DAIT/Rho STATISTICAL ANALYSIS PLAN
28 April 2022

A Phase 2, Double-blind, Randomized, Placebo-controlled Multicenter Study to Evaluate Efficacy, Safety, and Tolerability of JBT-101 in Systemic Lupus Erythematosus

VERSION: 2.0

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Document History

Version	Date	Change(s)	Author
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0.2	26 November 2021	Changes incorporated from team review	Kati Steinmiller
0.3	30 December 2021	Updates based on team comments	Lynette Keyes-Elstein
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1.0	29 March 2022	Final	Kati Steinmiller
2.0	28 April 2022	Update primary analysis to include a covariate for the screening Fibromyalgia Symptom Scale Score	Kati Steinmiller

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
ALT	Alanine Aminotransferase
ARCI-M	Addiction Research Center Inventory – Marijuana
AST	Aspartate Aminotransferase
BILAG	British Isles Lupus Assessment Group
BMI	Body Mass Index
C3	Complement component 3
C4	Complement component 4
CB1	Cannabinoid receptor type 1
CH50	Total complement
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DMARD	Disease Modifying Anti-Rheumatic Drugs
df	degrees of freedom
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture

FSS	Fibromyalgia Symptom Scale
GFR	Glomerular Filtration Rate
HCV	Hepatitis C Virus
ID	Identifier
IFNα	Interferon alpha
IFNγ	Interferon gamma
IL-1β	Interleukin – 1 beta
IL-6	Interleukin - 6
IRB	Institutional Review Board
IVRS	Interactive Voice-Response E-diary System
MAR	Missing at Random
max	maximum
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minimum
mITT	modified Intent-to-Treat
mm	millimeter
MMF	Mycophenolate mofetil
NCI	National Cancer Institute
NIAID	National Institute of Allergies and Infectious Diseases
NIH	National Institute of Health
NRS	Numerical Ratings Scale
NSAID	Non-steroidal Anti-inflammatory Drugs

PGA	Physician's Global Assessment
PK	Pharmacokinetic
PP	Per Protocol
PROMIS	Patient-Reported Outcomes Measurement Information System
q	Every
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SELENA SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
SPM	Specialized Pro-resolving Lipid Mediator
SRI	SLE Responder Index
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TNFα	Tumor Necrosis Factor alpha
VAS	Visual Analog Scale
WHO	World Health Organization

1. PROTOCOL SYNOPSIS

Title of the Protocol: A Phase 2, Double-blind, Randomized, Placebo-controlled Multicenter Study to Evaluate Efficacy, Safety, and Tolerability of JBT-101 in Systemic Lupus Erythematosus
ACE Protocol Number: ALE09
Protocol Chair(s): Meggan Mackay, M.D.
IND Holder: DAIT/NIAID, NIH
Objectives: To evaluate the efficacy, safety, tolerability, and biologic effects of JBT-101. The primary objective is to evaluate effect on inflammatory pain related to active musculoskeletal disease in SLE.
Hypotheses/Estimates: The hypothesis is that JBT-101 will provide clinical efficacy in SLE patients with at least moderate musculoskeletal disease activity by activation of pathways that resolve ongoing, adverse immune responses and inhibit inflammatory cytokine production associated with SLE.
Study Arms: four cohorts: JBT-101 5 mg q a.m. and JBT-101 5 mg q p.m. JBT-101 20 mg q a.m. and placebo q p.m. JBT-101 20 mg q a.m. and JBT-101 20 mg q p.m. Placebo q a.m. and placebo q p.m.
Study Design: One hundred eligible subjects will be randomized in a 1:1:1:1 ratio to one of four cohorts to receive either JBT-101 (three groups: 5 mg q a.m. and 5 mg q p.m., 20 mg q a.m. and placebo q p.m., 20 mg q a.m. and 20 mg q p.m.) or placebo for 84 days, then 28 days of follow-up. Subject visits to assess endpoints occur at six times: Days 1, 15 ± 3, 29 ± 3, 57 ± 3, 85 ± 3 and 113 ± 3.
Endpoints: **PRIMARY EFFICACY ENDPOINT:** The primary endpoint for evaluation of the primary objective will be improvement in maximum daily pain NRS scores in the treated groups relative to the control after 12 weeks of treatment. Longitudinal trends over the course of the treatment period will be modeled and used to estimate differences between means at baseline and Day 84 for each treatment group. **SECONDARY EFFICACY ENDPOINTS:** 1. The 7-day average of maximum daily pain NRS scores prior to Visits 1 (Day 1), 3 (Day 29), 4 (Day 57), 5 (Day 85), and 6 (Day 113) will be used to evaluate the number (%) of subjects with: • Changes in pain categories from Visit 1 (Day 1) to Visits 3 (Day 29), 4 (Day 57), 5 (Day 85) and 6 (Day 113) (See Section 6.2.2.2 *Pain Categories*)

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- Improvement of 30% from Visit 1 (Day 1) to Visits 3 (Day 29), 4 (Day 57), 5 (Day 85) and 6 (Day 113)
- Improvement of 50% from Visit 1 (Day 1) to Visits 3 (Day 29), 4 (Day 57), 5 (Day 85) and 6 (Day 113)
- Improvement of 75% from Visit 1 (Day 1) to Visits 3 (Day 29), 4 (Day 57), 5 (Day 85) and 6 (Day 113)
- Improvement of 100% from Visit 1 (Day 1) to Visits 3 (Day 29), 4 (Day 57), 5 (Day 85) and 6 (Day 113)

2. Trends in active musculoskeletal disease activity over the duration of the treatment period (i.e. Visit 1 (Day 1) through Visit 5 (Day 85)) will be evaluated longitudinally using multiple indices:
    - Physician assessed tender joint count
    - Physician assessed swollen joint count
    - Presence or absence of arthritis on the SELENA SLEDAI
    - Musculoskeletal domain of the BILAG 2004
3. Persistence of trends in musculoskeletal disease activity after stopping treatment will be evaluated at Visit 6 (Day 113)
4. Trends in overall SLE disease activity over the duration of the treatment period (i.e. Visit 1 (Day 1) through Visit 5 (Day 85)) will be evaluated longitudinally using multiple indices:
    - SLE Responder Index , where a responder is defined as having all of the following:
        - ≥4 point reduction in SELENA-SLEDAI score,
        - no new BILAG A or no more than 1 new BILAG B domain score, and
        - no deterioration from baseline in the Physician's Global Assessment defined as an increase of ≥0.3 points.
    - SELENA SLEDAI score
    - BILAG 2004 score
    - Physician’s Global Assessment
5. Persistence of trends in overall SLE disease activity after stopping treatment will be evaluated at Visit 6 (Day 113)
6. Trends in patient-reported outcomes over the duration of the treatment period (i.e. Visit 1 (Day 1) through Visit 5 (Day 85)) will be evaluated longitudinally using multiple indices:
    - Lupus Activity Patient Global Assessment
    - PROMIS-29 Short Form
    - PROMIS Item Bank v2.0 - Cognitive Function
7. Treatment Satisfaction Survey
8. Persistence of trends in patient-reported outcomes after stopping treatment will be evaluated at Visit 6 (Day 113)

SAFETY ENDPOINTS:

Safety will be evaluated by describing incidence of treatment emergent adverse events (TEAEs) from Visit 1 (Day 1) through Visit 6 (Day 113). The TEAEs will be identified by monitoring subject-reported AEs, Adverse Events of Special Interest, vital signs, medical history, physical examination, blood and urine laboratory safety tests, 12-lead electrocardiograms, including QT/QTc measurements, and Addiction Research Center Inventory-Marijuana scale. Analyses on the following specific events are planned.

