any other conventional systemic DMARD not covered above (other than methotrexate and hydroxychloroquine unless maintaining on a stable dose through the study as allowed in inclusion criteria)
    c. IA hyaluronic acid injections
    d. IA, IM, or IV corticosteroids including adrenocorticotropic hormone
    e. other psoriasis treatments not listed above (eg,, mycophenolate mofetil, retinoids, fumarates, or phototherapy [eg, PUVA, UVA, UVB, high potency topical corticosteroids]).
18. Exposure to leflunomide within 8 weeks prior to first dose of study drug (unless maintaining on a stable dose through the study as allowed in inclusion criteria).
19. Exposure to sulfasalazine and apremilast within 1 week prior to first dose of study drug (unless maintaining a stable dose through the study as allowed in inclusion criteria).
20. Chronic use of medium or high potency narcotic analgesics such as morphine or morphine-derived medications, fentanyl, hydromorphone, levorphanol, meperidine, methadone, or oxycodone at screening, as determined by investigator.
21. Received live vaccination ≤ 12 weeks prior to dosing or scheduled to receive a live vaccine within 12 weeks following the last dose of study drug.
22. Participating in another interventional clinical study or participated in a clinical study involving administration of a study drug within the following time period prior to dosing: 12 weeks, 5 half-lives, or twice the duration of the biological effect of the study drug (whichever is longer).

**General**

23. History of hypersensitivity or allergy to izokibep or its excipients.
24. Previously randomized or withdrawn from this study.
25. Active substance abuse (drug or alcohol) within 24 weeks prior to first dose of study drug, as determined by the investigator.
26. Any condition that compromises the ability of the subject to give written informed consent and/or subject's unwillingness or inability to comply with study procedures.

## 5.3. Lifestyle Considerations

Investigator should encourage subject to limit alcohol consumption to ≤2 per day, ≤7 alcoholic drinks per week. An alcoholic drink is defined as a 6 oz (175 mL) glass of wine, a 1 oz (30 mL) glass of hard liquor (eg, whiskey), or an 8 oz (250 mL) glass of beer.

## 5.4. Screen Failures

A screen failure occurs when a subject who consents to participate in the clinical study is not subsequently enrolled/randomized to the study. A minimal set of screen failure information will be collected to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography (ie, age, sex), screen failure reason, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times (ie, total of 3 screens including initial screen). Refer to Section 6.3.2 for details on rescreening.

## 5.5. Criteria for Temporarily Delaying Dosing

Subject should be dosed within the window as detailed in the SoA (Section 1.3).

All missed or delayed doses should be documented. If the investigator determines a subject should not be dosed within the defined window for a safety reason (eg, an AE, SAE), then a missed dose should be recorded.

## 5.6. COVID-19-related Precautions

Risk mitigation measures, including COVID-19-related precautions and procedures (including SARS-CoV-2 testing/screening) will be implemented based on the prevailing situation during the study conduct, at the investigator's discretion, and in accordance with local and institutional guidelines as applicable.

Subjects should be routinely monitored for any AEs at every visit, including signs or symptoms of infection. Should subjects demonstrate any symptoms or AEs (including known COVID-19 symptoms or tested positive for COVID-19), the symptoms or AEs will be reported to the site as per study procedures and assessed by the investigator. As with any AEs, AE data will be collected on the appropriate electronic case report form (eCRF).

If a subject has received, or is planning to receive, COVID-19 vaccination, the investigator should refer to vaccine considerations in eligibility criteria (Section 5.2) and concomitant medications (Section 6.8) requirements in the protocol.

# 6. Study Drug(s) and Concomitant Therapy

Study drug is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

## 6.1. Study Drug(s) Administered

The study drugs include izokibep and matching placebo.

**Table 3. Study Drug(s) Administered: Izokibep and Placebo**

| | Investigational drug | Placebo |
|---|---|---|
| Drug name | Izokibep | Placebo to izokibep |
| Pharmacological group | Biologic: IL-17A inhibitor | None |
| Form | Solution for injection | Solution for injection |
| Active ingredient per form | Each 2R (2 mL) glass vial contains 1.2 mL of izokibep (nominal concentration 80 mg/mL ±10%) | Not applicable |
| Route of administration | SC | SC |
| Nonactive ingredients (excipients) | 10 mM sodium phosphate<br>150 mM NaCl<br>0.5 mM EDTA | 10 mM sodium phosphate<br>150 mM NaCl<br>0.5 mM EDTA |
| Special storage recommendations | Vials are to be stored at 2°C to 8°C. Once removed from the refrigerator, the solution should be allowed to warm to room temperature (about 15 to 20 minutes) prior to administration. For further details, refer to Pharmacy Manual. | Store at room temperature (do not store above 25°C). Given placebo and izokibep will be provided in blinded, matching vials, both should be stored at 2°C to 8°C. Once removed from the refrigerator, the solution should be allowed to warm to room temperature (about 15 to 20 minutes) prior to administration. For further details, refer to Pharmacy Manual. |

Abbreviations: EDTA = ethylenediaminetetraacetic acid; IL = interleukin; NaCl = sodium chloride; SC = subcutaneous.

### 6.1.1. Dosage, Administration, and Schedule: Izokibep and Placebo

Study drug (izokibep 80 mg Q4W, izokibep 160 mg QW, izokibep 160 mg Q2W or placebo) will be dosed by SC injection. Study drug vials for placebo and izokibep will be visually indistinguishable.

Study drug doses are fixed and will not be adjusted for individual subjects during the study. Throughout treatment period, 2 SC injections are to be given for each study drug administration. The anatomical sites for administration of study drug are the upper arm, upper thigh, or abdomen.

At the study site, only authorized investigational site study staff members are to administer study drug (see Section 6.2). Subjects should be monitored for at least 1 hour after study drug

administrations at the following visits: Day 1/Week 0, Week 1, Week 2, Week 16, Week 17, and Week 18.

Subjects will be randomized to 1 of 4 dosing groups as follows:

- Group 1 (n = 100): placebo QW from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Weeks 16 to Week 51.
- Group 2 (n = 100): izokibep 160 mg QW from Day 1/Week 0 to Week 51.
- Group 3 (n = 100): izokibep 160 mg Q2W from Day 1/Week 0 to Week 50, with matching placebo Q2W until Week 51 for the weeks in between izokibep doses to maintain the blind.
- Group 4 (n = 25): izokibep 80 mg Q4W from Day 1/Week 0 to Week 48, with matching placebo QW until Week 51 for the weeks in between izokibep doses to maintain the blind.

The dosing schedule is described by a schema in Section 1.2.

## 6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.
2. Only subjects randomized in the study may receive study drug. All study drug must be stored prior to dispensing in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

### 6.3.1. Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, the sponsor or designee requires a copy of the site's written institutional review board (IRB)/independent ethics committee (IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 10.1.3). All subjects must personally sign and date the ICF before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and registered the subject as enrolled/randomized within the Interactive Response Technology (IXRS) system. The investigator is to document this decision and date in the subject's medical record. The screening period starts when the subject signs and dates the

ICF and ends when the subject is enrolled/randomized, or screen failed. The screening period is up to 28 days. Certain initial screening period procedures may be repeated during the original initial screening period. (Note: Repeating procedures during the original initial screening period is a part of screening and is not considered "rescreening"). These procedures include laboratory assessments due to value(s) out of range due to sampling error or that could be within range with repeat sampling. Laboratory value(s) out of range due to sampling error or that might be within range after medically appropriate supplementation may be repeated up to 2 times within the screening window before the subject is considered a screen failure.

All subjects who enter the screening period for the study receive a unique subject identification number assigned by the IXRS system. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

The subject identification number consists of 12 digits that correspond to the site number (9 digits) plus the sequential number (3 digits) as follows:

- Site number (first 9 digits)
    - first 3 digits correspond to the last 3 digits of the study protocol number (ie, 104)
    - middle 3 digits correspond to the 3-digit ISO 3166-1 number code for the country (eg, US country code = 840; for country codes with only 2 digits, a lead "0" will be added)
    - last 3 digits are sequential numbers given to sites within a country (eg, for a US site = 104840**001**).
- Sequential numbering of subjects within a site (last 3 digits)
    - the last 3 digits are sequential numbers assigned by IXRS within a site (eg, for US Site 104840001, their first subject = 104840001**001**).

A subject who is determined to be ineligible must be registered as a screen failure in the IXRS system.

### 6.3.2. Rescreening

Investigators may rescreen a subject if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Reasons to rescreen may include but are not limited to the following:

- Laboratory value(s) out of range due to sampling error or that might be within range after medically appropriate supplementation. (Note: Before screen failing and then rescreening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening period.)
- The subject has a medical condition that can be stabilized or resolved prior to the repeat screening/rescreening attempt
- Additional time is required following the subject's last dose of an excluded medication.

Investigators are encouraged to consult with the medical monitor prior to rescreening subjects for other reasons.

A subject must provide informed consent prior to the initiation of any rescreening procedures only if 30 or more days have elapsed since the date of the subject's initial informed consent. The subject is entered into rescreening in the IXRS system, and all screening procedures must be repeated except as noted in the inclusion/exclusion criteria. A subject may be screened up to 3 times (ie, no more than 2 rescreens). Near to the end of study enrollment, sites may be notified when no additional subjects will be screened or rescreened.

If a subject rescreens, a chest x-ray does not need to be repeated if a previous chest x-ray was performed $\leq$ 3 months prior to Day 1.

If a subject rescreens, hepatitis, TB, HIV, urinalysis, and electrocardiogram (ECG) tests do not need to be repeated if a previous test was performed < 60 days prior to Day 1.

### 6.3.3. Randomization

Subjects will be randomized to the study drug (izokibep QW, izokibep Q2W with alternating Q2W placebo, izokibep Q4W with placebo at other weeks, to maintain the blind or placebo QW) on Day 1 by IXRS system. Randomization will be based on a schedule generated by the sponsor or sponsor designee before the start of the study and will be centrally executed using the IXRS system. The subject, site personnel, and sponsor/Contract Research Organization (CRO) study personnel and designees will be blinded to the randomization treatment group assignment (ie, izokibep or placebo) and matching placebo administered on the weeks in between izokibep doses for the izokibep Q2W and Q4W arms will be used to blind the dosing schedule (QW or Q2W or Q4W). The randomization dates are to be documented in the subject's medical record.

Randomization will be stratified by any prior treatment with a systemic TNFi (Yes/No) and enthesitis (LEI > 0/LEI = 0).

Izokibep and matching placebo will be visually indistinguishable to prevent unblinding during preparation or administration of study material.

### 6.3.4. Site Personnel Access to Individual Treatment Assignments

Subject's treatment assignment should be unblinded only when knowledge of the treatment is essential for the further management of the subject in this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is requested to contact the medical monitor before unblinding any subject's treatment assignment, whenever possible, but must do so within 1 working day after the event. If an urgent therapeutic intervention is necessary which warrants unblinding prior to contacting the medical monitor, the investigator can directly access the IXRS system to unblind without medical monitor notification or agreement but must still contact the medical monitor within 1 working day after the event.

If an SAE requires an expedited regulatory report to be sent to 1 or more regulatory agencies, sponsor/designee's safety staff may unblind the intervention assignment for the subject. A copy of the report, identifying the subject's intervention assignment, may be sent to that regulatory agency in accordance with local regulations.

Please refer to the Study Pharmacy Manual for details.

