Clinical Study Protocol (Protocol Number: XYZ-101-RA-02)

Title: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of XYZ-101 in Adult Patients with Moderate-to-Severe Active Rheumatoid Arthritis with Inadequate Response to Methotrexate

1. Study Rationale

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by synovial hypertrophy, pannus formation, and progressive, irreversible bone and cartilage destruction. While the introduction of tumor necrosis factor (TNF) inhibitors and janus kinase (JAK) inhibitors has significantly advanced RA management, up to 40% of patients experience primary or secondary treatment failure, leaving a major unmet medical need for alternative mechanisms of action.

XYZ-101 is a fully humanized IgG1 monoclonal antibody designed with high affinity to bind the p19 subunit of interleukin-23 (IL-23), thereby selectively inhibiting the IL-23/Th17 inflammatory pathway. Downstream signaling of this pathway drives the differentiation of pathogenic Th17 cells, which secrete pro-inflammatory cytokines such as IL-17A, IL-17F, and TNF-alpha. These cytokines recruit neutrophils and activate synovial fibroblasts and osteoclasts. By neutralizing IL-23, XYZ-101 targets a distinct upstream nodal point, aiming to break the chronic inflammatory cycle and halt structural joint damage in patients who have failed conventional therapies.

2. Study Objectives and Hypotheses

2.1 Primary Objective & Hypothesis

- **Objective:** To evaluate the clinical efficacy of XYZ-101 compared to placebo in reducing disease activity in patients with moderate-to-severe active RA, as quantified by the change from baseline in the Disease Activity Score 28-joint count using C-reactive protein (DAS28-CRP) at Week 12.
- **Hypothesis:** Treatment with XYZ-101 will result in a statistically significant greater reduction in the DAS28-CRP score at Week 12 compared to treatment with placebo.

2.2 Secondary Objectives

- **Clinical Response:** To assess the superiority of XYZ-101 over placebo in achieving American College of Rheumatology 20%, 50%, and 70% (ACR20/50/70) response rates at Weeks 4, 8, and 12.
- **Safety & Tolerability:** To evaluate the safety profile, systemic tolerability, and laboratory safety of repeated subcutaneous doses of XYZ-101 over a 12-week period.
- **Patient-Reported Outcomes (PROs):** To evaluate the impact of XYZ-101 on physical function, pain, and health-related quality of life.
- **Pharmacokinetics & Immunogenicity:** To characterize the steady-state trough concentrations of XYZ-101 and assess the incidence of anti-drug antibodies (ADAs).

3. Study Design and Investigational Plan

3.1 Overall Design

This is a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study will consist of three distinct periods:

1. **Screening Period:** Up to 28 days to determine protocol eligibility.
2. **Double-Blind Treatment Period:** 12 weeks of active intervention or placebo.
3. **Safety Follow-Up Period:** 12 weeks following the final dose of the investigational product (IP) to evaluate prolonged safety and washout kinetics.

SCREENING: Up to 28 Days	
Randomization 2:1	
XYZ-101 Group	Placebo Group
N = 120	N = 60
Subcutaneous Injection	Subcutaneous Injection
Weeks 0, 4, 8	Weeks 0, 4, 8
WEEK 12: Primary Endpoint	

FOLLOW-UP: Safety Focus to Week 20

3.2 Randomization and Blinding

Approximately 180 eligible participants will be randomized in a 2:1 ratio via an Interactive Response Technology (IRT) system to receive either:

- **XYZ-101:** 150 mg administered via subcutaneous (SC) injection at Weeks 0, 4, and 8 (N = 120).
- **Placebo:** Matching volume-controlled sterile saline placebo SC injection at Weeks 0, 4, and 8 (N = 60).

Randomization will be stratified by geographic region and prior biologic use (biologic-naive vs. biologic-experienced). Participants, investigators, site staff, and the sponsor will remain strictly blinded to treatment assignments. Placebo syringes will be identical in appearance, packaging, and viscosity to the active XYZ-101 formulation.

3.3 Patient Population: Key Selection Criteria

Key Inclusion Criteria

1. Age 18 to 75 years at the time of screening.
2. Diagnosed with adult-onset Rheumatoid Arthritis ≥6 months prior to screening, fulfilling the 2010 ACR/EULAR classification criteria.
3. Moderate-to-severe active disease at screening, defined as meeting *all* the following:
    - ≥6 swollen joints (based on 66-joint count) and ≥6 tender joints (based on 68-joint count).
    - DAS28-CRP score ≥3.2.
    - Serum high-sensitivity CRP >5.0 mg/L.
4. Must be receiving a stable dose of Methotrexate (MTX; 15–25 mg/week, or 7.5–15 mg/week if documented intolerance) for ≥12 weeks prior to baseline, accompanied by a stable daily dose of folic acid.