1. Any Grade 3 or higher AE or SAE that, in the opinion of the blinded site investigator, is at least “possibly related to study product. Unless noted otherwise, grading is defined by the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) system version 4.0

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2. QTc prolongation > 500 msec total duration and > 60 msec from Visit 1 (Day 1) QTc interval prior to study drug administration
3. Mild/moderate and severe disease flares by SELENA SLEDAI Flare Index
4. BILAG 2004 disease flares, defined as one new BILAG A or two new BILAG B scores
5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x upper limit of normal and total bilirubin > 1.5 x the upper limit of normal (confirmed on repeat testing)
6. Tolerability, assessed by incidence of discontinuation of study product due to TEAEs at least "possibly" related to study product from Visits 1 (Day 1) through 5 (Day 85)
7. Psychotropic activity, assessed using the ARCI-M

MECHANISTIC ENDPOINTS:

1. Trends in C-reactive protein levels in the blood over the duration of the treatment period (i.e. Visit 1 (Day 1) through Visit 5 (Day 85)) will be evaluated longitudinally
2. Persistence of trends in C-reactive protein levels after stopping treatment will be evaluated at Visit 6 (Day 113)
3. Trends in pro-inflammatory cytokine levels over the duration of the treatment period (i.e. Visits 1 (Day 1), 3 (Day 29) and 5 (Day 85)) will be evaluated longitudinally using multiple indices:
    - Pro-inflammatory cytokines in serum
        i. IFNα, IFNγ, IL-6, TNFα, and IL-1β
        ii. Expression of other cytokines will be explored
    - Pro-inflammatory cytokines in whole blood with and without in vitro TLR stimulation
        i. IFNα, IFNγ, IL-6, TNFα, and IL-1β in supernatant of stimulated and unstimulated whole blood cells
    - Type 1 IFN gene signature in whole blood mRNA.
4. Persistence of trends in biomarkers of inflammation after stopping treatment will be evaluated at Visit 6 (Day 113)
5. Changes in bioactive lipids in plasma from Visit 1 (Day 1) (pre and post dose) to Visit 2 (Day 15) will be evaluated longitudinally using multiple indices:
    - Specialized Pro-resolving lipid Mediators (SPMs), including lipoxin A4
    - Anti-inflammatory eicosanoids
    - Pro-inflammatory eicosanoids
6. Changes in plasma concentrations of JBT-101 and its metabolites from Visit 1 (Day 1) (pre and post dose) to Visit 2 (Day 15)

EXPLORATORY ENDPOINTS:

1. Fibromyalgia Symptom Scale score, from Visit 1 (Day 1) to Visits 5 (Day 85) and 6 (Day 113)

Sample Size: 100 eligible subjects will be randomized within 24 months and followed for 112 days; the study duration is estimated to be 33 months.

Safety Stopping Guidance: The following events will trigger both a comprehensive DSMB Emergency Safety Review and a temporary halt in enrollment:

- After the first 20 subjects are randomized, the occurrence of a Grade 3 or higher unexpected SAE in 10% or more of the study participants who have received study drug
- Two grade 3 or above AEs with the same or similar preferred terms associated with CB1 agonists deemed at least possibly-related to study drug.

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• Determination of unexpected, significant, or unacceptable risks to subjects that contraindicate further dosing of additional subjects, in the opinion of the Protocol Chairs or DAIT • Any new safety information about JBT-101 from other clinical trials that would pose significant or unacceptable risk to subjects

2. INTRODUCTION

This statistical analysis plan includes pre-planned analyses related to the study objectives outlined in the protocol.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form “n (%).” Percentages will be rounded to one decimal place.

- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.

- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.

- Test statistics including *t* and *z* test statistics will be reported to two decimal places.

- *P*-values will be reported to four decimal places if greater than or equal to 0.0001. If less than 0.0001, the value will be reported as “<0.0001.” A *p*-value can be reported as “1.0000” only if it is exactly 1.0000 without rounding. A *p*-value can be reported as “0.0000” only if it is exactly 0.0000 without rounding.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. ANALYSIS SAMPLES

These definitions are intended to identify participants for inclusion in each population but handling of observations with respect to intercurrent events is discussed below for each estimand (Sections 7.2-7.4).

4.1. Modified Intent-to-Treat Population

The modified Intent-to-Treat population (mITT) will consist of all randomized subjects who have received at least one dose of study product. The mITT population will be used for all efficacy analyses and will include subjects under the treatment to which they were randomized, regardless of compliance with assigned treatment.

4.2. Per Protocol Population

The per protocol population (PP) will consist of mITT subjects who:

- complete Visit 3 (Day 29), without missing more than 7 days of study product between Visit 1 (Day 1) through Visit 3 (Day 29).
- have ≥ 80% compliance with study drug administration from Visits 1- 5 (Days 1-85), as assessed by numbers of capsules of study product returned to the site, excluding periods off study drug when directed per protocol by the site investigator or treating physician)
- complete the study without protocol violations deemed likely to affect the efficacy outcomes of interest

A masked data review panel will evaluate deviations from the protocol including, for example, violations of entry criteria, departures from assigned treatment regimen, modifications of concurrent therapy, failure to complete study visits, or administration of study procedures outside the specified visit windows to determine if occurrence of these deviations should exclude subjects from the PP population.

The PP population will be used for secondary efficacy.

4.3. Safety Population

The safety population will include all subjects for whom study treatment is initiated. The safety population will be used for all safety analysis. Analysis performed on the safety population will be according to the treatment actually received.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

The disposition of all enrolled subjects will be summarized in tables and listed by treatment group.

The numbers and percentages of subjects randomized, in each analysis sample, as well as reasons for early termination from the study will be presented. For subjects discontinuing study treatment early, the reasons for discontinuing study treatment early will also be presented.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for the mITT and PP samples by treatment group. Characteristics to be summarized include:

- Age at Screening
- Race
- Ethnicity
- Sex
- Disease duration at Screening
- Screening Fibromyalgia Symptom Scale Score (FSS)
- FSS summarized categorically as <13 versus >= 13
- Screening 7-day average maximum daily pain NRS (see Section 5.2.1)
- Screening 7-day average maximum daily pain NRS score summarized categorically as <= 6 vs >6
- Baseline 7-day average maximum daily pain NRS
- Number with baseline 7-day average maximum daily pain NRS < 4
- Patient global assessment
- Physician global assessment
- BILAG arthritis severity category, where the mutually exclusive categories are defined in a hierarchical fashion as follows:
  - i. Severe arthritis scored as improving, same, new, or worse;
    If not (i), then
  - ii. Moderate arthritis scored as improving, same, new, or worse;
    If not (ii), then
  - iii. Mild arthritis scored as improving, same, new, or worse;
    If not (iii), then
  - iv. Arthritis is not present.
- Arthritis present on SLEDAI
- Number of swollen joints
- Number of tender joints
- Number of tender and swollen joints
- Number on depression/anxiety medication
- Physical Function total score per the PROMIS 29

- Depression total score per the PROMIS 29
- Anxiety total score per the PROMIS 29
- Fatigue total score per the PROMIS 29
- Sleep Disturbance total score per the PROMIS 29
- Ability to Participate in Social Roles and Activities total score per the PROMIS 29
- Pain Interference total score per the PROMIS 29
- Pain Intensity score per the PROMIS 29
- SLEDAI score
- GFR by MDRD
- Number with C3 lower the limit of normal
- Number with C4 lower than the limit of normal
- Number with any DMARD use
- Number using each of the following DMARDs for treatment of SLE: abatacept, secukinemab, mycophenolate, azathioprine, methotrexate, leflunomide, tacrolimus and cyclosporine
- Number using hydroxychloroquine
- Number with Benlysta use
- Number with steroid use
- Oral steroid dose

Depression or anxiety medications will include the following: alprazolam, amitriptyline, armodafinil, buspirone, bupropion, citalopram, clonazepam, dexmethylphenidate, diazepam, duloxetine, escitalopram, fluoxetine, lorazepam, milnacipran, nortriptyline, paroxetine, quetiapine, sertraline, trazodone, venlafaxine.

Depression, anxiety, and fatigue total scores will be derived by summing the results of the 4 questions associated with each category on the PROMIS 29.

All oral steroid doses will be calculated in terms of prednisone equivalents. Methylprednisolone will be converted to prednisone dosage by multiplying by 1.25.

A listing of demographic and baseline characteristics for all randomized participants will be provided.

No hypothesis testing will be used to compare treatment arms with respect to demographic or baseline characteristics.

5.2.1. Screening 7-day Average Maximum Daily Pain NRS

Subjects will report maximum daily pain NRS scores using an interactive voice-response e-diary system (IVRS), which can be accessed by any phone that supports tone dialing. At the Screening visit, subjects will be registered and provided with credentials allowing access to the IVRS. Subjects will be instructed on how to record the maximum daily pain NRS score, including directions for recording scores at approximately the same time every day, preferably before bedtime.

To be eligible for the study, a subject must have a 7-day average of maximum daily pain NRS scores of at least 4. Once a subject enters 7 consecutive days of maximum daily pain NRS scores, the 7-day average will be calculated. If the average is 4 or greater, the subject's eligibility is permanently established, and the average will be saved for the NRS stratification value. If the subject's average is less than 4 based on the first 7 consecutive days, they will continue to enter data. After each daily data entry, a new consecutive 7-day average will be calculated. If the subject qualifies at any point during the screening period, eligibility is secured, and the average is stored for the NRS stratification value.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Major protocol deviations will be listed by site with information such as type of deviation, date of occurrence, whether notification to IRB was required, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation.

6.2. Treatment Adherence

Subjects are instructed to take 2 pills of study product (JBT-101 or matching placebo) by mouth daily, with at least 8 hours between doses and without regard to fed state, from Day 1 to Day 84. The first dose of study medication is administered in the clinic at the Day 1 visit.