## 6.4. Study drug Compliance

When subjects are dosed at the site, they will receive study drug directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

After Week 4, subjects may perform home dosing of study drug. Site staff will administer the first 2 doses of study drug and train the subject on handling and self administration of study drug during those study visits. Prior to beginning self-administration, the subject will need to self administer the following 2 doses of study drug at the site and demonstrate competency prior to being allowed to perform home dosing. Subject's caregiver or designee can also be trained on home dosing based on subject's preference. Only those subjects/caregivers or designees who demonstrate competency to perform home dosing will be allowed to do so; otherwise, the subject will need to return to the site for all study drug administrations.

When study drug(s) is/are administered at home by the subject/caregiver, compliance with study drug will be assessed at each visit. Compliance will be assessed by review of the subject dosing diary during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded and reported to sponsor (or designee).

A record of the quantity of study drug dispensed and administered to each subject must be maintained and reconciled with study drug and compliance records. Intervention dose dates, including intervention delays will also be recorded. Partial dose administration will be explained.

## 6.5. Dose Modification

No dose modifications are allowed in the study.

## 6.6. Continued Access to Study Drug After the End of the Study

There is no plan to continue access to study drug after the end of study. The choice of further therapy for PsA at the end of the clinical study depends on the subject's individual needs and is left at the physician's discretion.

## 6.7. Overdose

Excessive dosing of study drug should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE as specified in Section 8.3.

These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

## 6.8. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including route, dose, and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.8.1. Prior Therapies

Any treatments for PsA since initial diagnosis (as determined through medical history records or through subject interview) prior to study entry will be recorded in the source documents and on the eCRF, along with the reason for discontinuation.

A detailed history of prior DMARDs, biologics, and steroids use, response, and reason for discontinuation will be collected.

### 6.8.2. Concomitant Therapies

Subjects will be allowed to continue the following concomitant medications/treatments during the study provided the dose has been stable within the time defined in Section 5.1 prior to Day 1 and within the acceptable limits listed below, and must remain unchanged throughout the study:

- methotrexate ≤ 25 mg/week
- leflunomide ≤ 20 mg/day
- sulfasalazine ≤ 3 g/day
- apremilast ≤ 60 mg/day
- hydroxychloroquine ≤ 400 mg/day
- corticosteroids equivalent to prednisone ≤ 7.5mg/day
- NSAIDs, unless indicated for treatment of ISRs as described in Section 2.3.1
- Low potency opioid medications (tramadol or combination formula of paracetamol with codeine or with hydrocodone)

Use of methotrexate in combination with leflunomide is prohibited. Concomitant medications should be used in alignment with the approved label in the respective country, and per doses permitted per inclusion criteria.

### 6.8.3. Prohibited Medications

The following medications are prohibited from enrollment through Week 52, unless otherwise specified or unless study drug has been permanently discontinued:

1. all other biologic therapies with a potential therapeutic impact on PsA including but not limited to:
    a. IL-17 receptor inhibitors (eg, secukinumab, ixekizumab, bimekizumab, brodalumab)

   b. biologics with potential for or known association with progressive multifocal leukoencephalopathy (ie, natalizumab, rituximab, efalizumab)
   c. TNFi (eg, adalimumab, etanercept, infliximab, golimumab)
2. IM or oral gold
3. cytotoxic agents (eg, cyclophosphamide, D-penicillamine)
4. any other immunomodulatory therapy (eg, cyclosporine, azathioprine, tacrolimus, IV gamma-globulin, or Prosorba column therapy)
5. JAK inhibitors (eg, tofacitinib, upadacitinib)
6. other conventional systemic DMARDs (csDMARDs) (other than methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine with stable doses as specified in Section 6.8.2)
7. IA hyaluronic acid injections
8. IA, IM, or IV corticosteroids including adrenocorticotropic hormone. Corticosteroid injections into trigger points, tender points, bursae, or entheses are not permitted
9. other psoriasis treatments not listed above (eg, mycophenolate mofetil, retinoids, fumarates, vitamin D analogues, keratolytics, coal tar, or phototherapy [eg, PUVA, UVA, UVB, high potency topical corticosteroids unless indicated for injection site reactions to be used only on affected reaction area])
10. medium or high potency narcotic analgesics (eg, morphine or morphine-derived medications, fentanyl, hydromorphone, levorphanol, meperidine, methadone, or hydrocodone). Tramadol or combination formula of paracetamol with codeine or with hydrocodone are permitted at stable doses as specified in Section 6.8.2
11. live vaccines (during the study and for 12 weeks following the last dose of study drug)
12. any investigational agents

# 7. Discontinuation of Study drug and Subject Discontinuation/ Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.8.

## 7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a subject to permanently discontinue study drug. The reason for permanent discontinuation of study drug will be documented. If study drug is prematurely and permanently discontinued, the subject will be encouraged to remain in the study to be evaluated for safety and efficacy. Subjects should continue to complete study assessments as outlined in the SoA (Section 1.3) where possible, with the exception of study drug administration, and anti-drug antibody sample and PK sample collection. Reasons for removal from study drug include any of the following:

- subject request
- death
- lost to follow-up
- termination of study by sponsor
- emergency unblinding
- liver chemistry stopping criteria (see Section 7.1.1)
- serious infections
- the subject becomes pregnant while on study drug
- malignancy
- subject develops CTCAE v5.0 grade 3 or higher SAE or AE(s) that is considered by the investigator to be related to study drug
- subject develops an illness that, in the opinion of the Investigator, would interfere with his or her continued participation, if the risk of continuing with study drug outweighs the potential benefit
- subject uses prohibited concomitant medications, as defined in Section 6.8.3, that may present a risk to the safety of the subject in the opinion of the Investigator or the Medical Monitor
- subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study
- subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by the Investigator or Medical Monitor
- subjects with disease progression or not responding to treatment are to be withdrawn from study drug treatment based on Investigator's discretion

- Starting at Week 24, subjects who have not met clinical Disease Activity for PsA (cDAPSA) low disease activity (cDAPSA ≤ 14) at 2 consecutive visits (e.g. at Week 20 and Week 24) will be discontinued from study drug and can receive standard of care treatment as deemed appropriate by the Investigator.

Subjects with newly diagnosed IBD during the study must:

- discontinue study drug and be followed-up until resolution of active IBD symptoms
- be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist

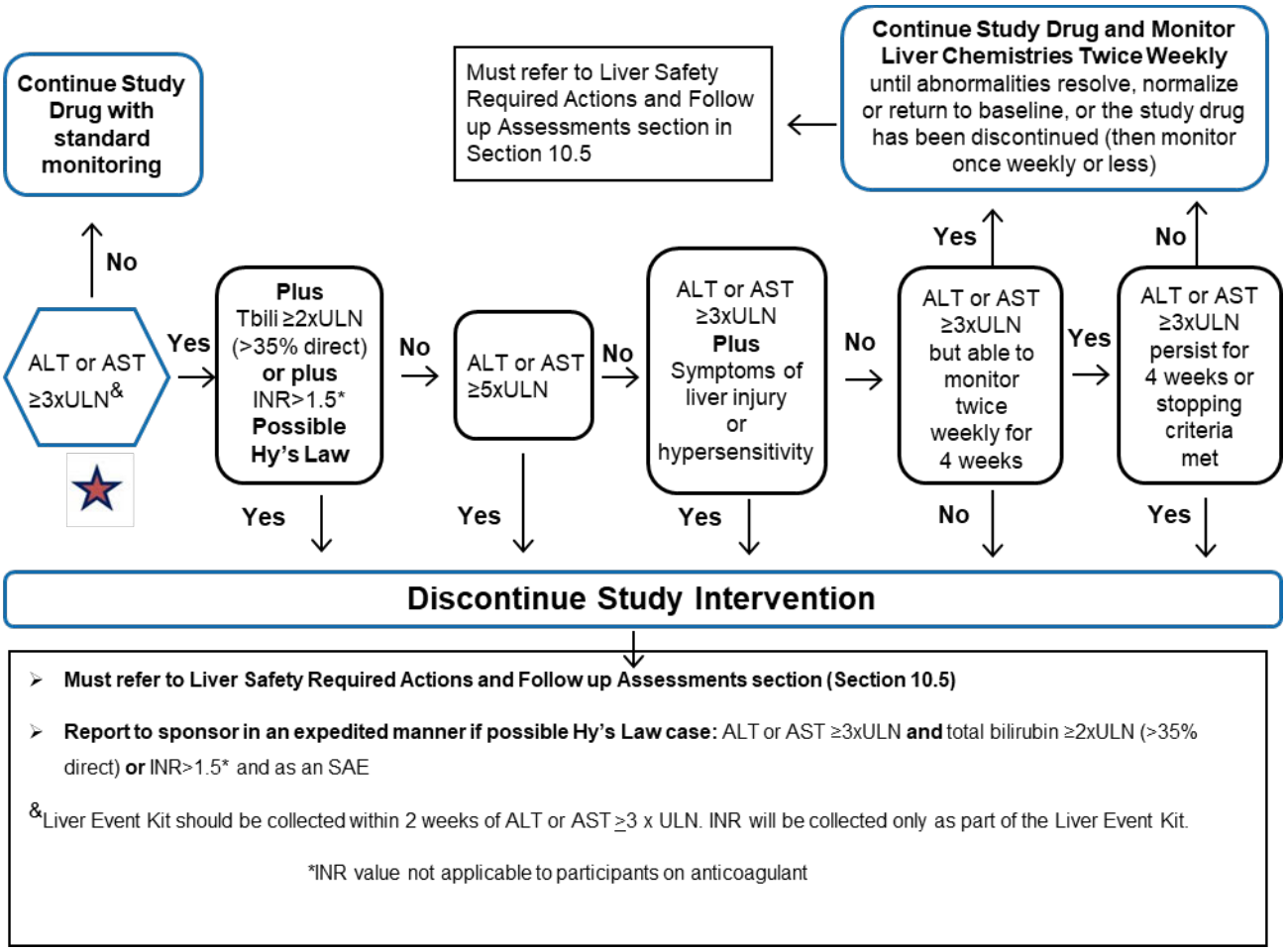
If the subject has a clinical laboratory value meeting any of the following criteria, study drug must be interrupted. The laboratory test must be repeated in 1 to 2 weeks at a scheduled or unscheduled visit. If any one of the following criteria are met and continues to be met at the repeat test and no alternative cause of the laboratory abnormality is identified, the study drug must be discontinued permanently and the subject may continue in the study for protocol-specified study assessments:

- neutrophil count < $1.0 \times 10^9$/L
- platelets < 50,000/$mm^3$
- hemoglobin < 8.5 g/dL with decrease of at least 2 g/dL from Baseline
- creatinine > 2 × Baseline
- any other laboratory abnormality that in the Investigator's judgement could indicate a medical condition that puts the subject's safety at risk and that cannot be readily treated (eg, hyperkalemia)

### 7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study drug for abnormal liver tests is required by the investigator when a subject meets 1 of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in the best interest of the subject (Figure 2). The investigator may consider rechallenge if a reasonable alternative explanation is identified, liver tests have returned to baseline levels, and after consultation with the medical monitor.

Figure 3. Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm[1]




Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; Tbili = total bilirubin; ULN = upper limit of normal. Note: INR will be collected only if ALT or AST ≥ 3 x ULN

[1] Liver Safety: Suggested actions and follow-up assessments can be found in Section 10.5.

### 7.1.2. Rechallenge

#### 7.1.2.1. Study Drug Restart or Rechallenge After Liver Stopping Criteria Met

Study drug restart/rechallenge after liver chemistry stopping criteria are met is allowed in this study. If the subject meets liver chemistry stopping criteria, do not restart/rechallenge the subject with study drug unless:

- liver tests have returned to subject's baseline values
- sponsor medical monitor approval is granted
- ethics and/or IRB approval is obtained, if required

NOTE: If study drug was interrupted for suspected intervention-induced liver injury, the subject should be informed of the risk of death, liver transplantation, hospitalization, and jaundice before resumption of dosing.