Key Exclusion Criteria

1. Diagnosis of other autoimmune inflammatory arthritides (e.g., psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus).
2. Prior exposure to any biologic therapy targeting the IL-12, IL-23, or IL-17 pathways.
3. History of relevant systemic or localized infection, including:
    - Active or latent Tuberculosis (TB) infection (confirmed by positive IGRA or QuantiFERON test at screening, without completed prophylactic treatment).
    - History of human immunodeficiency virus (HIV), active Hepatitis B, or active Hepatitis C.
4. Absolute Neutrophil Count (ANC) <1,500/cells/μL; Hemoglobin <8.5 g/dL; or Hepatic transaminases (AST/ALT) >2.0x the Upper Limit of Normal (ULN).

4. Study Endpoints

4.1 Primary Endpoint

- The mean change from baseline to Week 12 in the continuous **DAS28-CRP** score.

Note on DAS28-CRP Calculation: The index is calculated dynamically utilizing a validated formula incorporating the 28 tender joint count (TJC28), 28 swollen joint count (SJC28), the Patient Global Assessment of Disease Activity (PtGA) measured on a 100mm Visual Analog Scale (VAS), and the serum CRP value in mg/L.

4.2 Secondary Endpoints

- **Proportion of Responders:** Percentage of participants achieving an **ACR20 response at Week 12** (defined as a minimum 20% improvement in both tender and swollen joint counts, and a 20% improvement in at least 3 of 5 core metrics: PtGA, Physician Global Assessment, Patient Pain VAS, HAQ-DI, and acute phase reactant).
- Percentage of participants achieving **ACR50 and ACR70** responses at Weeks 4, 8, and 12.
- **Functional Status:** Mean change from baseline in the **Health Assessment Questionnaire-Disability Index (HAQ-DI)** score at Week 12.
- **Remission Rates:** Proportion of patients achieving clinical remission (defined as DAS28-CRP less than 2.6) at Week 12.

5. Safety, Tolerability, and Vigilance Considerations

5.1 Adverse Events Tracking

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be continuously monitored, recorded, and categorized from the signing of the Informed Consent Form (ICF) through the final safety visit at Week 20. AEs will be coded utilizing the Medical Dictionary for Regulatory Activities (MedDRA) and graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

5.2 Laboratory and Clinical Assessments

Safety assessments will be rigorously executed at every protocol-specified clinic visit (Weeks 0, 2, 4, 8, 12, and 20):

- **Hematology & Serum Chemistry:** Full metabolic panels, complete blood counts with differentials, and liver function profiles. Special attention will be paid to absolute neutrophil and lymphocyte counts due to the pathway's role in host defense.
- **Vital Signs & Physical Exams:** Automated blood pressure, heart rate, respiratory rate, and body temperature recorded prior to and 60 minutes post-injection.
- **Immunogenicity Testing:** Serum samples collected at Weeks 0, 4, 12, and 20 will evaluate the presence of anti-drug antibodies (ADAs). If positive, neutralizing antibody (nAb) titers will be assayed using a validated cell-based bioassay.

5.3 Stopping and Discontinuation Rules

An individual participant must permanently discontinue the investigational product if any of the following criteria are met:

- Any serious infection requiring intravenous (IV) anti-microbial therapy or hospitalization.
- Confirmed absolute neutrophil count (ANC) falling to less than 1,000 cells/µL.
- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) levels exceeding 5.0x ULN, or exceeding 3.0x ULN concurrent with total bilirubin exceeding 2.0x ULN.
- Development of a severe hypersensitivity or anaphylactic reaction immediately following drug administration.

6. Statistical Considerations

6.1 Sample Size Justification

A total sample size of 180 participants (120 in the XYZ-101 group; 60 in the Placebo group) provides approximately 90% power to detect a mean difference of 0.6 units in the change from baseline in DAS28-CRP at Week 12 between the active treatment group and the placebo group. This calculation assumes a common standard deviation of 1.1, utilizing a two-sided, two-sample t-test with a significance level (α) of 0.05, allowing for an anticipated 10% premature dropout rate.

6.2 Analysis Populations

- **Intent-to-Treat (ITT) Population:** Includes all randomized participants who receive at least one dose of the investigational product. The primary efficacy analysis will be performed on the ITT population.
- **Per-Protocol (PP) Population:** Includes all ITT participants who complete the full 12-week regimen without major protocol deviations.
- **Safety Population:** Includes all participants who receive at least one dose of the investigational product, analyzed according to the actual treatment received.

7. Regulatory and Ethical Conduct

This clinical study will be conducted in strict compliance with the ethical principles originating in the Declaration of Helsinki, the International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines, and all applicable national, local, and regional regulatory mandates. Prior to study initiation, this protocol and all patient-facing documentation must receive written approval from an Institutional Review Board (IRB) or Independent Ethics Committee (IEC).