6.2.1. Treatment Cohorts

Cohort	Approximate n	Days 1-84	
		A.M. Study Product	P.M. Study Product
1	25	JBT-101 5 mg	JBT-101 5 mg
2	25	JBT-101 20 mg	Placebo
3	25	JBT-101 20 mg	JBT-101 20 mg
4	25	Placebo	Placebo

Study drug will be dispensed at Days 1, 29, and 57. Subjects will receive A.M. and P.M. bottles of study drug, each containing 35 pills. Subjects are instructed to take one pill from the A.M. bottle and one pill from the P.M. bottle daily and are counseled not to combine study drug into a single bottle. Both A.M. and P.M. bottles containing unused study drug will be returned to the site at Days 29, 57 and 85. At these visits, site staff will count the number of pills returned and collected information from the subject on the number of pills that were lost. In addition, study drug is also counted and returned to the subject at the Day 15 visit to ensure compliance and appropriately counseling if any doses were lost or missed.

Due to the COVID-19 pandemic, it was allowable for study visits for Day 15 through Day 113 to be conducted remotely, which disrupted the return of study drug bottles to sites. When a remote visit was conducted for a drug dispensing or return visit, the site was instructed to collect additional information from the subject on the dates the first and last dose was taken from each bottle. Study drug was either shipped back to the study site or returned at a subsequent in clinic visit.

Interruption of continued dosing in individual subjects was allowed for safety reasons and at the discretion of the site investigator, if it was felt that interruption of dosing is in the best interest of the

subject. Other than in urgent situations, it was recommended that the site investigator discuss the reasons for interruption of dosing with the Protocol Chairs and DAIT/NIAID prior to interruption. Multiple on-off periods of treatment with study drug were permitted, as necessary in the judgment of the investigator for safety purposes. There was no dose modification in this study, other than temporary or permanent discontinuation.

The number of pills taken from each bottle will be computed as the number of pills in the bottle (i.e., 35) minus any pills lost or returned. Compliance will be calculated as the number of pills taken divided by the expected number of pills taken multiplied by 100. Compliance will be calculated overall for AM, PM and total daily doses. If a bottle is not returned, we will compute compliance under 2 scenarios:

- Case 1 (best): the number of pills taken is assumed to equal the number expected,
- Case 2: the number of pills taken is assumed to equal 35.

Compliance for individuals who failed to return bottles will be reviewed by the masked data review committee for exclusion from the PP population.

In-person Dispense or Return Visits

For each bottle, the expected number of pills taken will be derived as the difference between the return date and dispense date, minus any days that the drug was temporarily suspended at the discretion of the investigator. If the treatment discontinuation date is prior to the return date, the treatment discontinuation date is used. If the expected number of pills exceeds the number of pills dispensed, the expected number of pills is capped at 35. It will be assumed that 2 doses (one A.M. and one P.M.) were taken when study drug is dispensed on Day 1 and that 1 dose (one P.M.) was taken from the new bottle when study drug is dispensed on Days 29 and 57. It will be assumed that the A.M. dose was taken on the return visit prior to returning the bottle (Days 29, 57 and 85).

Remote Dispense or Return Visits

If a remote visit was conducted at a visit where drug was expected to be dispensed and/or returned, the expected number of pills taken will be derived as the difference between the reported first and/or last dose date for the bottle if the dispense and/or return date is missing, minus any days that the study drug was temporarily suspended at the discretion of the investigator. If the treatment discontinuation date is prior to the return date, the treatment discontinuation date is used. It will be assumed that 2 doses (one A.M. and one P.M.) were taken when study drug is dispensed in-person on Day 1 and that 1 dose (one P.M.) was taken from the new bottle when study drug is dispensed in-person on Days 29 and 57. It will be assumed that the A.M. dose was taken on the in-person return visit prior to returning the bottle (Days 29, 57 and 85). When a bottle is not dispensed and/or returned at an in-person visit, it will be assumed that 2 doses (one A.M. and one P.M.) were taken on the reported start and/or stop date.

In addition to determining compliance to the study drug while on treatment, the percent of the target 84 dosing days will also be computed. The % of target 84 dosing days will be calculated as the (treatment stop date – the treatment start date + 1 – number of days drug was temporarily withheld per the investigator) divided by 84 x 100. The number of days drug was temporarily withheld per the investigator will be calculated as the start date of study drug hold – date the study drug was resumed.

Study drug dosing will be listed by subject, visit and bottle. Information will include the date of dispense and return, number of pills returned, and number of pills lost.

7. EFFICACY EVALUATION

7.1. Overview of Efficacy Analysis Methods

7.1.1. Multicenter Studies

Study subjects will be recruited from 16 study sites. Since the number of subjects at some study sites is expected to be insufficient (<5 subjects) for evaluating site effects, study data will be analyzed as a whole, and no formal accommodation for site-to-site variation will be made.

7.1.2. Assessment Time Windows

Visit	Window (Days)
Screening	Up to -42*
Day 1 (Baseline)	N/A
Day 15	+/- 3
Day 29	+/- 3
Day 57	+/- 3
Day 85	+/- 3
Day 113	+/- 3

* Note: For subjects who consented prior to Version 4.0 of the ALE09 protocol, the screening window was shorter and was required to occur within 21 days of Day 1 (Baseline), rather than 42.

Allowable visit windows for all scheduled visits are provided in Table 7-1.

7.2. Estimand for the Primary Analysis

The estimand for the primary analysis will serve as the first step in assessing the study's primary objective, "to evaluate efficacy of JBT-101 for treatment of inflammatory pain related to active musculoskeletal disease in SLE". The estimand components are detailed below.

7.2.1. Primary Analysis Variable

The pain numerical ratings scale (NRS) is a single-item pain numerical rating scale for pain, which is a segmented numerical version of the visual analogue scale in which the respondent selects a whole number (0-10) that best reflects the intensity of their pain. The NRS is anchored by two terms describing average pain severity extremes, one of "no pain" (score of 0) and one of "worst pain imaginable" (score of 10). The subjects rank their worst pain in the previous day, at about the same

time each evening, so the recall period is about 24 hours of the most recent entry. The subjects record their maximum daily pain NRS score each day using an IVRS.

7.2.2. Population

The analysis will use the mITT population (Section 4.1).

7.2.3. Intercurrent Events and Strategies

Per protocol, individuals should take study treatment twice daily and take no narcotic analgesics for 84 days. Pain NRS should be recorded daily. Intercurrent events to consider for this study include:

1. Missed doses of study treatment
    - Chance missed doses due to participant error
    - Temporary interruption of dosing for safety or investigator discretion
    - Early discontinuation of study treatment for reasons detailed in Protocol Section 5.8.1, including participant request, investigator discretion, safety concerns, new or increases doses of concurrent therapies, or starting prohibited meds.
    - Premature study withdrawal
2. Missed NRS data
    - Unplanned missed reports due to participant failure to report
    - Premature study withdrawal

For the primary estimand, NRS data from the first through the last dose of study treatment will be included in the analysis. We assume that NRS data missing either by chance or monotonically after some point in time are “missing at random” such that unobserved trajectories are presumed to be consistent with observed trends. NRS data for days where doses were missed due to chance or temporary interruptions will be included in the analysis. However, NRS data will be excluded if entered into the IVRS:

- after discontinuation of study treatment,
- on days when narcotic analgesics were taken,
- after DMARDs were started,
- after any increase in dose of systemic corticosteroids for treatment of SLE, including increases from baseline dosing and initiation of new treatment,
- after violation of rules for allowed corticosteroid use for reasons not associated with SLE flares.
    - Specifically, per Protocol Section 5.6, *Prohibited Medications*, Table 2, increases of up to 20 mg/day that are decreased back to the baseline dose within 7 days are permitted, but not on more than 2 occasions during the study.

Days that narcotic analgesics were taken will be identified using the concomitant medication log. All medications with a WHO Drug ATC Code beginning with N02A will be considered a narcotic analgesic.

7.2.4. Primary Analysis and Population-Level Summary

The primary hypothesis for this study is that JBT-101 treatment will result in improvement in the maximum daily pain NRS scores in SLE patients with active musculoskeletal disease. The null and alternative hypotheses to be tested are:

H_0: Linear trends from Day 1 to Day 84 are equivalent for each JBT-101 cohort and placebo.

H_A: Linear trends from Day 1 to Day 84 are not equivalent across groups.

For the primary analysis, the maximum daily pain NRS scores from Day 1 through end of treatment (typically Day 84) will be modeled using a mixed-effects model. NRS data up to the day of last dose of study treatment will be included according to Section 7.2.3. The fixed effects will include treatment group, time, time^2, time- and time^2 by treatment group interactions, as well as the Screening 7-day average maximum daily pain NRS and Screening FSS score as covariates. In order to avoid convergence issues due to numerical scaling, time for this model will be defined as the fraction the planned treatment period ranging from 0 to 1, and equal to (assessment date – treatment start date)/83. Within-subject random effects for intercept and slopes for time and time^2 will be fit using an unstructured covariance matrix assuming a different structure for placebo and pooled active treatment groups. With the proposed scaling of the time variable, convergence problems are not anticipated. However, in the event of convergence problems, we will consider alternative covariance structures for random effects including: unstructured (2); compound symmetric with heterogeneous variances, and independent matrices with and without the assumption of different structures for placebo and pooled active treatment groups. The model with the lowest Akaike Information Criterion (AIC) will be selected.