Refer to Section 10.5 for details on the restart/rechallenge process.

If sponsor medical monitor approval to restart/rechallenge the subject with study drug is **not granted**, then the subject must permanently discontinue study drug and may continue in the study for protocol-specified study assessments.

## 7.2. Subject Discontinuation/Withdrawal from the Study

Reasons for removal of a subject from the study are:

- termination of study by sponsor
- death
- withdrawal of consent from study
- lost to follow-up

Withdrawal of consent from study:

- A subject may withdraw from the study at any time without jeopardizing subsequent medical care.
- At the time of discontinuing from the study, if possible, an End of Treatment visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. See Section 7.1 for procedures if the study drug is prematurely discontinued and does not withdraw from the study.
- The subject will be permanently discontinued from the study drug and the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and notify the sponsor or its designee.

## 7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 attempts at known

effective points of contact [eg, phone, e-mail, text], and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered lost to follow-up.

# 8. Study Assessments and Procedures

- Informed consent must be obtained before any study-related procedures are performed. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by the subject.
- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Day 1 corresponds to the date of the first dose of study drug.
- Visit/dosing windows of ±3 days on either side of the scheduled visits/dosing are permitted. In case of a delayed or missed dose, the investigator should return subjects on the original visit/dosing schedule in relation to Day 1 for subsequent doses. The window of ±3 days is relative to Day 1 and applicable for all subsequent visits/dosing. The minimum time between doses should be no less than 4 days and no more than 10 days.
- All assessments are to be completed before study drug administration, unless otherwise specified. It is recommended that patient-reported outcome assessments be completed first. X-rays required at Week 16 and at the End of Treatment visit may be completed ±3 days of dosing.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, chest x-rays) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3). The study site should make every attempt to have the same investigator conduct efficacy assessments throughout the study for each subject.

### 8.1.1. Composite Measures

The calculation of the composite scores will be performed by the sponsor or designee based on the assessments entered by the study investigator(s) on the appropriate eCRFs.

#### 8.1.1.1. American College of Rheumatology Response Criteria

The ACR criteria are standard criteria to measure the effectiveness of various arthritis medications or treatments in clinical trials. The ACR criteria were developed for rheumatoid arthritis but now are also frequently used for primary outcome measure in PsA clinical trials (American College of Rheumatology, 2019).

The ACR criteria are reported as percentage (%) improvement, comparing disease activity at 2 discrete timepoints (baseline and postbaseline comparison). The ACR criteria are indicated as:

- ACR20 is ≥ 20% improvement
- ACR50 is ≥ 50% improvement; ACR50 responders include ACR20 responders
- ACR 70% (ACR70) is ≥ 70% improvement; ACR70 responders include ACR20 and ACR50 responders

The ACR20 criteria require that the subject experiences an improvement in the following parameters compared to baseline:

- ≥ 20% reduction in TJC68 (see Section 8.1.3.1)
- ≥ 20% reduction in SJC66 (see Section 8.1.3.1)
- ≥ 20% reduction in 3 of 5 additional measures:
    - Subject's Assessment of Pain (see Section 8.1.2.3)
    - Subject's Global Assessment of Disease Activity (see Section 8.1.2.2)
    - Investigator's Global Assessment of Disease Activity (see Section 8.1.3.2)
    - HAQ-DI (see Section 8.1.2.6)
    - Acute phase reactant (C-reactive protein [CRP]).

Analyses of ACR50 and ACR70 include the same criteria as ACR20, with the use of a higher percentage improvement (50% and 70%, respectively) instead of 20% (European Medicines Agency, 2007).

The proportion of subjects achieving ACR20, ACR50, and ACR70 will be evaluated at Week 16.

#### 8.1.1.2. Disease Activity Score in 28 Joints

The Disease Activity Score in 28 joints (DAS28)-CRP was developed to measure disease activity in subjects with rheumatoid arthritis. It is a composite score derived from the following measures (Mease, 2011):

- 28 tender joint count (see Section 8.1.3.1)
- 28 swollen joint count (see Section 8.1.3.1)

- CRP
- Subject's Global Health Assessment (corresponds to Subject's Global Assessment of Disease Activity, see Section 8.1.2.2).

Generally, remission is considered achieved if the score is between 0 and < 2.6. Low activity corresponds to 2.6 to < 3.2. Moderate activity is between 3.2 and ≤ 5.1, while high activity is strictly above 5.1.

Change in DAS28-CRP composite score will be evaluated at Week 16.

#### 8.1.1.3. Disease Activity in Psoriatic Arthritis

The Disease Activity in Psoriatic Arthritis (DAPSA) is a composite score calculated by summing the following variables (Mease, 2011):

- 68 tender joint count (see Section 8.1.3.1)
- 66 swollen joint count (see Section 8.1.3.1)
- Subject's Assessment of Pain (see Section 8.1.2.3)
- Subject's Global Assessment of Disease Activity (see Section 8.1.2.2)
- CRP level in mg/dL.

Change in DAPSA and clinical DAPSA (cDAPSA; sum of the above variables, but omitting CRP) composite scores will be evaluated at Week 16.

Proportion achieving DAPSA and cDAPSA low disease activity (DAPSA/cDAPSA ≤ 14) and remission (DAPSA/cDAPSA ≤ 4) will be evaluated starting at Week 16.

#### 8.1.1.4. Psoriatic Arthritis Disease Activity Score

The Psoriatic Disease Activity Score (PASDAS) is a weighted index comprising the following assessments:

- 68 tender joint count (see Section 8.1.3.1)
- 66 swollen joint count (see Section 8.1.3.1)
- Subject's Global Assessment of Disease Activity (see Section 8.1.2.2)
- Investigator's Global Assessment of Disease Activity (see Section 8.1.3.2)
- 36-Item Short Form Survey (SF-36; see Section 8.1.2.8)
- Leeds Enthesitis Index (see Section 8.1.3.5)
- Leeds Dactylitis Index (see Section 8.1.3.6)
- CRP level in mg/dL.

The score range of the PASDAS is 0 to 10, with worse disease activity represented by higher scores. Change in PASDAS index will be evaluated at Week 16.

#### 8.1.1.5. Minimal Disease Activity and Very Low Disease Activity

The criteria for MDA were developed for rheumatoid arthritis, but a PsA-specific definition of MDA has been constructed (Coates et al, 2010). These criteria were validated and are now considered as a step towards "treatment to target" in PsA, ie, the goal of achieving remission or low disease activity state (Coates et al, 2010; Mease, 2011).

A subject is classified as in MDA when 5 of the following 7 criteria are met (Mease, 2011):

- 68 tender joint count ≤ 1 (see Section 8.1.3.1)
- 66 swollen joint count ≤ 1 (see Section 8.1.3.1)
- PASI ≤ 1 or BSA ≤ 3% (see Section 8.1.3.3)
- Subject's Pain Assessment (visual analogue scale [VAS]) ≤ 15 mm (see Section 8.1.2.3)
- Subject's Global Activity VAS ≤ 20 mm (corresponds to Subject's Global Assessment of Disease Activity, see Section 8.1.2.2)
- HAQ-DI ≤ 0.5 (see Section 8.1.2.6)
- Tender entheseal points ≤ 1 site out of 6 sites included in LEI (see Section 8.1.3.5).

A subject is classified as in very low disease activity (VLDA) when all 7 criteria described above are met.

The proportion of subjects achieving MDA and VLDA will be evaluated at Week 16.

### 8.1.2. Patient-reported Outcomes

#### 8.1.2.1. Subject's Global Impression of Change

Subjects will complete a global impression of change questionnaire at the designated study visits listed in SoA (Section 1.3).

The questionnaire consists of 1 self-administered item that assesses change in disease activity. Subjects will be asked to indicate their impression of change compared with start of treatment.

#### 8.1.2.2. Subject's Global Assessment of Disease Activity

Subject's global health assessment will be evaluated at the designated study visits listed in SoA (Section 1.3) using a VAS.

The VAS is a horizontal line, 100 mm in length, with anchor statements on the left (0 mm) and on the right (100 mm). The subject will be asked to place a single vertical line through the VAS at the point that best corresponds to their feeling of disease activity.

The score is obtained by measuring the distance from 0 to the line drawn by the subject.

#### 8.1.2.3. Subject's Assessment of Pain (VAS)

Pain will be assessed by the subject at the designated study visits listed in SoA (Section 1.3) using a VAS.

The VAS is a horizontal line, 100 mm in length, with anchor statements on the left (0 mm) and on the right (100 mm). The subject will be asked to place a single vertical line through the VAS at the point that best corresponds to their feeling of pain.

The score is obtained by measuring the distance from 0 to the line drawn by the subject.

#### 8.1.2.4. Subject's Assessment of Spinal Pain (NRS)

Spinal pain will be assessed by the subject at the designated study visits listed in SoA (Section 1.3) using a numeric rating scale (NRS).

The subject will be asked to circle the number between 0 and 10 that fits best to their spinal pain intensity, with "0" indicating "no pain" and 10 indicating "worst imaginable pain".

#### 8.1.2.5. Widespread Pain Index

The Widespread Pain Index (WPI) is a self-report measure used to assess bodily distribution of pain and to specifically quantify the degree of widespread body pain and assess for centralized pain features. The WPI assesses the presence of pain in 19 designated body locations over the past 7 days (eg, neck, right upper arm, left lower leg). Each location is equal to a score of 1. Items are summed to yield a total score, with higher scores indicating greater widespread pain (Dudeney et al, 2019).

The WPI will be presented in local language and is to be completed by the subject at the designated study visits listed in SoA (Section 1.3).

#### 8.1.2.6. Health Assessment Questionnaire – Disability Index

The HAQ-DI questionnaire is a patient-reported outcome that is self-administered by the subject. It covers 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities.

The HAQ-DI will be presented in local language and is to be completed by the subject at the designated study visits listed in SoA (Section 1.3).

#### 8.1.2.7. Psoriatic Arthritis Impact of Disease

The PsAID is a questionnaire developed by EULAR to assess the subject's physical and psychological domains related to PsA. The questionnaire used in clinical trials consists of 9 questions (PsAID-9; Gossec et al, 2014).

The PsAID-9 score gives a number between 0 and 10. A higher score on the PsAID-9 indicates more impact of the disease. A score below 4 out of 10 is considered a patient-acceptable status. A change of 3 or more points is considered a relevant absolute change.

The PsAID-9 questionnaire will be presented in local language and is to be completed by the subject at the designated study visits listed in the SoA (Section 1.3).

The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

#### 8.1.2.8. Short Form-36

The acute Short Form-36v2 Health Survey (SF-36) is 36-item questionnaire that measures 8 dimensions related to functioning and well being including physical functioning, role-function, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

The SF-36 questionnaire will be presented in local language and is to be completed by the subject at the designated study visits listed in the SoA (Section 1.3).

The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

#### 8.1.2.9. Functional Assessment of Chronic Illness Therapy-Fatigue

The FACIT measurement system was originally developed to assess health-related quality of life in subjects with chronic illnesses. The additional questions of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) survey were compiled to assess anemia-related fatigue (Mease, 2011).

The FACIT-F comprises 13 items in total and each item is answered based on a 5-point Likert scale. Responses of "not at all", "a little bit", "somewhat", "quite a bit", and "very much" are available for each question, and correspond to scores of 0, 1, 2, 3, and 4, respectively.

