Regulatory Briefing Document

Product Name: XYZ-101
Active Ingredient: Humanized IgG1 monoclonal antibody targeting interleukin-23 (IL-23p19)
Indication: Treatment of adult patients with moderate-to-severe active Rheumatoid Arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs)
Meeting Type: Pre-Phase III Type B Meeting
Date: June 19, 2026

1. Introduction & Purpose of Meeting

The Sponsor is developing XYZ-101, a novel humanized monoclonal antibody that selectively targets the p19 subunit of interleukin-23 (IL-23). This Briefing Document accompanies the Sponsor's request for a Type B meeting to achieve alignment with the Agency on the global Phase III clinical development program intended to support a future Biologics License Application (BLA).

The primary objectives of this meeting are to:

- Obtain feedback on the adequacy of the completed Phase II safety and efficacy data.
- Gain concurrence on the design, patient population, endpoints, and statistical analysis plan for the pivotal Phase III protocol (Study XYZ-301).
- Confirm that the proposed nonclinical and clinical pharmacology packages are sufficient to support marketing approval.

2. Product Overview & Mechanism of Action

XYZ-101 is a recombinant humanized IgG1 kappa monoclonal antibody that binds with high affinity (K_d = 1.2×10^{-11} M) to the p19 subunit of the IL-23 cytokine. By blocking IL-23 from binding to its cell-surface receptor, XYZ-101 selectively inhibits the differentiation, proliferation, and survival of Th17 cells, downstream halting the production of pro-inflammatory cytokines including IL-17A, IL-17F, and TNF-alpha.

Nonclinical Summary

- **In Vitro:** XYZ-101 demonstrated potent neutralization of IL-23-induced STAT3 phosphorylation in human peripheral blood mononuclear cells (PBMCs).
- **In Vivo:** In a collagen-induced arthritis (CIA) cynomolgus monkey model, weekly subcutaneous administration of XYZ-101 at doses ≥ 5 mg/kg resulted in statistically significant reductions in paw swelling, bone erosion, and inflammatory cell infiltration.
- **Toxicology:** A 26-week repeated-dose toxicity study in cynomolgus monkeys at doses up to 100 mg/kg/week (representing a 50-fold margin over the maximum proposed human dose) revealed no adverse target organ toxicity, no systemic immunosuppression, and no pre-neoplastic lesions.

3. Clinical Development Summary: Phase II Data

The clinical efficacy and safety of XYZ-101 were evaluated in a Phase IIb, randomized, double-blind, placebo-controlled, dose-ranging study (**Study XYZ-201**) in patients (N = 240) with moderate-to-severe active RA who had an inadequate response to methotrexate (MTX-IR). Patients were randomized 1:1:1:1 to receive subcutaneous doses of XYZ-101 (50 mg, 150 mg, or 300 mg) or placebo every 4 weeks (q4w) for 24 weeks, against a background of stable MTX.

3.1 Efficacy Results at Week 12 (Primary Endpoint)

The study met its primary endpoint, showing a statistically significant, dose-dependent reduction from baseline in the Disease Activity Score 28-C-reactive protein (DAS28-CRP) at Week 12 for the 150 mg and 300 mg cohorts compared to placebo.

Outcome Measure	Placebo (n=60)	XYZ-101 50mg (n=60)	XYZ-101 150mg (n=60)	XYZ-101 300mg (n=60)
Mean Delta DAS28-CRP	-0.8	-1.4	-2.3*	-2.5*
ACR20 Response (%)	28.3%	41.6%	63.3%*	68.3%*
ACR50 Response (%)	11.7%	20.0%	38.3%*	41.7%*

ACR70 Response (%)	3.3%	6.7%	18.3%*	21.7%*

**p < 0.001 compared to placebo*

3.2 Safety and Tolerability Summary

XYZ-101 was generally well-tolerated across all dose groups through Week 24.

- **Treatment-Emergent Adverse Events (TEAEs):** Occurred in 48% of the pooled XYZ-101 groups vs. 42% in the placebo group. The most common TEAEs (≥ 5%) were nasopharyngitis, upper respiratory tract infections, and mild injection-site reactions.
- **Serious Adverse Events (SAEs):** Reported in 3 patients (1.6%) in the active treatment arms (one case of localized cellulitis, one case of cholecystitis, and one non-fatal lower respiratory tract infection) compared to 1 patient (1.7%) in the placebo arm.
- **Laboratory Findings:** Transient, mild elevations in ALT/AST (less than 2x ULN) were observed in 4% of patients, balancing evenly across groups. No cases of neutropenia (< 1.0×10^{-9} L) or severe hypersensitivity were reported.