The primary hypothesis will be tested using the 3 degrees of freedom contrast comparing the difference in predicted means ($\hat{\mu}$) from Day 1 to Day 84 for each JBT-101 group versus placebo. That is,

$$(\hat{\mu}_{84} - \hat{\mu}_1)_{cohort\ i} - (\hat{\mu}_{84} - \hat{\mu}_1)_{Placebo} = 0 \text{ for i=1 to 3.}$$

Denominator degrees of freedom will be estimated using the Kenward-Rogers approach. If the 3 df test is significant (α=0.05, two-sided), Bonferroni-corrected tests for three 1 df pairwise comparisons with placebo will be performed (i.e., uncorrected p-values will be multiplied by 3). If the 3 df test is not statistically significant, confidence intervals for the 1df pair-wise comparisons with placebo will still be presented, but this information will be used for hypothesis generation and planning of future studies.

Setting the Screening 7-day average maximum daily pain NRS and Screening FSS score at their means for the analysis population, model-based estimates for means at Days 1 and 84, slopes, mean change from Day 1 to Day 84 along with standard errors and 95% confidence intervals will be presented for each treatment group. In addition, each active treatment arm will be compared to placebo by presenting the differences in mean change from Day 1 to Day 84 along with standard errors and 95% confidence intervals.

7.2.5. Sensitivity Analyses Supporting the Primary Analysis

Sensitivity analyses analogous to the primary analysis will be performed separately for each of the following modifications to the estimand framework.

- **Population modifications:**
  - PP population (Section 4.2)
- **Intercurrent Event Strategy modifications**:
  - NRS data entered into the IVRS after discontinuation of study treatment and on days where DMARDs or narcotics were taken will be included in the analysis. This constitutes a conservative evaluation of the treatment effect.
- **Analysis modifications:**
  - Test equivalence of the fixed effects longitudinal trends among treatment groups; a 9df test comparing intercepts, time slopes, and time^2 slopes for placebo versus each active treatment, simultaneously.

7.3. Secondary Estimands Supporting the Primary Objective

The secondary analyses will support the primary analysis by providing a deeper understanding of events. P-values for all inferential analyses will be presented as a description of strength of evidence of relationships rather than tests of hypotheses. As such, no corrections for multiplicity are planned. Unless otherwise noted, all secondary analyses will be conducted using the mITT population. Additional analyses may be repeated on the PP population to further explore findings.

7.3.1. Secondary Estimands based on the Primary Analysis Variable

Unless otherwise noted, the following secondary analyses will be performed using the intercurrent event strategy detailed in Section 7.2.3 and the primary analysis model described in Section 7.2.4.

- Model-based estimates for means at Days 1, 28, and 56, adjusted for “Screening 7-day average maximum daily pain NRS” and “Screening FSS Score” at their baseline means, and for mean change from Day 1 to Days 28 and 56 along with standard errors and 95% confidence intervals will be presented for each treatment group. In addition, each active treatment arm will be compared to placebo by presenting the differences in mean change from Day 1 to Days 28 and 56 along with standard errors and 95% confidence intervals.
- Model-based estimates for mean changes (with SEs and 95% CIs) from Day 1 to Days 28, 56, and 84 for placebo and for all JBT-101 dose groups pooled will be presented along with estimates for the mean difference between placebo and pooled active treatments at each specified time point. The difference between placebo and pooled active treatments will be evaluated at Day 84; the p-value from the appropriate contrast statement will be presented (1df t-test).
- To evaluate the dose response for the change from Day 1 to Day 84, linear and quadratic orthogonal contrasts derived from the dose vector, {0,10,20,40} will be evaluated. Coefficients for the linear and quadratic dose-effect contrasts are shown in the table below.

	Coefficients for orthogonal contrasts			
	0 a	10 b	20 c	40 d
linear	-0.591608	-0.253546	0.0845154	0.7606388
quadratic	0.5640761	-0.322329	-0.644658	0.4029115

- To evaluate the impact of the Screening 7-day average maximum daily pain NRS on trends over time, the primary analysis model will be modified to include its interactions with time and time^2.
- Analyses analogous to the primary analyses using % change in NRS from baseline as the outcome variable, where baseline is defined as the average maximum daily NRS in the 7 days prior to dosing.
- To evaluate the persistence of trends after treatment is stopped, the primary analysis model will be modified to include a variable for "time post-treatment" and its interaction with treatment group, where

  Time post-treatment = 0, if participant is on treatment;
  = (assessment date – last treatment date)/83, if participant has stopped treatment.

  For this analysis, observations beyond Day 84 will be included.

- The primary analysis model will be modified to control for possible baseline imbalances of any of the following covariates:
  - Depression/Anxiety Medication Status: a dichotomous indicator variable will be created to indicate if a was taking a medication for anxiety or depression at baseline
  - Depression per PROMIS 29: a baseline depression score will be derived using the 4 depression questions on the PROMIS 29 at baseline. The total depression score will range from 4 to 20 (see Appendix 13.8).
  - Anxiety per PROMIS 29: a baseline depression score will be derived using the 4 depression questions on the PROMIS 29 at baseline. The total anxiety score will range from 4 to 20 (see Appendix 13.8).
  - Fatigue per PROMIS 29: a baseline fatigue score will be derived using the 4 fatigue questions the PROMIS 29 at baseline. The total fatigue score will range from 4 to 20 (see Appendix 13.8).
  - Musculoskeletal BILAG score: an ordinal variable characterizing the musculoskeletal score at baseline defined as A=3, B=2, C=1, D/E=0
  - Total number of baseline tender joints
  - Total number of baseline swollen joints
  - Total number of baseline tender and swollen joints
  - Baseline DMARD and/or immunobiologic use
  - Baseline MMF use
  - Baseline Steroid use

  Only covariates with p-values ≤0.05 after backwards selection from the full model will be included.

  Model-based estimates for means at Days 1, 28, 56, and 84, adjusted for all covariates at their baseline means, and for mean change from Day 1 to Days 28, 56, and 84 along with standard errors and 95% confidence intervals will be presented for each treatment group. In addition, each active treatment arm will be compared to placebo by presenting the differences in mean change from Day 1 to Days 28, 56, and 84 along with standard errors and 95% confidence intervals.

7.3.2. Pain and Improvement Categories

Variables: The **pain category** for Visit x is defined using the average of maximum daily pain NRS score recorded during the 7 days preceding Visit *x.* For example, a Visit 3 occurring on Day 29 will use NRS scores over the 7-day interval from Day 22 to Day 28. For the 7-day average for Visit *x,* all available values reported in the 7-days interval will be used, but no imputation will be done for missing pain NRS scores. If no pain scores are available for the 7 days prior to Visit *x,* the 7-day average for Visit *x* will remain missing. Pain categories will be derived at Visits 1, 3, 4, 5 and 6 as follows:

No Pain	7-day average of maximum daily pain NRS ≤ 1
Mild Pain	7-day average of maximum daily pain NRS > 1 and ≤ 3
Moderate Pain	7-day average of maximum daily pain NRS > 3 and ≤ 7
Severe Pain	7-day average of maximum daily pain NRS > 7

In addition, the **improvement category** for Visit x is defined using the observed change in pain categories from the Visit 1 to Visits 3, 4, 5, and 6 as follows:

Major Improvement	Improvement by at least 2 pain categories from Visit 1
Improvement	Improvement by 1 pain category from Visit 1
No change	No change in pain category from Visit 1
Worsening	Worsening by at least 1 pain category from Visit 1

Population: For analyses on change from baseline variables, only individuals from the mITT population with an available post-baseline assessment are included.

Intercurrent Events: The intercurrent event strategy is as detailed in Section 7.2.3.

Analyses: The number and percent of subjects in each pain and improvement category will be presented by treatment group for each visit. For each post-baseline visit and treatment group, this table will also include the p-value for a test of symmetry to help identify notable shifts (e.g., towards improvement or worsening) from baseline (Visit 1).

Unless missing data are missing-completely-at-random (MCAR), suggesting subject loss is consistent across treatment groups and unrelated to treatment or disease, these estimates may be biased especially at later time points where more missing data are expected due to participant attrition. As such, treatment groups will be compared under the MAR assumption using estimates and tests derived from logistic regression models fit using the generalized estimating equation (GEE) approach. For these analyses, the pain categories will be dichotomized to “no pain or mild pain” and “moderate or severe pain”. The improvement categories will be dichotomized to “improvement” or “no

improvement". Proportional odds models may be explored if there are sufficient numbers across ordinal categories.

For each dichotomous outcome, the model will include fixed effects for visit, treatment, and the visit*treatment interaction and be fit using the GEE approach under the binomial distribution with the logit link. The model will be fit with an unstructured within-subject correlation structure across visits unless convergence problems arise, in which case an exchangeable correlation structure will be assumed.