The FACIT-F questionnaire will be presented in local language and is to be completed by the subject at the designated study visits listed in the SoA (Section 1.3).

### 8.1.3. Investigator's Assessments

The following investigator assessments should be performed by an independent and blinded assessor, if available, who should not perform any other study related procedures.

- Psoriasis Area Severity Index (PASI)
- body surface area (BSA)
- TJC and SJC Assessment
- Dactylitis assessments
- Enthesitis assessments
- modified nail psoriasis severity index (mNAPSI)

In order to minimize variability, the same assessor should evaluate the subject at each visit for the duration of the trial. A back-up assessor should be identified. The assessor should be a qualified medical professional (e.g. nurse, physician's assistant, or physician) or be pre-approved by the Medical Monitor or Sponsor as an assessor after review of assessor training and experience. Any assessor must be trained and competent in performing such assessments. It is the responsibility of the Investigator to ensure that all assessors are qualified and trained to perform assessments and that all training is documented. If the assessor is not available, the pre-identified back-up assessor should perform such assessments.

#### 8.1.3.1. Joint Assessments

Joints are palpated for the purpose of determining if they are tender and/or swollen, the latter implying the presence of active synovitis, and both implying the presence of inflammation (Mease, 2011).

Joint assessment will be performed at the designated study visits listed in the SoA (Section 1.3) for 68 tender and 66 swollen joint count. The tender and swollen joint counts will be used to determine the response (ACR; see Section 8.1.1.1) and disease activity (DAS28-CRP, DAPSA, PASDAS, MDA, and VLDA; see Sections 8.1.1.2 to 8.1.1.5).

Table 4 shows an overview of the joints assessed for tenderness and swelling (Sokka and Pincus, 2005), and of which joint counts will be used for each composite measure.

A rule of thumb is to apply approximately 4 kg/cm$^2$ of pressure (enough to blanch the tip of the examiner's fingernail) at the joint line (Mease, 2011). To ensure the most accurate assessment of change, the joint counts should be undertaken by the same person in each individual subject where possible.

Documentation of the total number of tender joints and total number of swollen joints will be done on a joint count worksheet provided by the sponsor.

**Table 4. Tender and Swollen Joint Counts**

| | **ACR/DAPSA/PASDAS/ MDA/VLDA** | | **DAS28** | |
|---|---|---|---|---|
| **Joints (bilateral assessment)** | **68 tender joint count** | **66 swollen joint count** | **28 tender joint count** | **28 swollen joint count** |
| Temporomandibular (R, L) | 2 joints | 2 joints | - | - |
| Sternoclavicular (R, L) | 2 joints | 2 joints | - | - |
| Acromioclavicular (R, L) | 2 joints | 2 joints | - | - |
| Shoulder (R, L) | 2 joints | 2 joints | 2 joints | 2 joints |
| Elbow (R, L) | 2 joints | 2 joints | 2 joints | 2 joints |
| Wrist (R, L) | 2 joints | 2 joints | 2 joints | 2 joints |
| Hand (R, L) | | | | |
| MCP joints I-V | 10 joints | 10 joints | - | - |
| PIP joints I-V | 10 joints | 10 joints | - | - |
| DIP joints II-V | 8 joints | 8 joints | - | - |
| Hip (R, L) | 2 joints | - | - | - |
| Knee (R, L) | 2 joints | 2 joints | 2 joints | 2 joints |
| Ankle (R, L) | 2 joints | 2 joints | - | - |

| | | | | |
|---|---|---|---|---|
| Foot (R, L) | | | | |
| Tarsus | 2 joints | 2 joints | - | - |
| MTP joints I-V | 10 joints | 10 joints | 10 joints | 10 joints |
| PIP joints I-V (toes) | 10 joints | 10 joints | 10 joints | 10 joints |

Abbreviations: ACR = American College of Rheumatology; DAPSA = Disease Activity in Psoriatic Arthritis; DAS28 = Disease Activity Score in 28 joint; DIP = distal interphalangeal; L = left; MCP = metacarpophalangeal; MDA = Minimal Disease Activity; MTP = metatarsophalangeal; PASDAS = Psoriatic Disease Activity Score; PIP = proximal interphalangeal; R = right; VLDA = very low disease activity.

#### 8.1.3.2. Investigator's Global Assessment of Disease Activity

Investigator's global health assessment related to subject's disease activity will be evaluated at the designated study visits listed in SoA (Section 1.3) using VAS.

The VAS is a horizontal line, 100 mm in length, with anchor statements on the left (0 mm) and on the right (100 mm).

The investigator will be asked to place a single vertical line through the VAS at the point that best corresponds to the subject's disease activity.

The score is obtained by measuring the distance from 0 to the line drawn by the investigator.

#### 8.1.3.3. Psoriasis Area and Severity Index and Affected Body Surface Area

Psoriasis Area and Severity Index is an index used to express the severity of psoriasis. Because its performance characteristics are diminished in subjects with low lesional burden, it is not typically calculated in subjects with < 3% BSA involvement with psoriasis lesions (Mease, 2011).

After start of treatment, PASI will only be assessed if psoriasis affects ≥ 3% of subject's BSA at baseline. The BSA assessment measures the total area of the body affected by psoriasis.

Psoriasis Area and Severity Index evaluates the severity of erythema, induration, and desquamation in 4 body sections (head, arms, trunk, and legs).

Psoriasis Area and Severity Index and affected BSA will be assessed at the designated study visits listed in the SoA (Section 1.3).

#### 8.1.3.4. Modified Nail Psoriasis Severity Index

The Nail Psoriasis Severity Index is a numeric, reproducible, objective, simple tool for evaluation of nail psoriasis (Rich and Scher, 2003). Nail bed psoriasis includes onycholysis, splinter hemorrhages, hyperkeratosis, and "oil-drop change", while nail matrix psoriasis includes pitting, leukonychia, lunular red spots, and nail plate crumbling (Mease, 2011).

A modification of this system, the modified Nail Psoriasis Severity Index (mNAPSI), is a shorter and more feasible scoring system that has demonstrated excellent interrater reliability and has been used in PsA clinical trials (Mease, 2011; Cassell et al, 2007). For each fingernail, 7 groups of features are evaluated: pitting, onycholysis and oil-drop dyschromia, nail plate crumbling,

leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula. Pitting, onycholysis and oil-drop dyschromia, and crumbling (including fragmentation and horizontal ridging of the nail bed) are graded from 0 to 3 in severity. Leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula are graded as either present or absent.

An mNAPSI will be calculated at the designated study visits listed in the SoA (Section 1.3).

#### 8.1.3.5. Leeds Enthesitis Index and Spondyloarthritis Research Consortium of Canada Enthesitis Index

The LEI and the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index are both used to assess enthesitis in subjects with PsA. The LEI assesses 6 entheseal sites, while the SPARCC Enthesitis Index assesses enthesitis at 16 anatomical sites (see Table 5). Tenderness on examination will be recorded as either present (1) or absent (0) for each of the sites, for an overall score range of 0 to 6 (LEI) and 0 to 16 (SPARCC Enthesitis Index). Higher count represents greater enthesitis burden (Mease, 2011).

The investigator will assess the 16 sites of the SPARCC Enthesitis Index plus 2 sites of the LEI (right and left medial condyle femur; see Table 5) at the designated study visits listed in the SoA (Section 1.3).

**Table 5. Entheseal sites assessed for enthesitis according to SPARCC and LEI**

| Anatomical sites assessed for tenderness | SPARCC (16 sites) | LEI (6 sites) |
|---|---|---|
| Supraspinatus insertion into the greater tuberosity of the humerus | R, L | - |
| Lateral epicondyle humerus | R, L | R, L |
| Medial epicondyle humerus | R, L | - |
| Achilles tendon | R, L | R, L |
| Greater trochanter | R, L | - |
| Medial condyle femur | - | R, L |
| Plantar fascia insertion at the calcaneus | R, L | - |
| Quadriceps insertion into the superior border of the patella | R, L | - |
| Patellar tendon insertion at the inferior pole of the patella | R, L | - |

Abbreviations: L = left; LEI = Leeds Enthesitis Index; R = right; SPARCC = Spondyloarthritis Research Consortium of Canada.

#### 8.1.3.6. Leeds Dactylitis Index

Using the Leeds Dactylitis Index, one can quantify the size and tenderness of a swollen digit, enabling differentiation between tender and nontender dactylitis. Each of 20 digits (ie, all fingers and toes) will be evaluated for size (circumference close to the base measured in millimeter) and tenderness. For use in clinical trials, circumferences of the affected and contralateral digits are

measured using a measuring tape or a precalibrated loop. The circumference of the affected digits, circumference of contralateral digits, and tenderness of affected fingers are all assessed for a total score. A difference in digital circumference of > or =10% is used to define a finger with dactylitis (Mease, 2011; Kaeley et al, 2018).

The presence or absence of tenderness at 20 digits and the circumference of each digit will be assessed and documented by the investigator at the designated study visits listed in the SoA (Section 1.3).

#### 8.1.3.7. Investigator Question on Presence of Axial Involvement

The presence of axial involvement will be recorded at baseline.

Investigator will respond Yes/No to the following question: *"Does the subject have axial involvement?"*.

#### 8.1.3.8. Radiographic Assessment and modified total Sharp score

Radiographs of hands, wrists, and feet will be performed at baseline, Week 16, and Week 52 or EOT in order to evaluate the presence and extent of PsA-related structural damage over the course of the study. Radiograph of the pelvis will be performed at baseline.

Radiographs of hands, wrists, and feet will be performed if subjects discontinue the study drug after Week 16 and it has been at least 12 weeks from the date of last radiographs obtained. Radiographs should be obtained as close as possible to the last dose of study drug.

Psoriatic arthritis radiographic progression will be measured by the modified total Sharp score (mTSS). The mTSS is a detailed scoring method evaluating erosions, joint space narrowing, (sub)luxation, ankylosis, gross osteolysis, and pencil in cup phenomena. It typically assesses joints of the hands and feet, including the second to fifth distal interphalangeal joints of both hands (van der Heijde et al, 2005).

The maximum score for erosions is 5 in the joints of the hands and 10 in the joints of the feet. Scores for erosions are as follows: 0 = no erosions; 1 = discrete erosion; 2 = large erosion not passing the midline; 3 = large erosion passing the midline.

A combination of the above scores may lead to a maximum of 5 per entire joint in the hands, and 5 at each site of the joint (for the entire joint a maximum of 10) in the feet. The joint space narrowing score is based on the following features: 0 = normal; 1 = asymmetrical or minimal narrowing up to a maximum of 25%; 2 = definite narrowing with loss of up to 50% of the normal space; 3 = definite narrowing with loss of 50 to 99% of the normal space or subluxation; 4 = absence of a joint space, presumptive evidence of ankylosis, or complete luxation.

Gross osteolysis and pencil in cup are scored separately. In the final summary score, joints with 1 of these abnormalities get the maximum score assigned for both erosions and for joint space narrowing. The maximum possible scores are 320 for erosions, 208 for joint space narrowing, and 528 for the total score.

## 8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

### 8.2.1. Medical and Medication History

A complete medical and medication history, as well as history of alcohol and nicotine use, will be obtained from each subject during the screening visit. An updated medical history will be obtained at the Day 1 visit prior to study drug administration and updated as necessary throughout the study.

A PsA history obtained at screening will capture date of onset of PsA and psoriasis (if applicable).

Any systemic treatment for plaque psoriasis and PsA (ie, DMARDs, biologics, steroids) since diagnosis will be recorded. Any other treatment used for any other reasons (including contraception) prior to randomization will be recorded as per eCRF Completion Guidelines.

