Statistical Analysis Plan (SAP) for Phase 2 Ilizomab Study

1. Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical analyses for the Phase 2 clinical trial evaluating the safety and efficacy of Ilizomab in patients with moderate to severe Systemic Lupus Erythematosus (SLE). This SAP is designed in accordance with International Council for Harmonization (ICH) guidelines and regulatory requirements.

2. Study Design

- Type: Multicenter, randomized, double-blind, placebo-controlled trial
- Sample Size: Approximately 150 participants, randomized 1:1 (Ilizomab:Placebo)
- Duration: 24 weeks of treatment + 12 weeks of follow-up
- Dosing: Ilizomab administered [route, frequency, and dosage]

Primary Endpoint Assessment: Week 24

3. Study Objectives and Endpoints

Primary Objective:

• To evaluate the efficacy of Ilizomab in reducing disease activity in patients with moderate to severe SLE using the Systemic Lupus Erythematosus Responder Index (SRI-4) at Week 24.

Secondary Objectives:

- Assess changes in SLE Disease Activity Index 2000 (SLEDAI-2K) scores from baseline.
- Evaluate the impact of treatment on biomarkers associated with SLE activity.
- Assess improvements in patient-reported outcomes (PROs) using validated instruments.
- Evaluate the safety and tolerability of Ilizomab over the study duration, including rates of adverse events (AEs), serious adverse events (SAEs), and immunogenicity.

Primary Endpoint:

• Proportion of participants achieving SRI-4 response at Week 24.

Secondary Endpoints:

- Mean change in SLEDAI-2K score from baseline.
- Proportion of patients achieving low disease activity state.
- Corticosteroid tapering success (≤5 mg/day prednisone by Week 24).
- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs).
- Rate of anti-drug antibody (ADA) development.

4. Analysis Populations

- Intent-to-Treat (ITT) Population: All randomized participants.
- Per Protocol (PP) Population: Participants who adhere to study procedures without major protocol deviations.
- Safety Population: All participants who receive at least one dose of Ilizomab.

5. Statistical Methods

Primary Analysis:

- A logistic regression model will be used to compare SRI-4 response rates between Ilizomab and placebo groups, adjusting for baseline disease activity, treatment arm, and key demographic factors.
- Significance Level (Alpha): 0.05 (two-sided).
- Power: The study is designed to have 80% power to detect a clinically meaningful difference in SRI-4 response between treatment arms, assuming a 20% difference in response rate.
- Multiplicity Adjustment: To control for multiple comparisons due to the interim analysis, a Lan-DeMets spending function with an O'Brien-Fleming boundary will be used to adjust the alpha level across analyses.

Secondary Analyses:

- Mixed-effects models for repeated measures (MMRM) will assess changes in SLEDAI-2K over time.
- Kaplan-Meier survival analysis will be used for time-to-response analyses.

- Analysis of covariance (ANCOVA) will assess treatment effects on continuous endpoints.
- 6. Safety Analysis
 - Adverse Events (AEs):
 - Incidence, severity, and relationship to Ilizomab will be summarized descriptively.
 - Serious Adverse Events (SAEs) will be listed with causality assessments.
 - Treatment-emergent adverse events (TEAEs) will be categorized.
 - Immunogenicity Analysis:
 - The proportion of patients developing anti-drug antibodies (ADAs) will be summarized.
 - Laboratory Safety Data:
 - Changes in liver function tests, hematology parameters, and renal function markers.
 - Vital Signs & ECG Monitoring:
 - Descriptive summaries of blood pressure, heart rate, and ECG trends.

7. Interim Safety Analysis

- A planned interim analysis will occur when 50% of participants complete Week 24 assessments.
- An independent Data Safety Monitoring Board (DSMB) will review interim data for safety signals.
- Stopping criteria: Excessive AEs or lack of efficacy will be predefined.
- Multiplicity Adjustment for Interim Analysis:
 - The interim analysis will use a Lan-DeMets spending function with an O'Brien-Fleming boundary to adjust for multiple looks at the data while maintaining overall type I error control.
 - If the interim results cross the predefined boundary for efficacy, the study may be stopped early for overwhelming efficacy.

8. Handling of Missing Data

- Multiple Imputation (MI) will be used for missing primary endpoint data.
- Last Observation Carried Forward (LOCF) will be used for sensitivity analyses.

9. Data Cutoff and Reporting

- The final data cut-off date will be set once all patients have completed Week 24 assessments or withdrawn.
- Statistical outputs will include tables, figures, and listings (TFLs) per regulatory guidelines.