The focus of the analysis will be on estimation of treatment effects. For each visit, estimated odds-ratios (with 95% CI) for pairwise comparisons with placebo and probabilities (with 95% CI) for each treatment group will be presented. The p-values for the 3 degree-of-freedom tests comparing each active treatment versus placebo at each visit will be presented. Since the difference between active treatment groups and placebo at Visit 5 (i.e., Day 84, end of treatment period) is of key interest, p-values for pairwise comparisons of each active group versus placebo will be presented. P-values are uncorrected for multiple comparison and will be interpreted with caution.

7.3.3. Percent Improvement Responder Status

At each visit, dichotomous responder status variables will be defined to indicate 30%, 50%, 75% or 100% improvement. The responder status for various percentage thresholds will be derived using the % change in pain, defined as follows:

$$\%\ change\ in\ pain = \frac{Visit\ 1_{7AVG} - Visit\ x_{7AVG}}{Visit\ 1_{7AVG}} \times 100$$

Where *x* is Visit 3 (Day 29), Visit 4 (Day 57), Visit 5 (Day 85) and Visit 6 (Day 113). The subscript 7AVG denotes the 7-day average maximum daily pain NRS score calculated using the 7 days prior to the

associated visit, as described for pain categories in Section 7.3.2. Positive values represent improvement.

If the % change in pain is greater than or equal to the percentage threshold, a subject will be considered a responder for that threshold at the associated visit. For example,

responder_30 = 1, %change in pain is ≥ 30%;
= 0, % change in pain < 30%;
= missing, if % change in pain is missing.

The population, intercurrent event strategy, and analyses for the response status variables will be analogous to those outlined in Section 7.3.2, *Pain and Improvement Categories*.

7.4. Estimands Supporting Secondary Objectives

P-values for all inferential analyses will be presented as a description of strength of evidence of relationships rather than tests of hypotheses. As such, no corrections for multiplicity are planned. Unless otherwise noted, all secondary analyses will be conducted using the mITT population.

7.4.1. Evaluation of Active Musculoskeletal Disease Activity

7.4.1.1. Physician Tender Joint Count

Variable: The Physician tender joint count will be assessed at Visit 1 and Visits 3 through 6. This assessment must be conducted in-person by a physician. Tenderness will be assessed in 68 joints, which include: upper—temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal and distal interphalangeal; lower—hip, knee, ankle, tarsus, metatarsophalangeal and interphalangeal. The change in the total number of tender joints from Visit 1 to each post-baseline visit will be computed.

Population: Analyses will use the mITT population. Inferential analysis will use the subset of the mITT subjects with at least one post-baseline assessment (Section 4.1).

Intercurrent Event Strategy: Physician tender joint count data, the intercurrent event strategy is as detailed in Section 7.2.3.

Population-level summary: Descriptive statistics on the physician tender joint count will be presented for each visit. The change in physician tender joint count from Visit 1 (Day 1) to Visits 3 (Day 26), 4 (Day 57), 5 (Day 85), and 6 (Day 113) will be evaluated using a repeated measures mixed model. The fixed effect model will be fit with no intercept and include interaction terms for the baseline tender joint count (centered at the baseline mean for the mITT population)-by-visit (categorical) and treatment group*visit. Parameter estimates for the treatment group*visit effects will be the estimated treatment means at each visit adjusted for differences at baseline. The random effects will include subject-level intercepts and slopes for time and time squared (as defined in Section 7.2.4) using separate unstructured covariance structures for placebo and pooled active treatments. This model is analogous to fitting separate analysis of covariance models for each visit but takes advantage of the multiple measures within subject to generate unbiased estimate in the presence of missing data under the missing-at-

random assumption. Model-based estimates and 95% CI for mean change from baseline will be presented for each treatment group at each post-baseline time-point. Estimated treatment group differences in mean change from baseline versus placebo with 95% CI will also be presented at each post-baseline time-point. The p-value for the test of overall treatment group effect will be presented at Day 85. If this p-value is <0.05, then p-values for pairwise comparisons of active groups versus placebo will be presented. Denominator degrees of freedom will be estimated using the Kenward-Rogers approach.

The post-treatment time point, Visit 6 (Day 113), is not included in this model. To explain, in order to account for missing data under the missing-at-random assumption, the estimated subject-level trajectories over time (i.e., random effects) are used to estimate fixed-effect for treatment at each visit. If active treatment is effective in reducing joint counts, then that effect could wane after treatment is stopped. Hence, including this post-treatment time point in the random effect model that estimates subject-level trajectories over time could bias the fixed effects treatment estimates. Should model results show interesting treatment effects during the treatment period, the persistence of trends after treatment is stopped may be explored by modifying the model to include Visit 6 (Day 113) as a fixed effect and exploring different random effect models to appropriately account for a possible post-treatment change in subject-level trajectories.

7.4.1.2.Physician Swollen Joint Count

Variable: The Physician swollen joint count will be assessed at Visit 1 and Visits 3 through 6. This assessment must be conducted in-person by a physician. Swollenness will be assessed in 66 joints, which include: upper—temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal and distal interphalangeal; lower—hip, knee, ankle, tarsus, metatarsophalangeal and interphalangeal. The change in the total number of swollen joints from Visit 1 to each post-baseline visit will be computed.

The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.1.3.Physician Tender and Swollen Joint Count

Variable: The number of joints that are both tender and swollen will be calculated at Visit 1 and Visits 3 through 6 using the Physician Tender Joint Count (as described in Section 7.4.1.1) and Physician Swollen Joint Count (as described in Section 7.4.1.2). The change in the total number of joints that are both tender and swollen from Visit 1 to each post-baseline visit will be computed.

The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.1.4.SELENA SLEDAI Score

Variable: At Visit 1 and Visits 3 through 6, study investigators complete the SLEDAI scale by indicating of presence of 24 SLE disease manifestations during the preceding 30 days. The original SLEDAI instrument includes an evaluation of proteinuria based on the protein:

creatinine ratio derived from a 24-hour urine. For this study, the protein: creatinine ratio will typically be derived from the spot urine assessment, although a 24-hour urine may be used if the spot urine assessment is not available. Each of the 24 disease manifestations has an assigned weight (see Appendix 13.3). Two systems can score a maximum of 8 points each, 2 systems can score a maximum of 4 points each, 3 systems can score a maximum of 2 points each, and 2 systems can score a maximum of 1 point each. The SLEDAI total score will be computed as the sum of the weights for the items indicated as present and can range from 0 to 105 points. If a component of the SLEDAI that is assessed using laboratory results (Questions 11-14, 20-21 or 23-24) was missed at a visit, then the missing data will be imputed by using the last observation carried forward approach. If a component of the SLEDAI is missed over consecutive visits, then the subsequent components will not be imputed. If any other component was missed, the score will not be computed.

The change in the SLEDAI total score from Visit 1 to each post-baseline visit will be computed.

The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.1.5.BILAG 2004 Total Score

Variable: The British Isles Lupus Assessment Group (BILAG) 2004 (2009 Revision) instrument will be completed at Screening, Visit 1, and Visits 3 through 6 for all subjects.

The rules for scoring the BILAG 2004 are in Appendix 13.4 BILAG 2004 Index Scoring. In each of the nine body system categories (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematological) subjects are assessed on a variety of disease activity criteria. Each category is then scored as an A, B, C, or D/E, where A indicates most severe disease activity and D/E indicates inactive/no disease activity. For this study the following additional scoring rules are applied:

1. According to the scoring algorithm, D means "Inactive disease but previously affected", and E means "System never involved". Since we may not know whether the subject has ever experienced involvement in a particular system prior to starting the study, we will not attempt to distinguish between D and E. Subjects will be assigned the score “D/E” if they did not meet the criteria for A, B, or C at the particular visit.

2. In the Renal category, some of the scoring rules require looking at previous measurements to assess change (e.g., GFR < 80 ml/min per 1.73 m^2 and having fallen to < 67% of previous value). BILAG is collected at Screening and may require further information (e.g., a pre-screening GFR) in order to ascertain a score. Under the following circumstances, sites will be asked to report recent (within 3 months of Screening) results in an attempt to fully score the renal category at Screening:
    - Urine protein: creatinine ratio ≥ 50 mg/mmol
    - Serum creatinine > 1.47 mg/dL (or 130 μmol/L)
    - GFR < 80 ml/min per 1.73 m^2

    However, if these data are not available and it can be confirmed that that the Renal category would not score to an A, the subject may proceed in the study. Since it is not possible to determine if the score is a B, C or D/E in these cases, the subject will be missing a Renal score at Screening.

3. In the Renal category, the original instrument includes an evaluation of proteinuria based on the protein: creatinine ratio derived from a 24-hour urine. For this study, the protein: creatinine ratio will typically be derived from the spot urine assessment although a 24-hour urine may be used if the spot urine assessment is not available.