Any changes in concomitant medication will be recorded throughout the study, from Day 1 until End of Study at Week 65.

### 8.2.2. Physical Examination

A complete physical examination will include, at a minimum, assessments of the dermatological, cardiovascular, respiratory, gastrointestinal, and neurological systems.

Clinically significant findings observed prior to first dose of study drug should be listed as medical history in the eCRF and reported as AEs if observed after first dose of study drug.

### 8.2.3. Physical Measurements

Height and weight measurements are to be performed at the designated study visits listed in the SoA (Section 1.3) and data will be recorded in cm and kg, respectively. Height and weight are to be measured without shoes.

### 8.2.4. Vital Signs

Vital signs will be measured in a sitting position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

### 8.2.5. Electrocardiograms

Triplicate 12-lead ECGs will be obtained one minute apart after subject has been supine for at least 5 minutes as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, intervals.

### 8.2.6. Chest X-ray

Chest x-ray (posterior/anterior or anterior/posterior) in addition to the TB blood test will be performed at screening in subjects who do not have a chest x-ray available within 3 months of screening. A subject must not be included in the study if his/her chest x-ray reveals evidence of active TB or fungal infection (refer to Section 5.2). Women of childbearing potential must have a negative pregnancy test before an x-ray is performed.

### 8.2.7. Hospital Anxiety and Depression Scale

Depression and anxiety will be monitored with the Hospital Anxiety and Depression scale (HADS). The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with other inflammatory skin diseases (Langley et al, 2010). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating a worse state. A score < 8 is considered to be normal, whereas a score of ≥ 11 is considered clinically significant (Snaith, 2003).

The HADS questionnaire will be presented in local language and is to be completed by the subject at the designated study visits listed in the SoA (Section 1.3).

### 8.2.8. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    a. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    b. All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    c. If laboratory values from nonprotocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded within source documents.

### 8.2.9. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing in WOCBP will be conducted throughout the study. A serum pregnancy test will be performed at screening and urine pregnancy testing will be performed at subsequent visits as detailed in the SoA (Section 1.3).
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation or regulatory agency, to establish the absence of pregnancy at any time during the subject's participation in the study.

- The investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy.

### 8.2.10. Hepatitis Testing

All subjects will be tested for the presence of HBV and HCV at screening. A positive result for the HBsAg will be exclusionary. Samples negative for HBsAg will be tested for HBsAb and HBcAb. If test results are positive for HBcAb or HBsAb, then HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary. Positive HCV antibody tests at screening will be tested for HCV RNA by PCR; any detectable HCV RNA will be exclusionary.

### 8.2.11. Inflammatory Bowel Disease Screening

Given that subjects with psoriatic arthritis appear to have a higher lifetime risk of IBD compared to the general population and given that approved IL-17 inhibitors have reported worsening or new onset IBD in clinical trials, all subjects will be screened for IBD by history and a subset will undergo additional laboratory screening. During screening, all subjects will be assessed for the following symptoms within the last year:

- prolonged or recurrent diarrhea without established etiology
- prolonged or recurrent abdominal pain without established etiology
- blood in stool without established etiology
- any other symptoms in the opinion of the Investigator that may be suggestive of IBD

If any are marked affirmative, a fecal calprotectin test must be performed.

- If the resulting fecal calprotectin level is > 150 - 500 µg/g, the subject must undergo a GI consultation and obtain documented approval from the GI consultation to enroll in the clinical trial before continuing with the screening process. If the consultation cannot be completed within the screening window, the subject will be screen-failed but may rescreen.
- fecal calprotectin levels > 500 ug/g will be exclusionary.

### 8.2.12. Tuberculosis Test

Determination of TB status will be required before the subject's inclusion in the study. A QuantiFERON test (or equivalent) will be performed on each subject to assess the TB status at screening. Subjects with a positive test result may not be included in the study (refer to Section 5.1). T-SPOT TB test may be used to establish eligibility if agreed upon with the medical monitor.

#### 8.2.13. Rheumatoid Factor and Anti-cyclic Citrullinated Peptide Antibodies

All subjects will be tested for the presence of RF and anti-CCP antibodies at screening. Since these parameters are a potential indicator for rheumatoid arthritis, only subjects with a negative test result are eligible for participation in the study (refer to Section 5).

#### 8.2.14. Home Study Drug Administration Diary

The subject (or caregiver/designee) will complete a diary for every study dose taken outside of the study site (ie, at home). The study drug should be administered on the dates as directed by the site staff. Information regarding the study drug administration (eg, date and time of study drug administration, if the full dose was administered) will be recorded in the study drug administration diary. Instructions on proper study drug administration will be provided to the subject (caregiver/designee). Subjects will be instructed to call the study site if they are having problems administering the study drug or have missed or delayed administering a dose. Subjects will be instructed to bring the study drug administration diary to each study visit.

## 8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

Adverse events will be reported by the subject (or, when appropriate, by a care giver).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The investigator is responsible for following up all AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

#### 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until the 8-week follow-up visit at the timepoints specified in the SoA (Section 1.3).

All AEs will be collected from the first dose of study drug until the 4 weeks after the last dose of study drug as specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from investigator's knowledge of the event, as indicated in Section 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor pharmacovigilance team.

### 8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

### 8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.3.

### 8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor or designee will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor or designee policy and forwarded to investigators as necessary.

### 8.3.5. Pregnancy

- Details of all pregnancies after the start of study drug and until 8 weeks after the last dose of study drug in female subjects and, if indicated, female partners of male subjects will be collected.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of a pregnancy in a female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner, as applicable).

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 10.3.4)
- The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/pregnant female partner and the neonate, and the information will be forwarded to the sponsor or designee.
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor or designee as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study subjects/pregnant female partner, he/she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study drug.

### 8.3.6. Events of Special Interest

Based on the class effects or potential risks with IL-17 inhibitors, the following events of special interest (preferred term) will be monitored:

- Candida infection
- Inflammatory bowel disease.

In addition, based on the potential risk with an IL-17 receptor inhibitor the following events of special interest will also be monitored:

- suicidal ideation
- malignancies
- MACE (major adverse cardiovascular and cerebrovascular events : cerebrovascular accident and transient ischemic attack, non-fatal myocardial infarction or unstable angina, cardiovascular death)
- TB
- infections (serious, opportunistic, or fungal only)
- cytopenias
- systemic hypersensitivity reactions.

### 8.3.7. Overdose

These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt). Refer to Section 6.7.

*If an overdose occurs associated with an SAE in the course of the study, then the investigator follows the immediate safety reporting requirement for SAE with describing the overdose in an SAE description.*

## 8.4. Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of izokibep as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual by the sponsor or designee. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of izokibep. Each plasma sample will be divided into 2 aliquots (1 each for PK, and a backup). Samples collected for analyses of izokibep (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples.
- Study drug concentration information will not be reported to investigative sites.
- Pharmacokinetic samples will be shipped frozen from clinical sites to the central laboratory and later shipped from central laboratory to the PK laboratory for analysis. The PK plasma samples will be stored in a secure storage space with adequate measures to protect confidentiality.
- The PK plasma samples will be retained while research on izokibep or interventions of this class or PsA continues but no longer than 20 years or other period as per local requirements.

## 8.5. Genetics

Not applicable.

## 8.6. Biomarkers

Not applicable.

## 8.7. Immunogenicity Assessments

- Antibodies to izokibep will be evaluated in serum samples collected from all subjects according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from subjects who discontinued study drug or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual by the sponsor or designee.
- Samples testing positive for binding antibodies may be further characterized and may be tested for neutralizing antibodies.
- The detection and characterization of antibodies to izokibep will be performed using a validated assay method by or under the supervision of the sponsor.
- The immunogenicity serum samples will be retained while research on izokibep or interventions of this class or PsA continues but no longer than 20 years or another period as per local requirements.

## 8.8. Health Economics

Refer to Section 8.1.2.8.

# 9. Statistical Considerations

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

## 9.1. Statistical Hypotheses

The primary objective of this study is to demonstrate that izokibep (160 mg dosed QW or 160 mg dosed Q2W) is superior to placebo in the proportion of subjects achieving ACR50 at Week 16 of the study. The statistical null and alternative hypotheses to be used to assess the primary objective are:

$H_0$: $\pi_{ABY} - \pi_{PBO} = 0$

$H_A$: $\pi_{ABY} - \pi_{PBO} \neq 0$

Where $\pi_{ABY}$ and $\pi_{PBO}$ are the proportion of subjects achieving ACR50 at Week 16 among subjects randomly assigned to receive izokibep and placebo, respectively. One set of hypotheses will be tested for each dose frequency of izokibep 160 mg (QW and Q2W).

Analogous statistical hypotheses will be used for the secondary objective of assessing the proportion of subjects achieving PASI90 at Week 16 among subjects with ≥ 3% BSA psoriasis at baseline, the proportion of subjects achieving resolution of enthesitis at Week 16 among subjects that had enthesitis at baseline, achievement of MDA at Week 16, the proportion of subjects achieving ACR20 at Week 16 compared to baseline, the proportion of subjects achieving improvement in PsAID of at least 3 units at Week 16 compared to baseline in subjects with PsAID ≥ 3 at baseline.

The statistical null and alternative hypotheses to be used to assess the secondary objective of change in physical function of HAQ-DI from baseline to Week 16 are:

$H_0$: $\mu_{ABY} - \mu_{PBO} = 0$

$H_A$: $\mu_{ABY} - \mu_{PBO} \neq 0$

Where $\mu_{ABY}$ and $\mu_{PBO}$ are the mean change from baseline to Week 16 among subjects randomly assigned to receive izokibep and placebo, respectively. One set of hypotheses will be tested for each dose frequency of izokibep 160 mg (QW and Q2W).

### 9.1.1. Multiplicity Adjustment and Type I Error Rate

Hypotheses tested will be adjusted to control the familywise error rate in the strong sense at $\alpha = 0.05$, 2-sided.

The statistical comparisons for the primary efficacy endpoint and the secondary endpoints, all at Week 16, will be carried out in sequential order. The primary endpoint, comparing izokibep dosed QW to placebo, will be tested first, with significance concluded if $p < 0.05$.

Testing of secondary endpoints, comparing izokibep dosed QW to placebo, will only be carried out if all prior tests, including the tests of the primary endpoint, first show significance with $p < 0.05$. If all primary and secondary endpoints, comparing izokibep doses QW to placebo, are

significant, testing of izokibep doses Q2W to placebo will begin and follow the same order. As long as all prior tests are significant, testing will proceed in the following order:

- The primary endpoint, achieving ACR50 at Week 16, comparing izokibep dosed QW to placebo.
- The first secondary endpoint, achieve PASI90 at Week 16 in subjects with ≥ 3% BSA psoriasis at baseline, comparing izokibep dosed QW to placebo.
- The second secondary endpoint, achieving resolution of enthesitis at Week 16 in subjects that had enthesitis (LEI > 0) at baseline, comparing izokibep dosed QW to placebo.
- The third secondary endpoint, achieving MDA at Week 16, comparing izokibep dosed QW to placebo.
- The fourth secondary endpoint, achieving ACR20 at Week 16, comparing izokibep dosed QW to placebo.
- The fifth secondary endpoint, achieving improvement in PsAID of at least 3 units at Week 16 compared to baseline in subjects with PsAID ≥ 3 at baseline, comparing izokibep dosed QW to placebo.
- The sixth secondary endpoint, change in physical function of HAQ-DI from baseline to Week 16, comparing izokibep dosed QW to placebo.
- The primary endpoint, achieving ACR50 at Week 16, comparing izokibep dosed Q2W to placebo.
- The first secondary endpoint, achieve PASI90 at Week 16 in subjects with ≥ 3% BSA psoriasis at baseline, comparing izokibep dosed Q2W to placebo.
- The second secondary endpoint, achieving resolution of enthesitis at Week 16 in subjects that had enthesitis (LEI > 0) at baseline, comparing izokibep dosed Q2W to placebo.
- The third secondary endpoint, achieving MDA at Week 16, comparing izokibep dosed Q2W to placebo.
- The fourth secondary endpoint, achieving ACR20 at Week 16, comparing izokibep dosed Q2W to placebo.
- The fifth secondary endpoint, achieving improvement in PsAID of at least 3 units at Week 16 compared to baseline in subjects with PsAID ≥ 3 at baseline, comparing izokibep dosed Q2W to placebo.
- The sixth secondary endpoint, change in physical function of HAQ-DI from baseline to Week 16, comparing izokibep dosed Q2W to placebo.

