Clinical Study Report (CSR) Synopsis

Protocol Number: XYZ-101-RA-02
Investigational Product: XYZ-101 (Fully humanized IgG1 anti-IL-23p19 monoclonal antibody)
Phase of Development: Phase II

1. Study Objectives and Design

Objectives

Primary: To evaluate the efficacy of subcutaneous (SC) administrations of XYZ-101 (150 mg) compared with placebo in reducing disease activity at Week 12, as measured by the change from baseline in the Disease Activity Score 28-joint count using C-reactive protein (DAS28-CRP).

Secondary: To evaluate the clinical response rates based on American College of Rheumatology (ACR20/50/70) criteria at Weeks 4, 8, and 12; to evaluate safety and tolerability; and to assess changes in physical function via the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Methodology

This was a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, parallel-stratified study conducted at 24 investigative sites globally. Eligible patients were randomized in a 2:1 ratio to receive either XYZ-101 150 mg SC or matching volume placebo SC at Weeks 0, 4, and 8. The total treatment duration was 12 weeks, followed by an 8-week safety follow-up period through Week 20.

2. Patient Disposition and Demographics

Participant Disposition

A total of 242 patients were screened, of whom 180 were randomized.

- **XYZ-101 Group (N = 120):** 112 (93.3%) completed the 12-week double-blind treatment phase. Reasons for premature discontinuation included: adverse events (n = 4, 3.3%), withdrawal of consent (n = 3, 2.5%), and protocol deviation (n = 1, 0.8%).
- **Placebo Group (N = 60):** 53 (88.3%) completed the 12-week treatment phase. Reasons for premature discontinuation included: lack of efficacy (n = 5, 8.3%) and withdrawal of consent (n = 2, 3.3%).

Baseline Characteristics (Intent-to-Treat Population)

Demographics and baseline disease activity metrics were well-balanced between the two parallel treatment arms, representing a population with high unmet clinical need:

Parameter	Placebo (N = 60)	XYZ-101 150 mg (N = 120)
Mean Age (Years)	52.4 (± 10.8)	53.1 (± 11.2)
Female Biological Sex (%)	78.3%	80.0%
Mean RA Duration (Years)	6.2 (± 4.1)	5.9 (± 3.8)
Mean Baseline DAS28-CRP	5.82 (± 0.74)	5.79 (± 0.71)
Mean Tender Joint Count (TJC-28)	14.2 (± 4.1)	13.9 (± 4.3)
Mean Swollen Joint Count (SJC-28)	11.4 (± 3.2)	11.1 (± 3.5)
Mean Concomitant MTX Dose (mg/week)	16.8 (± 3.1)	17.2 (± 2.9)

3. Efficacy Results

Primary Endpoint

The primary efficacy analysis was performed on the Intent-to-Treat (ITT) population utilizing a Mixed Model for Repeated Measures (MMRM) framework, with missing data handled via restricted maximum likelihood estimation.

At Week 12, the XYZ-101 treatment group demonstrated a highly statistically significant and clinically meaningful reduction in disease activity compared to the placebo arm.

- **XYZ-101 150 mg (n = 120):** Least Squares (LS) mean change from baseline in DAS28-CRP was -**2.14** (SE: 0.12).
- **Placebo (n = 60):** LS mean change from baseline was -**0.82** (SE: 0.16).
- **Treatment Difference:** -1.32 (95% CI: -1.72 to -0.92; ***p* < 0.0001**).

Secondary Endpoints

Clinical response rates measured by ACR criteria at Week 12 showed strong, consistent separation from placebo:

- **ACR20:** Significantly higher in the XYZ-101 group compared to placebo (**64.2% vs. 28.3%**; $p < 0.001$).
- **ACR50:** Achieved by **38.3%** of XYZ-101 patients compared to **11.7%** of placebo patients ($p < 0.001$).
- **ACR70:** Achieved by **18.3%** of XYZ-101 patients compared to **3.3%** of placebo patients ($p = 0.004$).
- **Functional Status (HAQ-DI):** The LS mean change from baseline to Week 12 in the HAQ-DI score was significantly greater with XYZ-101 compared to placebo (-0.48 vs. -0.14; $p < 0.001$).
- **DAS28 Remission (< 2.6):** At Week 12, **22.5%** of patients in the XYZ-101 group achieved clinical remission compared to **5.0%** in the placebo group ($p = 0.003$).

4. Safety and Tolerability Results

Summary of Adverse Events (Safety Population)

XYZ-101 exhibited a favorable safety profile. The overall incidence of Treatment-Emergent Adverse Events (TEAEs) was 54.2% in the active arm compared to 46.7% in the placebo arm.

Safety Parameter	Placebo (N = 60)	XYZ-101 150 mg (N = 120)
Any TEAE	28 (46.7%)	65 (54.2%)
Severe TEAE (Grade ≥ 3)	1 (1.7%)	3 (2.5%)
Serious Adverse Events (SAEs)	1 (1.7%)	2 (1.7%)
TEAEs Leading to Discontinuation	0 (0.0%)	4 (3.3%)

Most Common TEAEs (≥ 5% in the Active Arm)

1. **Injection Site Reactions:** Erythema and mild pruritus occurred in 10.8% (n = 13) of the XYZ-101 group vs. 3.3% (n = 2) in the placebo group. All cases were transient, graded as mild (CTCAE Grade 1), and resolved without intervention.
2. **Headache:** Reported in 7.5% (n = 9) of active subjects vs. 5.0% (n = 3) of placebo subjects; all cases were mild-to-moderate.
3. **Nasopharyngitis:** Reported in 5.8% (n = 7) of active subjects vs. 5.0% (n = 3) of placebo subjects.

Serious Adverse Events & Discontinuations

There were two SAEs reported in the XYZ-101 group. One notable case involved a 54-year-old female with comorbid type 2 diabetes who developed severe community-acquired lobar pneumonia (*Streptococcus pneumoniae*) on Study Day 42, which required hospitalization and intravenous antibiotic therapy.

Per protocol safety rules, the event led to the permanent discontinuation of the IP. The event resolved fully following standard clinical management, and the patient was discharged in stable condition. The second active-arm SAE was a mechanical bone fracture deemed unrelated to the IP. No deaths or systemic anaphylactic reactions occurred during the study.

Laboratory and Systemic Vigilance

No clinically meaningful, systemic trends or treatment-emergent shifts were noted in vital signs, ECG parameters, or metabolic chemistry. Transient, isolated drops in absolute neutrophil counts (ANC) down to Grade 1 or 2 (1,500 - 1,000 cells/ μL) occurred in 4 patients on active treatment, but none fell below the protocol's strict stopping threshold (< 1,000 cells/ μL) or correlated with local injection complications. Anti-drug antibodies (ADAs) were detected in 4.2% (n = 5) of XYZ-101 treated patients, with low titers and no apparent impact on clinical efficacy or systemic safety metrics.

5. Conclusion

Subcutaneous administration of XYZ-101 (150 mg) over 12 weeks demonstrated clear, robust clinical efficacy with statistically significant reductions in RA disease activity (DAS28-CRP) and marked improvements in physical function (HAQ-DI) and ACR clinical response rates. XYZ-101 was well tolerated, showing an acceptable safety margins profile consistent with targeted upstream IL-23/Th17 pathway inhibition. These positive data strongly justify and support the progression of XYZ-101 into confirmatory Phase III clinical development trials.