A numerical BILAG total score will be computed using the coding scheme proposed by Yee et al. For each of the nine domains, a numerical score will be assigned based on the BILAG score as follows: A=12, B=8, C=1 and D/E=0. A single numerical BILAG total score will be calculated for each participant visit as the summation of the numerical scores for each of the nine domains. The change in the BILAG total score from Visit 1 to each post-baseline visit will be computed.

The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.1.6.Arthritis on the SELENA-SLEDAI

Variable: The SELENA SLEDAI score is assessed as described in Section 7.4.1.4, *SELENA SLEDAI Score*. Question 9 on this instrument (see Appendix 13.3) assesses arthritis (present or absent), defined as more than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).

The change (improved, no change, worsened) from Visit 1 to each post-baseline visit will be computed. In addition, for evaluating longitudinal trends, a dichotomous response status variable at each follow-up visit will be defined as follows:

- Improvement: Change from baseline score of “Improved” (e.g., present to not present)
- No Improvement: Change from baseline score of “No Change” or “Worsened”

The population and intercurrent event strategy will be analogous to those outlined in Section 7.3.2, *Pain and Improvement Categories*.

Analyses: Descriptive statistics summarizing the number and percentage of subjects with arthritis marked as present or absent will be summarized by treatment group and visit. The change (improved, no change, worsened) from Visit 1 to each post-baseline visit will also be summarized descriptively by treatment group and visit. To help identify notable shifts from baseline, either improvement or worsening, the p-value for McNemar’s test for symmetry will also be presented for each post-treatment visit and treatment group.

The longitudinal GEE models for the presence/absence of arthritis and the dichotomous response status variables will be analogous to those outlined in Section 7.3.2, *Pain and Improvement Categories*.

7.4.1.7.BILAG-based Arthritis Severity Assessment

Variable: At Visit 1 (baseline), the ordinal BILAG-based arthritis severity category is defined as per Section 5.2. The definition of “Improvement” during the treatment period (i.e., Visits 3 (Day 29), 4 (Day 57) and 5 (Day 85)) depends on baseline severity category, as follows:

i. If the BILAG-based arthritis severity category is Severe at baseline, then improvement is demonstrated if
   - The Arthritis Severe item is scored as Improved or Not Present at least once on Days 29, 57 or 85, AND the Arthritis Severe item is not scored as Worse or New on any of those days, AND the Arthritis Moderate item is not scored as Worse or New on any of those days, or if
   - The Arthritis Severe item is scored as Not Present on Day 85.

ii. If the BILAG-based arthritis severity category is Moderate at baseline, then improvement is demonstrated if
   - The Arthritis Moderate item is scored as Improved or Not Present at least once on Days 29, 57 or 85, AND the Arthritis Severe item is not scored as Worse or New on any of those days, AND the Arthritis Moderate item is not scored as Worse or New on any of those days, or if
   - The Arthritis Moderate item is scored as Not Present on Day 85.

iii. If the BILAG-based arthritis severity category is Mild at baseline, then improvement is demonstrated if
   - The Arthritis Mild item is scored as Improved or Not Present at least once on Days 29, 57 or 85, AND the Arthritis Severe item is not scored as Worse or New on any of those days, AND the Arthritis Moderate item is not scored as Worse or New on any of those days, AND the Arthritis Mild item is not scored as Worse or New on any of those days, or if
   - The Arthritis Mild item is scored as Not Present on Day 85.

The population for these analyses is limited to the subset of individuals who have arthritis at Visit 1 and who have data available for Visits 3-5. The intercurrent event strategy requires complete data.

Analyses: Descriptive statistics summarizing the number and percentage of subjects who improved during the treatment period will be presented by treatment group for each baseline BILAG-based arthritis severity category and overall. The help identify notable differences among treatment arms in the proportion who improved, the p-value for the Mantel-Haenszel chi-squared test after adjusting for baseline BILAG-based arthritis severity category. If this p-value is <0.05, pair-wise comparisons for each active arm versus placebo will also be presented.

7.4.1.8. Physician's Global Assessment

Variable: The Physician's Global Assessment (PGA) will be completed at Screening, Visit 1, and Visits 3 through 6. The PGA utilizes a 0 to 3 visual analogue scale that is anchored by the following descriptors:

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The change in the PGA from Visit 1 to each post-baseline visit will be computed.

The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.1.9. SLE Responder Index

Variable: The SLE Responder Index (SRI) will define a responder as having met all of the following conditions:

- ≥ 4 point reduction in the SELENA SLEDAI score from Visit 1 (Day 1)
- No new BILAG A or no more than 1 new BILAG B domain score from Visit 1 (Day 1)
- No deterioration from baseline in the PGA, defined as an increase of ≥ 0.3 points from Visit 1 (Day 1)

The population, intercurrent event strategy, and analyses for the response status variables will be analogous to those outlined in Section 7.3.2, *Pain and Improvement Categories*.

7.4.2. Evaluation of Patient-reported Outcomes

7.4.2.1. Lupus Activity Patient Global Assessment

Variable: The Lupus Activity Patient Global Assessment will be completed at Screening, Visit 1, and Visits 3 through 6. The Lupus Activity Patient Global Assessment utilizes a 0 to 100 mm visual analogue scale that is anchored by the two descriptors: not active (score of 0) and extremely active (score of 100). The recall period for this assessment is one week.

The change in the Lupus Activity Patient Global Assessment from Visit 1 to each post-baseline visit will be computed.

The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.2.2. PROMIS-29 Short Form

Variable: The PROMIS-29 will be completed at Screening, Visit 1, and Visits 3 through 6. The PROMIS-29 contains 29 items which include 4 items each from the following domains known to impact activities of daily living: physical function, sleep disturbance, depression, anxiety, fatigue, pain interference, pain intensity, and social role satisfaction. The final item is an 11-point pain intensity numerical rating scale (NRS) by which the subject rates their average pain over the past 7 days from 0 (no pain) to 10 (worst pain imaginable). With the exception of physical function, which does not include a time frame, all item banks reference the past 7 days. Two scores are available for each PROMIS domain: the total raw score and transformed score (T-score). To find the total raw score for a domain, all items must be answered. The total raw score will be derived as the sum of the values associated with the response to each question (see Appendix 13.8). The total raw summed score can range from 4 to 20 for each domain. The total raw summed score will then be translated into a T-score for each participant using the associated table in the scoring guide found in

Attachment 14.1. The T-score will be analyzed in this study. The change in the T-score from Visit 1 to each post-baseline visit will be computed for each domain.

Analysis: The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.2.3. PROMIS v2.0 – Cognitive Function Short Form 8a

Variable: The PROMIS v2.0 Cognitive Function will be completed at Screening, Visit 1, and Visits 3 through 6. The PROMIS Cognitive Function will be scored using the 8-question short form. Two scores are available for the PROMIS Cognitive function scoring: the total raw score and transformed score (T-score). To find the total row score, all items must be answered. The total raw score will be derived as the sum of the values associated with the response to each question (see Appendix 13.9). The total raw score can range from 8 to 40. The total raw summed score will then be translated into a T-score for each participant using the associated scoring table in the scoring guide found in Attachment 14.1. The T-score will be analyzed in this study. The change in the T-score from Visit 1 to each post-baseline visit will be computed.

Analysis: The population, intercurrent event strategy, and analyses will be analogous to those specified in Section 7.4.1.1, *Physician Tender Joint Count*.

7.4.2.4. Treatment Satisfaction Survey

At the end of treatment, both the subject and the physician will complete separately a survey asking what treatment assignment they think that the subject received (JBT-101, placebo, can't tell), whether the subject received benefit from the assigned treatment (yes or no), and whether the subject or physician would choose to continue that treatment (yes or no).

Analysis: The number and percentage of subjects will be presented for each question and answer by treatment group.

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4.3 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

Safety will be analyzed in each dose group through the reporting of adverse events (AEs), vital signs, physical examination findings, ECG findings, and changes in routine laboratory values.

Listings will be prepared for all safety measurements. All listings will be sorted in order of treatment, subject identifier (ID), and time of assessment (e.g., visit, time, and/or event).}

8.2. Extent of Exposure

Duration of exposure will be defined as the last dose date – first dose date + 1. Descriptive statistics will be presented by treatment arm.

8.3. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 23.0). The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. As such, no additional data manipulation is needed to identify events.

AEs will be collected from screening through study termination. Treatment-emergent AEs will be identified as those with an onset date on or after the first dose of study medication. If the start of the AE in relation to the start of study medication cannot be established (e.g., the start date for the AE is missing), then the AE will be considered treatment-emergent. If an abnormal laboratory finding or an abnormal pre-dose ECG is reported as an AE on the first day of study drug (Day 1), these events will not be considered treatment emergent since these assessments occur prior to treatment initiation. All data tabulations will be of only treatment-emergent events while non-treatment-emergent AEs will be listed separately.