## 9.2. Analysis Sets

Full Analysis Set

For assessing the primary and secondary efficacy objectives, all subjects randomized will be included in the analyses as the Full Analysis Set. Intercurrent events such as missed or discontinued treatment and protocol deviations will be addressed as described in the definition of the estimands in Section 9.3. Subjects will be included according to randomized treatment assignment.

Safety Analysis Set

For assessing the safety objectives, all subjects randomized who receive at least 1 administration of test material will be included in the summaries and analyses. In the event that a subject receives incorrect study drug, that subject will be grouped according to treatment received, and such subjects will be listed and counted in the final report.

PK Analysis Set

For assessing PK parameters, all subjects who receive at least 1 administration of test material and have at least 1 sample collected and analyzed for drug concentration will be included in summaries and analyses.

ADA Analysis Set

For assessing ADA, all subjects who receive at least 1 administration of test material and have both baseline ADA and at least 1 postdose ADA measurements will be included in summaries and analyses.

## 9.3. Statistical Analyses

### 9.3.1. General Considerations

All data collected will be summarized by planned timepoint without imputation. Continuous data will be summarized with count, mean, Q1, median, Q3, standard deviation, minimum, and maximum. Change from baseline will additionally include standard error. Categorical data will be summarized with count and percent. Time to event data will be summarized with product-limit estimators of median and quartiles.

All hypothesis tests will be reported with 2-sided *p*-values. Comparison of QW dosing to placebo will use only subjects assigned to receive izokibep 160 mg QW or placebo; comparison of Q2W dosing to placebo will use only subjects assigned to receive izokibep 160 mg Q2W or placebo; comparison of Q4W izokibep to placebo will use only subjects assigned to receive izokibep 80 mg Q4W or placebo. All confidence intervals will be 2-sided with nominal 95% coverage.

Data will be summarized by planned timepoint, using data collected at the visit. Study day will be calculated as postbaseline date minus randomization date, plus 1 (except that study day for pre-randomization dates will not include the plus 1). Day range windows will not be applied for summaries (but may be applied for protocol deviations). Baseline values will be the last value collected before randomization and change from baseline will be calculated as postbaseline value minus baseline value.

Stratified tests will use the strata of prior TNFi use (Yes/No) and enthesitis at baseline (LEI = 0 versus > 0) from the randomization process. If a subject is incorrectly classified into a stratum during the randomization process, the analysis will use the correct classification, not the classification used during randomization.

Primary and secondary endpoints will be tested using only three treatment groups: izokibep 160 mg Q2W, izokibep 160 mg QW and placebo. The treatment group receiving izokibep 80 mg Q4W will only be used for exploratory analyses and endpoints.

### 9.3.2. Primary Endpoint and Estimand

The primary endpoint is ACR50 response, as defined in Section 3. The primary analysis will occur when all subjects have had the opportunity to complete at Week 16 visit or discontinued the study.

The statistical comparisons for the primary efficacy endpoint and the secondary endpoints, all at Week 16, will be carried out in sequential order. The primary endpoint, comparing izokibep dosed QW to placebo, will be tested first, with significance concluded if $p < 0.05$. Testing of secondary endpoints, comparing izokibep dosed QW to placebo, will only be carried out if all prior tests, including the tests of the primary endpoint, first show significance with $p < 0.05$. If all primary and secondary endpoints, comparing izokibep doses QW to placebo, are significant, testing of izokibep doses Q2W to placebo will begin and follow the same order.

The primary efficacy analyses will use the treatment policy estimands, using all available data from all randomized subjects regardless of treatment discontinuation, concomitant medication, protocol deviations, or other actions. Subjects will be analyzed in the group to which they are randomized. Subjects who do not have an evaluation for a dichotomous endpoint at a given timepoint will be imputed as nonresponders.

The null hypothesis of equal response rates will compare each dosing regimen of izokibep to the placebo group. A stratified test of response rates will be used. Within each of the strata used for randomization, the response rate for each treatment group and corresponding standard error will be calculated. If a subject is incorrectly classified into a stratum during the randomization process, the analysis will use the correct classification, not the classification used during randomization. The difference in response rates (risk difference) will be calculated for each stratum. The common risk difference among the strata and associated standard error will be estimated by combining the observed risk differences using Cochran-Mantel-Haenszel weighting. The estimated risk difference divided by the standard error will be used as the test statistic and a *p*-value calculated assuming that the test statistic follows a standard normal distribution under the null hypothesis. Analyses at earlier timepoints when data to calculate the ACR50 are collected will also be presented using the same methodology. *P*-values from earlier timepoints will be presented for descriptive purposes, not part of the alpha-preserving multiple testing strategy.

A tipping point analysis will be performed in order to evaluate the robustness of the results of the primary analysis. This analysis will use simulations to assess the impact of different response rates in subjects with missing primary endpoint data, and how different the response rates must be to change the conclusions of the study. The tipping point analysis will impute mean response

rates in the two groups. Imputed response rates will be based on the response rates among subjects with observed primary endpoint data at Week 16. Sets of imputed mean response rates will include the observed response rates ($\hat{\pi}_{ABY}$, $\hat{\pi}_{PBO}$), and rates that differ in increments of ±0.02, adjusted independently in each arm. For each set of imputed mean response rates, 1000 simulations will be reported. Within each simulation, a random number mechanism will be used to assign each subject who is missing the primary endpoint at Week 16 to either response or non-response. The primary stratified analysis will be reported on each simulation, and the probability that the null hypothesis of equal response rates is rejected will be reported for each set of imputed response rates. A graphical output will summarize the rejection probability for various sets of response rates. The same tipping point analysis will be performed with another dose regimen of izokibep group, ie, izokibep Q2W compared to the placebo group.

Other sensitivity and supplementary analyses will be used to assess the impact of missing data assumptions and other intercurrent events. These will be defined before the database is unblinded.

### 9.3.3. Secondary Endpoints and Estimands

The secondary endpoints will be tested analogously. Testing of secondary endpoints, comparing izokibep dosed QW to placebo, will only be carried out if all prior tests, including the tests of the primary endpoint, first show significance with $p < 0.05$. If all primary and secondary endpoints, comparing izokibep doses QW to placebo, are significant, testing of izokibep doses Q2W to placebo will begin and follow the same order. As long as all prior tests showed statistically significant differences compared to placebo, testing will proceed using $\alpha = 0.05$. If any comparison (primary or secondary) results in $p > 0.05$, $p$-values for subsequent comparisons will be reported but not considered conclusive.

The treatment policy strategy similar to the primary endpoint will be used to construct estimands for each secondary endpoint. Subjects will be included in the analysis regarding treatment discontinuation, concomitant medication, protocol deviations, or other actions.

For the secondary endpoint of achieving PASI90 at Week 16, the analysis only includes subjects with ≥ 3% BSA psoriasis at baseline. For the secondary endpoint of achieving resolution of enthesitis at Week 16, the analysis only includes subjects that had enthesitis at baseline. For the secondary endpoint of achieving an improvement in PsAID of at least 3 units at Week 16 compared to baseline, the analysis only includes subjects with PsAID ≥ 3 at baseline.

The following secondary endpoints will be analyzed as dichotomous endpoints and analogously to the primary endpoint:

- proportion of subjects achieving PASI90 at Week 16 in subjects with ≥ 3% BSA psoriasis at baseline
- proportion of subjects achieving resolution of enthesitis at Week 16 in subjects that had enthesitis (LEI > 0) at baseline
- proportion of subjects achieving MDA
- proportion of subjects achieving ACR20

- proportion of subjects achieving improvement in PsAID of at least 3 units at Week 16 compared to baseline in subjects with PsAID ≥ 3 at baseline

Subjects who have missing data at Week 16 will be imputed as nonresponders and included in the analysis.

The secondary endpoint of change in physical function of HAQ-DI from baseline to Week 16 will be analyzed as a continuous variable. The treatment policy strategy will be used to construct estimands for change in physical function of HAQ-DI from baseline to Week 16. Subjects will be included in the analysis regarding treatment discontinuation, concomitant medication, protocol deviations, or other actions. A mixed-effects model with repeated measures will be used for change in physical function of HAQ-DI. The model will use available data of change in physical function of HAQ-DI from baseline at all scheduled postbaseline assessments. The model includes the baseline physical function of HAQ-DI, treatment group, and stratification variables as covariates. If a subject is incorrectly classified into a stratum during the randomization process, the analysis will use the correct classification, not the classification used during randomization.

Sensitivity analyses will use analysis of covariance on change in physical function of HAQ-DI from baseline to Week 16, with stratification variables used for randomization also included as covariates, along with baseline physical function of HAQ-DI.

Sensitivity analysis for physical function of HAQ-DI will also use multiple imputations. Physical function of HAQ-DI missing as Week 16 will be replaced with the imputed value from the imputation dataset. The imputation dataset will be created from the placebo subjects who have complete data.

### 9.3.4. Exploratory Endpoints

Exploratory endpoints will be analyzed analogously to primary and secondary endpoints, with the exception of a prespecified alpha-controlling testing strategy. Exploratory endpoints of dichotomous measurements will be analyzed analogously to primary endpoints. Exploratory endpoints of continuous measurements will be analyzed analogously to the secondary endpoint of change in physical function of HAQ-DI from baseline to Week 16. *P*-values for exploratory endpoints will be considered descriptive and not considered conclusive.

All primary, secondary and exploratory endpoints defined for comparing izokibep 160 mg QW or izokibep 160 mg Q2W to placebo will also be reported for comparing izokibep 80 mg Q4W to placebo.

Dose-response will be investigated through analyses of the primary and secondary endpoints, which will use all four treatment arms (izokibep 160 mg QW, izokibep 160 mg Q2W, izokibep 80 mg Q4W and placebo) in a single analysis for each endpoint. A p-value for the global test of the hypothesis that all groups have identical response rates will be reported for each endpoint, not subject to type I error rate control or any multiple comparison procedure. P-values will also be reported for all pairwise comparisons for each endpoint. Dose-response relationships will be assessed qualitatively from these analyses.

Pharmacokinetic concentration data will be summarized by dose group at all planned collection times with mean, geometric mean, minimum, and maximum. Pharmacokinetic parameters will be determined where possible from the plasma concentrations of izokibep. Pharmacokinetic data collected from this study may be combined with PK data collected from other studies for a comprehensive modeling of drug concentrations.

### 9.3.5. Safety Analyses

Safety data will include summaries of exposure, AEs, TEAEs, SAEs, and laboratory data. No inferential statistics (*p*-values) will be reported for safety data.