4. Proposed Phase III Clinical Design Summary

The Sponsor proposes a single, pivotal, phase III global study (**Study XYZ-301**) to confirm the efficacy and long-term safety profile of XYZ-101.

Screening Period: Up to 4 weeks		
Randomization (1:1:1) / Total N = 600		
Arm A: XYZ-101 150mg	Arm B: XYZ-101 300mg	Arm C: Placebo SC
SC q4w	SC q4w	SC q4w
Wk 24 Primary Endpoint	Wk 24 Primary Endpoint	Wk 24 Blinded Escape
Continue to Wk 52	Continue to Wk 52	Rerandomized to Active Tx to Wk 52

Protocol Framework

- **Study Population:** Adults with moderate-to-severe active RA (defined by ≥ 6 tender joints, ≥ 6 swollen joints, and ≥ hsCRP 5 mg/L) who have had an inadequate response to conventional synthetic DMARDs (csDMARDs) or biologic DMARDs (bDMARDs).
- **Sample Size:** Approximately 600 patients globally (200 per arm) to provide greater than 90% power to detect a difference of 1.2 units in mean change of DAS28-CRP between the active arms and placebo.
- **Stratification Factors:** Prior biologic exposure (bDMARD-naive vs. bDMARD-experienced) and Geographic Region.
- **Early Escape Architecture:** At Week 24, patients randomized to placebo who do not achieve a minimum 20% improvement in both tender and swollen joint counts will be blindly transitioned to receive XYZ-101 150 mg for the remainder of the 52-week evaluation period.

5. Key Regulatory Questions & Sponsor Positions

Question 1: Phase III Design Sufficiency

Does the Agency agree that the design of the proposed pivotal Study XYZ-301, including the target population, sample size, and duration of 52 weeks, is sufficient to support a future BLA submission for the indication of moderate-to-severe Rheumatoid Arthritis?

- **Sponsor Position:** Yes. The Sponsor believes that a 600-patient, placebo-controlled study utilizing a validated enrichment strategy (stratifying by prior bDMARD use) aligns with ICH E9 guidelines. The study duration of 52 weeks provides adequate long-term exposure data to characterize the maintenance of response and safety profile required for chronic biologic therapies in RA.

Question 2: Primary Endpoint Selection

Does the Agency concur with the selection of the change from baseline in DAS28-CRP at Week 24 as the primary efficacy endpoint for registration?

- **Sponsor Position:** The Sponsor proposes DAS28-CRP at Week 24 because it is a continuous, highly sensitive, and universally validated index of disease activity that demonstrates strong correlation with structural radiographic outcomes. Because clinical differentiation in Phase II was

starkly evident by Week 12, a Week 24 endpoint provides a robust, stable window to establish definitive superiority over placebo before the clinical necessity of the early-escape crossover.

Question 3: Long-Term Safety Monitoring Strategy

Are the proposed safety monitoring strategies, including standard laboratory evaluations, protocol-specified monitoring for opportunistic infections, and hepatic safety stopping rules, sufficient to monitor safety over long-term administration?

- **Sponsor Position:** Yes. Based on the Phase II safety profile and known mechanisms of IL-23 path blockers, the primary risks are limited to mild infections. The protocol mandates screening for latent tuberculosis (TB) via IGRA testing, hepatitis B/C screening at baseline, and routine hematology/chemistry panels every 4 weeks. Standard stopping rules for confirmed ALT/AST greater than 3x ULN will be strictly enforced.

Question 4: Special Populations

Does the Agency recommend executing additional dedicated clinical pharmacology studies or pharmacokinetic (PK) evaluations in special populations (e.g., hepatic or renal impairment) prior to initiating Phase III, or can these populations be adequately evaluated via a population PK approach using data collected during Phase III?

- **Sponsor Position:** The Sponsor proposes that dedicated studies are not warranted. Monoclonal antibodies are cleared via intracellular catabolism into peptides and amino acids rather than hepatic CYP450 metabolism or renal excretion. The Sponsor intends to perform robust population PK modeling utilizing sparse sampling from elderly patients and patients with mild-to-moderate renal/hepatic impairment enrolled directly within the Phase III trial.

6. Conclusion

The Phase II clinical data for XYZ-101 show strong proof-of-concept and clear dose differentiation with an acceptable safety profile. The Sponsor looks forward to discussing these data and aligning on the proposed Phase III development timeline to deliver a highly selective, optimized therapy to patients suffering from debilitating rheumatoid arthritis.