An overall summary table will be developed to report the number of events and the number and percentage of subjects having at least one event in the following categories:

- AEs
- AEs indicated as serious
- Adverse Events of Special Interest (AESIs)
- AESIs by the following AESI criteria:
    - QTc prolongation > 500 msec total duration and > 60 msec from Visit 1 (Day 1) QTc interval prior to study drug administration
    - Severe disease flares by SELENA SLEDAI Flare Index and/or a new BILAG A score except in musculoskeletal domain
    - Aspartate aminotransferase or alanine aminotransferase ≥ 3 x upper limit of normal and total bilirubin > 1.5 x the upper limit of normal, present on repeat testing
- AEs that lead to study drug discontinuation
- AEs deemed at least possibly related to study drug that led to study drug discontinuation
- AEs with an outcome of death
- AEs that were reported as being related to a study drug
- AEs reported by severity
- Grade 3 or higher AE deemed at least possibly related to study drug

In addition, AEs classified by MedDRA SOC, and preferred term will be summarized for each treatment group and overall, for each of the following:

- All AEs
- All SAEs

Summary tables will present the total number of events, the number and percentage of subjects experiencing the events, and the incidence density for each treatment arm and overall. If a subject experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of subjects experiencing the events, a subject will only be counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of subjects in the safety population. To account for differential follow-up time between treatment arms, incidence density will be presented and calculated for each treatment arm as the number of AEs divided by the time of exposure aggregated across participants (person-weeks).

For the pre-specified safety endpoints, including Grade 3 or higher related AEs, QTc prolongation AESIs, elevated liver function test AESIs, and all related AEs, Poisson regression models will be fit. Point estimates for incidence densities with 95% CIs will be presented for each arm. In addition, for each active arm, the incidence density ratio compared with placebo will be presented with the 95% CIs.

Separate data listings will be provided for treatment-related AEs and AEs leading to study drug discontinuation.

8.4. Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be listed and summarized in the same manner described in Section 8.3. Separate displays listing and summarizing death, including time to death and cause of death, will also be created.

8.5. Clinical Laboratory Evaluation

Clinical laboratory measurements include serum chemistry, hematology, urinalysis (microscopic and spot protein: creatinine), anti-dsDNA antibodies, C3, C4, and C-reactive protein. Laboratory results will be reported from a central lab. However, sites can additionally report unscheduled results performed locally in the EDC. Local results will be converted to standardized units where possible. Changes in laboratory parameters that represent increases NCI-CTCAE severity grade over time are captured as AEs and summarized as described in Section 8.3.

For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each treatment group and overall. For categorical laboratory results, the number and percentage of subjects reporting each result will be presented for each treatment group and overall.

Laboratory data will be plotted to show patterns over time. Summary statistics including 25th percentile, median, and 75th percentile will be plotted for each visit by treatment group. Lines connecting individual subject results from subjects with grade 2 or higher values will be overlaid on each figure. For lab results that are not gradable, results from subjects with values outside of 2 *upper limit of

normal or 0.5*lower limit of normal will be overlaid. Tests with qualitative results (such as “present” or “positive”) will not be plotted.

8.6. Other Observations Related to Safety

8.6.1. Disease Flares

Disease flares will be assessed using BILAG and SLEDAI scoring criteria. BILAG 2004 disease flares will be defined as one new BILAG A or two new BILAG B scores from the previous visit. A BILAG flare will not be considered resolved until the score returns to a score of D/E. For example, a BILAG score of C at Visit 1 that increases to a B at Visit 2, decreases to a score of C at Visit 3, and increases to a score of B at Visit 4, will only be considered as new BILAG B score at Visit 2.

The SELENA SLEDAI flare instrument assesses SLE flares based on changes in the SLEDAI score, the PGA, medication use, other disease activity criteria and hospitalization due to SLE. See Appendix 13.3 for more information on scoring of the SELENA SLEDAI flare instrument. For each subject, yes/no variables will be created to indicate whether a subject had a mild/moderate flare or whether a subject had a severe flare at each visit. A subject will only be counted as the flare type of maximum severity. E.g., if a subject has a severe flare, they will not be counted as also having a mild/moderate flare.

The number and percent of subjects experiencing any flare overall during the study and the number and percentage of subjects experiencing each of the following flare types will be summarized descriptively:

- One new BILAG A score
- Two new BILAG B scores
- Mild/moderate SELENA SLEDAI flare
- Severe SELENA SLEDAI flare
- Severe SELENA SLEDAI flare, excluding those trigged **only** by the new prescription of major immunosuppressive for SLE activity criterion

In addition, the number and percent of subjects experiencing at least one flare by each visit will be summarized descriptively overall and by flare type.

In addition, the total number of flares and incidence density defined as the number of flares divided by the person-time of exposure aggregated in each treatment arm will be presented overall and for each flare type. A Poisson regression model will be fit and incidence density ratios with 95% CI for each active arm will be presented compared to placebo. Timeline plots indicating flares over time for each subject will be presented by treatment arm.

8.6.2. ARCI-M

The ARCI-M questionnaire will be completed by subjects at Visit1 (Day 1) pre- and post-dosing, Visit 3 (Day 29) and Visit 5 (Day 85). This is a 12-item true/false questionnaire developed by the National Institutes of Drug Abuse, designed to detect the full range of subjective responses experienced by marijuana users. An answer of true has an assigned value of 1 and an answer of false has an assigned value of 0. The ARCI-M score will be computed as the sum of the assigned values for all 12 questions and can range from 0 to 12. If a question is missed, the score will not be calculated.

The number and percentage of subjects experiencing an increase of ≥ 1 from the Visit 1 (Day 1) pre-dose assessment will be presented at Visit 1 (Day 1) post-dose, Visit 3 (Day 29) and Visit 5 (Day 85).

8.6.3. New or Increased SLE Medications

Medications will be collected in an ongoing log throughout the study. The following medications for SLE are either expected to remain stable or are disallowed during the course of the study:

- Systemic corticosteroids (including oral, intra-articular, intravenous and intramuscular)
- Cyclophosphamide or anti-TNFalpha biologic agents
- Rituximab, ocrelizumab, anti-CD22 monoclonal antibody
- Methotrexate, mycophenolate, azathioprine, leflunomide, belimumab, cyclosporine, or tacrolimus
- Narcotic analgesics for SLE activity

The above medications will be identified using the coded medication data. Any of these medications that are newly prescribed or increased in dose following treatment initiation will be flagged and the study day of the new or increase will be recorded.

A time to event analysis will be performed on the time from treatment initiation until first new or increase in medication for SLE. Participants who prematurely terminate from the study will be censored at the time of last follow-up. The probability of event will be presented graphically using Kaplan-Meier curves by treatment group. Kaplan-Meier estimates of event-free survival and confidence intervals using Greenwood's formula for standard error will be reported by treatment group at Day 85. A log rank test (2-sided α=0.05) will be performed to test the hypothesis that there is no difference between the survival curves by treatment arm.

9. OTHER ANALYSES

9.1. Use of Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version 2017.03). Medications reported on the CRF will be categorized for analysis as prior, concomitant, or after study treatment by comparing the medication start and stop dates with the first and last dose of study medication dates. Prior medications will have both the medication start and stop dates prior to the first dose of study medication date. After medications will have both the medication start and stop dates after the last dose of study medication date. All other medications will be classified as concomitant, indicating that use of the medication overlapped with use of the study medication by at least one day.

Medications received prior to, concomitant with, and after study medications will be listed.

10. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The Autoimmune DSMB will be chartered to review safety data and to make recommendations regarding

continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly. The discontinuation of study treatment will also be periodically reported to the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Section 8.3.2.1 of the protocol states, “In the event of convergence problems using an unstructured covariance matrix with within-subject random effects for intercept and slopes for time and time^2, that the covariance structure will be simplified by dropping the random effect for time^2.” Upon exploration of masked data, convergence problems can be avoided by rescaling the time variable as detailed in Section 7.2.4. However, we have also included the option to explore alternative covariance structures. In addition, the Dunnett’s correction for multiple comparisons was planned for the pairwise step-down test. However, the operational characteristic of this correction when using Kenward-Rogers degrees of freedom are unknown. Hence, we have opted to use a simple Bonferroni-correction, which should not be overly conservative for 3 comparisons.

Section 8.3.2.1 of the protocol states, “The fixed effects model will include treatment group, time, time^2, time- and time^2 by treatment group interactions, as well as the Screening 7-day average maximum daily pain NRS as a covariate.” An additional covariate for the Screening FSS Score will be added to the model. Including both the Screening 7-day average maximum daily pain NRS and Screening FSS Score as covariates should adequately control for random imbalances of baseline pain between the treatment arms. The decision to add Screening FSS Score as a covariate was agreed upon prior to finalization of Version 1.0 of the SAP, however due to an oversight was not included in Version 1.0. This issue was identified after database lock and unblinding, but prior to conducting the unblinded analyses. Since there was email documentation (see Appendix 13.11) that this edit was intended to be made prior to finalizing Version 1.0 of the SAP, the study team revised the SAP to Version 2.0 to include this covariate.