Exposure will include the number of doses administered (including complete and incomplete doses) and reasons for missed or incomplete doses. Exposure will be reported through the planned collection of the primary endpoint and for the entire study. For subjects assigned to receive placebo who later receive izokibep, exposure will further be summarized by placebo and izokibep. Compliance will be summarized by placebo and izokibep and by phase (placebo controlled and after crossing over to active).

Adverse events and SAEs reported before the first administration of the study drug will be listed. All summaries will include only treatment-emergent events. The number of subjects who report 1 or more AEs, the number who report 1 or more severe AEs, the number who report 1 or more SAEs, and the number who report 1 or more AEs that lead to discontinuation of study drug will be summarized by treatment group during the primary phase of the study and overall. Subjects assigned to receive placebo who later receive izokibep will additionally be summarized by phase (placebo-controlled and after crossing over to active).

Laboratory data including ADAs will be summarized by treatment group and overall, at each planned collection timepoint.

## 9.4. Interim Analysis and Early Stopping Rules

No interim analyses will be conducted for the purpose of stopping the study or altering the study design.

The DMC will review unblinded efficacy data when approximately 120 subjects have had the opportunity to complete the Week 12 visit. Data from the first 105 subjects randomly assigned to receive izokibep 160 mg QW, izokibep 160 mg Q2W or placebo will be used for these DMC summaries. The DMC may make a recommendation on further development activities for izokibep based on this data review. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The study team operationalizing the day-to-day of the study, the subjects, and the investigators will remain blinded to these interim results until after the study is completed.

The primary analysis of primary and secondary endpoints will occur after all subjects have had an opportunity to complete the Week 16 assessments (have completed the Week 16 assessments, or have completed a subsequent timepoint assessment, or permanently discontinued the study before Week 16). For the primary and secondary objectives, this will include all data for all subjects for the final analysis, and so it will be the final analysis. The final analysis will be conducted at the end of the study when all subjects have completed the study or permanently

discontinued the study. For the primary endpoint, all available data at visits after Week 16 will be included in the summaries at these timepoints, but some subjects will be ongoing and may have data collected after the primary analysis is reported. Data collected at subsequent timepoints may be summarized when all data at that timepoint have been collected. All data collected for the primary endpoint for all subjects through the end of the study will be reported in a subsequent analysis, but the *p*-values from each comparison of a regimen of izokibep to placebo in this subsequent analysis will not be used for any alpha-preserving hypothesis testing. Investigators, site personnel, and all sponsor personnel who have contact with subjects will remain blinded to individual subject treatment assignments until the final analysis.

When the primary efficacy analysis is conducted, safety data will be summarized. Summaries will include all safety data through Week 16 and all available safety data on all subjects through the end of the study. All safety data will be summarized through the end of the study when all subjects have completed all visits.

At various timepoints after the primary analysis is reported, data may be summarized for regulatory submissions, to plan additional studies, or for other corporate needs.

## 9.5. Sample Size Determination

Response rates for ACR50 are expected to be 20% for placebo and 45% for a dose regimen of 160 mg izokibep (QW or Q2W or both). With 100 subjects receiving placebo and 100 subjects receiving a dose regimen of 160 mg izokibep, there will be 97% power to show a difference in the primary endpoint of ACR50 response rate. If a 45% response rate is observed with a dose regimen of izokibep, the 2-sided 95% confidence interval for the true response rate will have a half-width of approximately 10 percentage points.

Up to 60% of subjects are expected to have enthesitis at baseline, based on the LEI. Response rates, proportion of subjects who have LEI = 0 at Week 16, are expected to be 25% for placebo and 60% for subjects receiving izokibep, with on treatment groups combined. With 50 subjects with enthesitis at baseline receiving placebo and 50 subjects receiving a dose regimen of izokibep, there will be 95% power to show a difference in the secondary endpoint of resolution of enthesitis. A lower rate of enthesitis at baseline will result in a lower power, but power will be at least 80% with the same assumptions on response rate, if 30 subjects with enthesitis at baseline receive placebo and 30 subjects receive a dose regimen of izokibep.

With 25 subjects receiving izokibep 80 mg Q4W, the 2-sided 95% confidence interval for the true response rate will have a half-width of up to approximately 20 percentage points.

# 10. Supporting Documentation and Operational Considerations

## 10.1. Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - applicable International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- Approval for protocols and any substantial amendments to the protocol that requires health authority approval prior to initiation will be obtained except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable) and all other applicable local regulations.

### 10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor or designee with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

- The investigator or his/her representative will explain, in a language and at a level of complexity understandable by the subject, the nature of the study, including the risks and benefits, to the subject and answer all questions regarding the study and its alternatives.
- Subjects must be informed that their participation is voluntary, and they may withdraw their consent to participate in the study at any time. Subjects will be required to sign and date a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF.
- If the Informed Consent form is amended during the study, subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

### 10.1.4. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that the subject's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that the subject's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members and by inspectors from regulatory authorities.
- The sponsor and investigator will implement appropriate measures to monitor and identify any breach of security leading to accidental or unlawful destruction, loss, alteration, unauthorized disclosure, or access to that data. In the event of a personal data breach, the sponsor and investigator will take appropriate measures to address the breach, including measures to mitigate its adverse effects. The investigator will notify the sponsor without undue delay after having become aware of the breach. Such notification will contain the details of a contact point where more information can be obtained, a description of the nature of the breach (including, where possible, categories and approximate number of data subjects and personal data records concerned), its likely consequences and the measures taken or proposed to address the breach including, where

appropriate, measures to mitigate its possible adverse effects. Upon becoming aware of any data breach, the sponsor will notify all competent data protection authorities of the breach, where required by local regulations. Where feasible and permissible by applicable law, such notification will occur within 72 hours of becoming aware of the breach. Such notification will contain the details of a contact point where more information can be obtained, a description of the nature of the breach (including, where possible, categories and approximate number of data subjects and personal data records concerned), its likely consequences and the measures taken or proposed to address the breach including, where appropriate, measures to mitigate its possible adverse effects.

- Taking into account the nature, scope, context, and purpose of the processing, and the risks for the rights and freedoms of natural persons, the investigator will implement technical and organizational measures to ensure adequate security and confidentiality of the data. Such measures will include without limitation pseudonymization and data encryption in transit and at rest, identity and access management procedures to restrict physical and logical access to the data, network perimeter and endpoint protection using firewalls and other intrusion detection systems, documented policies taking account of the state of the art, and regular training of all personnel responsible for the processing of personal data.

### 10.1.5. Dissemination of Clinical Study Data

The results of the study will be reported in a clinical study report generated by the sponsor and will contain eCRF data from all study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with the performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator see Section 10.1.9) shall be the property of the sponsor as author and owner of copyright in such work.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law including posting company-sponsored study information on the US National Institutes of Health website www.clinicaltrials.gov.

### 10.1.6. Monitoring and Data Quality Assurance

- Qualified, assigned monitors from the sponsor (or designee) will conduct regular on-site and remote monitoring visits to monitor various aspects of the study. These visits and communications, along with regular inspection of the eCRFs, will be conducted to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of data against source documents, and occurrence of AEs, etc. The investigator must provide the monitor with full access to all source and study documents.

- All subject data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.
- Guidance on completion of eCRFs will be provided.
- The investigator or site staff will promptly report to the sponsor (or designee) all deviations that occur at their clinical site, and report protocol deviations to their IRB/EC according to local requirements
- Sponsor (or designee) may audit investigator sites regarding, but not limited to, the informed consent process, presence of required documents, adherence to protocol, accountability and storage of drug supplies, comparison between eCRF with source documents, etc. All medical records and study-related documents must be available for audit, and the investigator and study staff agree to participate and cooperate in audits conducted in a reasonable manner.
- Government regulatory authorities and ethics committees may also inspect the investigator site during or after the study. The investigator or designee should contact the sponsor (or its designee) immediately if this occurs. The investigator must cooperate fully with regulatory authorities or other audits conducted in a reasonable manner.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however if required by the applicable regulatory requirements or by an agreement with the sponsor.
- No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- Quality tolerance limits will be defined before the start of the study and monitored by the CRO and sponsor during the course of the study. They will also be reported in the clinical study report.

### 10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress

notes), computer printouts, screening logs, and recorded data from automated instruments. Information from medical records and other source documents will be promptly transcribed to the appropriate section of the eCRF. The eCRF is not considered and should not be used as source documentation.

- Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

### 10.1.8. Study and Site Start and Closure

**Study Start**

The study start date is the date on which the first subject is enrolled into the study.

**Study/Site Termination**

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Total number of subjects included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

### 10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. The clinical study agreement/site contract will cover additional details regarding publications.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 10.2. Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- All study-required laboratory tests will be performed by a central laboratory, with the exception of:
    - urine pregnancy test
- Investigators must document their review of each laboratory safety report.

**Table 6. Protocol-required Safety Laboratory Tests**

| Laboratory Tests | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet count<br>Red blood cell (RBC) count<br>Hemoglobin<br>Hematocrit | RBC indices:<br>Mean corpuscular volume<br>Mean corpuscular hemoglobin<br>%Reticulocytes | White blood cell count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical chemistry[1,2] | A1C | Alanine aminotransferase/serum glutamic-pyruvic transaminase | Alkaline phosphatase[3] | Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase |
| | Blood urea nitrogen | Calcium | C-reactive protein[4] | Creatinine |
| | Glucose (nonfasting) | High-density-lipoprotein (HDL) | International normalized ratio* | Potassium |
| | Sodium | Total and direct bilirubin | Total cholesterol | Total protein |
| Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, by dipstick<br>• Microscopic examination (if blood or protein is abnormal) | | | |
| Pregnancy testing | • Highly sensitive serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) at screening[5] | | | |
| Other screening tests | • Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only)<br>• Hepatitis B virus testing: hepatitis B surface antigen, hepatitis B surface antibodies, hepatitis B core antibodies, hepatitis B virus DNA as outlined in Section 8.2.10)<br>• Hepatitis C virus antibody<br>• Human immunodeficiency virus testing<br>• Tuberculosis testing: QuantiFERON test<br>  • Note: T-SPOT tuberculosis test may be acceptable if agreed upon with the medical monitor<br>• Rheumatoid factor/anti-cyclic citrullinated peptide<br>• Fecal calprotectin (as needed, per section 8.2.11) | | | |
| Other tests | • Pharmacokinetics<br>• Anti-drug antibody | | | |

| Laboratory Tests | Parameters |
|---|---|

NOTES:
* INR will only be measured if ALT or AST ≥ 3 x ULN as detailed in Section 7.1.1. A separate blood sample for INR testing will be included in the Liver Event Monitoring Kit at the time of repeat testing for ALT or AST, as detailed in Section 7.1.1.
[1] Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver Chemistry Stopping Criteria and Section 10.5 Liver Safety: Suggested Actions and Follow-up Assessments and Study drug/Rechallenge Guidelines.
[2] Estimated glomerular filtration rate will be calculated at screening using the modification of diet in renal disease study equation.
[3] If alkaline phosphatase is elevated, consider fractionating.
[4] Postbaseline C-reactive protein results will be blinded to sites/investigators.
[5] After screening, local urine pregnancy testing will be performed unless serum testing is required by local regulation, regulatory agency, or Institutional Review Board/Independent Ethics Committee.

## 10.3. Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1. Definition of Adverse Events

**AE Definition**

- An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

**Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE

unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae

- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE

**Events NOT Meeting the AE Definition**

- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the first dose of study drug that do not worsen; such events should be recorded in the medical history eCRF
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition
- The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

### 10.3.2. Definition of SAE

**An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:**

**a. Results in death**

**b. Is life threatening**

The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or

outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

### 10.3.3. Recording and Follow-up of Adverse Event and/or Serious Adverse Event

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the required eCRF/SAE form.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the required eCRF/SAE form.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all subject identifiers, with the exception of the

subject number, will be redacted on the copies of the medical records before submission.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Severity**

The investigator is responsible for assessing the severity for each AE and SAE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0):

- **Mild**: **(Grade 1)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)**: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Severe (Grade 3)**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Life-threatening (Grade 4)**: Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)**: Events that result in death.

Many common AEs are able to be graded according to CTCAE. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in CTCAE version 5.0 as stated above. Additional considerations when assessing severity are outlined below:

- The seriousness of an AE should not be confused with its severity. Severity is a measure of intensity (eg, Grades 1 through 5 or mild, moderate, severe, etc.), whereas seriousness is based on subject/event outcome as defined by the criteria in Section 10.3.2.
- It is important to distinguish between category (AE versus SAE) and intensity (Grades 1 to 5) of AEs. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.
- An AE of severe intensity is not necessarily considered serious. For example, nausea that persists for several hours may be considered grade 3 nausea, but not an SAE. On the other hand, minor cardiac chest pain that results in hospitalization may be considered Grade 1 but would be a SAE.

**Assessment of Causality**

The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The investigator will use clinical judgment in the assessment of causality according to the following categories:

- **Not Related**: A causal relationship can be definitively excluded, and another documented cause of the AE is most plausible.
- **Related**: A causal relationship is clinically/biologically plausible and there exists a plausible time sequence between onset of the AE and administration of the study drug.

Additional factors in the assessment of causality include the following:

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

| **Follow-up of AEs and SAEs** |
|---|
| • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.<br>• If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.<br>• New or updated information will be recorded in the originally submitted documents.<br>• The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information. |

### 10.3.4. Reporting of SAEs

| **SAE Reporting to Sponsor/Designee via the SAE Report Form** |
|---|
| • The primary mechanism for reporting an SAE to the sponsor/designee will be the SAE Report Form.<br>• All SAEs will be reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from investigator's knowledge of the event.<br>• Email transmission of the SAE Report Form is the preferred method to transmit this information to the sponsor/designee. In the rare circumstance email is not available, the SAE Report Form may be sent by facsimile as a back-up reporting method.<br>• Investigator signature is required to be collected on the SAE Report Form prior to submission. With rare exception, the form may be sent without signature in order to meet the reporting deadline, however investigator signature is required to be obtained as soon as possible after submission.<br>• Contacts for SAE reporting can be found on the SAE Report Form. |
| **SAE Reporting to the Sponsor via Backup SAE Report Form** |
| • E-mail transmission of the backup paper SAE Report Form is the backup method to transmit SAE information to the sponsor if the EDC system is unavailable or the reporting pathway via EDC is not yet active.<br>• Backup SAE Report forms should be sent to the contact information provided in the SAE Completion Guideline.<br>• The site will enter the SAE data into EDC system as soon as it becomes available. Refer to separate SAE Completion Guideline for additional information about submitting SAE information. |

- Investigator signature is required to be collected on the SAE Report Form prior to submission. With rare exception, the form may be sent without signature in order to meet the reporting deadline, however the investigator signature is required to be obtained as soon as possible after submission (refer to SAE Completion Guideline).

## 10.4. Contraceptive and Barrier Guidance

### 10.4.1. Definitions

**Woman of Childbearing Potential**

Women in the following categories are considered WOCBP (fertile):

- Following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 follicle-stimulating hormone measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

**Note:** Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

### 10.4.2. Contraception Guidance

| **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:** |
|---|
| **Highly Effective Methods[b] that have Low User Dependency** *Failure rate of < 1% per year when used consistently and correctly.* |
| • Implantable progestogen-only hormone contraception associated with inhibition of ovulation |
| • Intrauterine device |
| • Intrauterine hormone-releasing system |
| • Bilateral tubal occlusion |
| • Azoospermic partner (vasectomized or due to a medical cause)<br>*Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*<br>Note: Documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview. |
| **Highly Effective Methods[b] that are User Dependent** *Failure rate of < 1% per year when used consistently and correctly.* |
| Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<br>• oral<br>• intravaginal<br>• transdermal<br>• injectable. |
| Progestogen-only hormone contraception associated with inhibition of ovulation<br>• oral<br>• injectable. |
| Sexual abstinence<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.* |
| **Effective Methods[c] that are Not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.* |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action |
| • Male or female condom with or without spermicide |
| • Cervical cap, diaphragm, or sponge with spermicide |
| • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods) |
| a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. |

b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) Considered effective, but not highly effective failure rate of ≥ 1% per year.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

## 10.5. Liver Safety: Actions and Follow-up Assessments and Study drug Restart/Rechallenge Guidelines

Phase 2 liver chemistry stopping criteria are designed to assure subject safety and to evaluate liver event etiology. The guidelines provided below are based on the EASL Clinical Practice Guidelines: Drug Induced Liver Injury (2019) and Food and Drug Administration 2009 Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation.

**Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments**

| **Liver Chemistry Stopping Criteria** | |
|---|---|
| **ALT or AST-absolute** | ALT or AST ≥ 5 × ULN |
| **ALT or AST Increase** | ALT or AST ≥ 3 × ULN persists for ≥ 4 weeks |
| **Bilirubin[1,2]** | ALT or AST ≥ 3 × ULN **and** total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) |
| **International Normalized Ratio (INR)[2]** | ALT or AST ≥ 3 × ULN **and** INR > 1.5 |
| **Cannot Monitor** | ALT or AST ≥ 3 × ULN and cannot be monitored twice weekly for 4 weeks |
| **Symptomatic[3]** | ALT or AST ≥ 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity |
| | |
| **Suggested Actions, Monitoring, and Follow-up Assessments** | |
| **Actions** | **Follow-up Assessments** |
| • **Immediately** discontinue study drug.<br>• Report the event to the sponsor/designee **within 24 hours**.<br>• Complete a serious adverse event (SAE) eCRF if the event met the criteria for an SAE.[2]<br>• Perform follow-up assessments as described in the Follow-up Assessment column.<br>• Monitor the subject until liver chemistry test abnormalities resolve, stabilize, or return to baseline. | • Viral hepatitis serology.<br>• Obtain blood samples for pharmacokinetic (PK) analysis after the most recent dose.[4]<br>• Obtain serum creatine phosphokinase, lactate dehydrogenase, gamma glutamyl transferase, glutamate dehydrogenase, and serum albumin.<br>• Fractionate bilirubin if total bilirubin ≥2 × ULN. |

| | |
|---|---|
| **MONITORING:**<br>**<u>If ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5:</u>**<br>• Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 hours**.<br>• Monitor subject twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline.<br>• A hepatology consultation is recommended.<br>**<u>If ALT or AST ≥ 3 × ULN AND total bilirubin < 2 × ULN and INR ≤ 1.5:</u>**<br>• Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours**.<br>• Monitor subjects twice weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline, or the study drug has been discontinued; then decrease monitoring to once weekly or less.<br>• **Do not restart/rechallenge** subject with study drug unless allowed per-protocol and sponsor approval is granted. | • Obtain complete blood count with differential to assess eosinophilia.<br>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the eCRF.<br>• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF.<br>• Record alcohol use on the liver event alcohol intake form.<br>If ALT or AST ≥3 × ULN AND total bilirubin ≥2 × ULN or INR > 1.5 obtain the following in addition to the assessments listed above:<br>• Antinuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins.<br>• Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week.<br>• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.<br>• Liver biopsy may be considered and discussed with local specialist if available, for instance:<br>o In subjects when serology raises the possibility of autoimmune hepatitis. |

| | |
|---|---|
| | ○ In subjects when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study drug.<br>○ In subjects with acute or chronic atypical presentation.<br>• If liver biopsy conducted provides biopsy information. |

Abbreviation: ALT = alanine transaminase; AST = aspartate transaminase; eCRF = electronic case report form; ULN = upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT or AST ≥ 3 × ULN **and** total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE.** The INR stated threshold value will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study drug prior to the blood sample draw on the eCRF. If the date/time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Laboratory Manual.

## 10.6. Abbreviations and Definitions

| Abbreviation | Definition |
|---|---|
| ACR | American College of Rheumatology |
| ACR20 | American College of Rheumatology 20% |
| ACR50 | American College of Rheumatology 50% |
| ACR70 | American College of Rheumatology 70% |
| ADA | anti-drug antibody |
| AE | adverse event |
| anti-CCP | anti-cyclic citrullinated peptide |
| AUC | area under the concentration-time curve |
| $AUC_{0-\tau}$ | area under the concentration-time curve over the dose interval |
| $AUC_{0-\infty}$ | area under the concentration-time curve extrapolated to infinity |
| BSA | body surface area |
| CASPAR | ClASsification of Psoriatic Arthritis criteria |
| cDAPSA | clinical Disease Activity in Psoriatic Arthritis |
| CFR | Code of Federal Regulations |
| $C_{max}$ | maximum observed plasma concentration |
| COVID-19 | coronavirus disease of 2019 |
| CRO | contract research organization |
| CRP | C-reactive protein |
| CV% | coefficient of variation |
| csDMARD | conventional-synthetic disease-modifying anti-rheumatic drugs |
| DAPSA | Disease Activity in Psoriatic Arthritis |
| DAS28 | Disease Activity Score in 28 joints |
| DMARD | disease-modifying antirheumatic drug |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| EDC | electronic data capture |
| FACIT-F | Functional Assessment of Chronic Illness Therapy – Fatigue |
| eCRF | electronic case report form |
| GCP | Good Clinical Practice |
| HADS | Hospital Anxiety and Depression scale |

| Abbreviation | Definition |
|---|---|
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HRT | hormonal replacement therapy |
| IA | intra-articular |
| IBD | inflammatory bowel disease |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | independent ethics committee |
| IL | interleukin |
| IM | intramuscular |
| IRB | institutional review board |
| IV | intravenous(ly) |
| IXRS | Interactive Response Technology |
| JAK | janus kinase |
| LEI | Leeds Enthesitis Index |
| MCS | Mental Component Summary |
| MDA | minimal disease activity |
| mNAPSI | modified Nail Psoriasis Severity Index |
| mTSS | modified total Sharp score |
| NOAEL | no observed adverse effect level |
| NRS | numeric rating scale |
| NSAID | nonsteroidal anti-inflammatory drug |
| PASDAS | Psoriatic Disease Activity Score |
| PASI | Psoriasis Area and Severity Index |
| PASI90 | Psoriasis Area and Severity Index response of 90% |
| PCR | polymerase chain reaction |
| PCS | Physical Component Summary |

| Abbreviation | Definition |
|---|---|
| PK | pharmacokinetic(s) |
| PsA | psoriatic arthritis |
| PsAID | Psoriatic Arthritis Impact of Disease |
| PsO | Psoriasis |
| QW | every week |
| Q2W | every 2 weeks |
| Q4W | every 4 weeks |
| RF | rheumatoid factor |
| SAE | serious adverse event |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus |
| SC | subcutaneous(ly) |
| SF-36 | Short Form-36v2 Health Survey |
| SoA | Schedule of Activities |
| SPARCC | Spondyloarthritis Research Consortium of Canada |
| $t_{½}$ | half-life |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| Th | T-helper |
| $t_{max}$ | time to maximum observed concentration |
| TNF | tumor necrosis factor-alpha |
| TNFi | tumor necrosis factor-alpha inhibitor(s) |
| US | United States |
| VAS | visual analogue scale |
| VLDA | very low disease activity |
| WOCBP | women of childbearing potential |
| WPI | Widespread Pain Index |

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