12. REFERENCES

1. Yee CS, Cresswell L, Farewell V et al. Numerical scoring for the BILAG-2004 index. Rheumatology 2010;49:1665_9.

13. APPENDICES

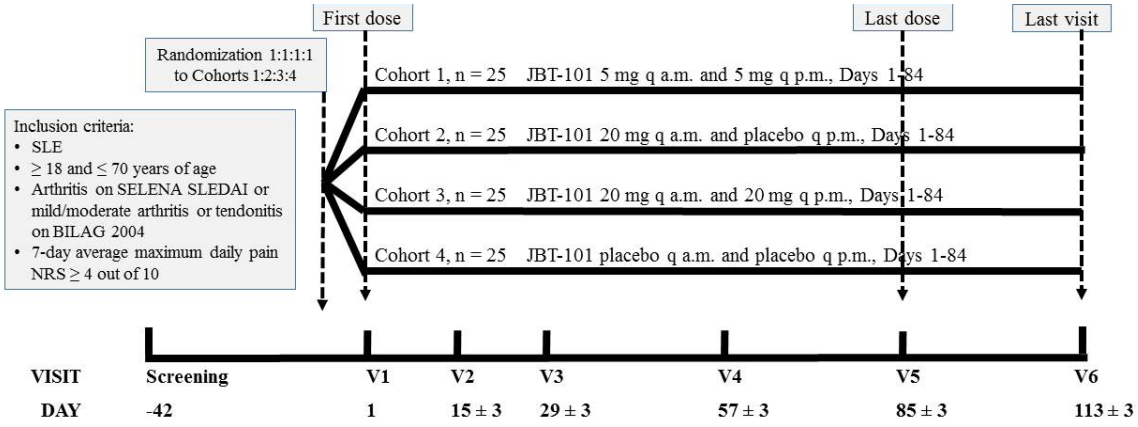
13.1. Schedule of Events

		Treatment					Post Treatment		Unscheduled Visit
Time Point	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Early Withdrawal Visit** *(if needed)*	
Visit Windows (Days)	**Up to -42**	**Day 1**	**Day 15 ± 3**	**Day 29 ± 3**	**Day 57 ± 3**	**Day 85 ± 3**	**Day 113 ± 3**		
Clinical Blood Draw (mL)	20-23	11	8	11	11	11	11	11	11
Research Blood Draw (mL)	NA	48.5	34	10.5	NA	40.5	40.5	40.5	NA
Visit Draw Total (mL)	20-23	59.5	42	21.5	11	51.5	51.5	51.5	11
General Assessments									
Informed Consent	X								
Demographics	X								
Verify Eligibility Criteria		X							
Medical History	X								
Assess reproductive and birth control	X								
Last menstrual period	X	X[B]		X[B]	X[B]	X[B]	X[B]	X[B]	
Prior/ Concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X	X	X	X	X	X
Register subject in IVRS system	X								
Randomization, prior to Day 1	X								
Vital signs: Weight, blood pressure and pulse[C], respiratory rate, and temperature (& height at Visit 1)	X	X	X	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X	X	X	X
12-lead electrocardiograms, QT/QTc analyses	X	X[D]				X			
Patient Reports									
Maximum daily pain NRS score[E]	Reported daily by subject via IVRS								
Review reported pain NRS scores	Site personnel will review subject reported data each week								
Addiction Research Center Inventory-		X[D]		X		X		X[F]	
Lupus Activity Patient Global Assessment		X		X	X	X	X	X	
PROMIS-29 Short Form		X		X	X	X	X	X	
PROMIS Item Bank v2.0 - Cognitive		X		X	X	X	X	X	
Fibromyalgia Symptom Scale	X	X				X	X	X	
Treatment Satisfaction Survey[G]						X		X[G]	
Physician Assessment									
66/68 Joint Count		X		X	X	X	X	X	
SELENA SLEDAI	X	X		X	X	X	X	X	
BILAG 2004	X	X		X	X	X	X	X	
Physician's Global Assessment	X	X		X	X	X	X	X	
Treatment Satisfaction Survey						X		X[G]	

		Treatment					Post Treatment		Unscheduled Visit
Time Point	**Screeni**	**1**	**2**	**3**	**4**	**5**	**6**	**Early Withdra**	
Visit Windows (Days)	**Up to -**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day**		
Clinical Laboratory Assessments									
Infectious Disease: Hepatitis B and C	X								
Tuberculosis screening test[I]	X								
Follicle stimulating hormone[J]	X								
Hematology: CBC with differential cell	X	X[L]	X	X	X	X	X	X	X[M]
Chemistry: Complete metabolic panel[K]	X	X[L]	X	X	X	X	X	X	X[M]
Anti-dsDNA antibodies, C3, C4	X	X[L]		X	X	X	X	X	X[M]
C-reactive protein		X[L]		X		X	X	X	X[M]
Urinalysis: Microscopic, & spot	X	X[L]		X	X	X	X	X	X[M]
Urine pregnancy test[B]	X[N]	X[L]		X	X	X	X	X	X[M]
Blood Draws for Mechanistic Specimen Collection									
Whole blood Pro-Inflammatory		X[L]		X		X	X	X	
Plasma: Metabolipidomic profile/JBT-		X[DL]	X						
RNA: IFNα signature (2.5mL)		X[L]		X		X	X	X	
Serum: Future Use[O] (5mL)		X[L]		X		X	X	X	
PBMC: Future Use[O] (30mL)		X[L]	X			X	X	X	
Study Product									
Dispense study product[P]		X		X	X				
Administer study product in clinic[Q]		X							
Study product pill count			X	X	X	X	X	X	

A. The screening period can be any duration between 7 and 42 days prior to Visit 1 (Day 1), provided the duration is adequate to ensure the subject meets all inclusion and exclusion criteria and drug can be shipped to the site on time for that subject. Screening can take place over more than one visit to the clinic. Screening laboratory tests, other than HIV, hepatitis, or pregnancy testing, can be repeated at the investigator's discretion.
B. For women of childbearing potential.
C. Seated (> 5 minutes) blood pressure and pulse.
D. Will be measured at Visit 1 (Day 1) both before and 2.5 to 3.5 hours after administration of study product in the clinic.
E. Record within 24 hours after most recent diary entry to prevent reporting of the same data.
F. ARCI-M will be assessed at the Early Withdrawal Visit if a subject is withdrawn from the study or discontinues the study prior to Visit 6 (Day 113).
G. At the end of treatment, both the subject and physician will complete a Treatment Satisfaction Survey. If a subject withdrawals from treatment prior to Day 85, the Treatment Satisfaction Survey will be completed at the Early Withdrawal Visit.
H. Infectious disease screen including HIV antibody, hepatitis B surface antigen, hepatitis C virus (HCV) antibody with HCV RNA (PCR) if antibody positive (unless documented as negative within 12 weeks prior to the Screening visit).
I. TB testing will be done centrally using a QuantiFERON® blood test. Testing is optional if skin or blood testing was done within 12 months before Visit 1 (Day 1), with documented negative results. See section 6.1.10 *Tuberculosis Screening* for repeat testing options.
J. For women > 45 and ≤ 55 years of age with no menses for < 2 years.
K. Complete metabolic panel includes at least glucose, urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and calculated glomerular filtration rate.
L. Blood and urine tests will be performed prior to study product administration.
M. Laboratory tests as relevant to the reason for the unscheduled visit.
N. Pregnancy test at screening can be done through a blood or urine test.
O. If the subject provides written informed consent, blood samples, including serum, plasma, mRNA, and PBMC culture supernatants, will be stored for future unspecified studies related to JBT-101 or SLE.
P. Study product will be dispensed in women of childbearing potential only if urine pregnancy test is negative.
Q. The first dose of study product at Visit 1 (Day 1) will be taken in clinic from the dispensed study product. The subject will be observed for 30 minutes or until stable in the judgment of the investigator, whichever is longer.

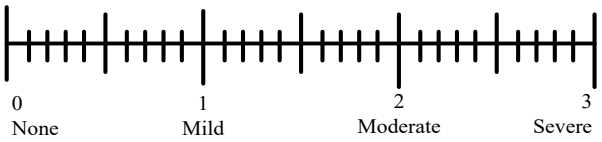
13.2. Study Flow Chart



13.3. SELENA SLEDAI and Flare Index

***Note: The Physician's Global Assessment must be completed AFTER lab results have been received and the 24 descriptors included in the SELENA-SLEDAI above have been assessed.**

PHYSICIAN'S GLOBAL ASSESSMENT:
(3in)



Length of line (measure from 0 to vertical assessment by tenths using markings provided) _____

Date of PGA Assessment (dd/mon/yyyy): _____

SELENA-SLEDAI					
Check "Present" if descriptor is present at the time of visit or in the preceding 30 days.					
#	Descriptor	Definition	Present	Absent	Weight
1	**Seizure**	Recent onset. Exclude metabolic, infectious, or drug cause, or seizure due to past irreversible CNS damage.	❑	❑	**8**
2	**Psychosis**	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.	❑	❑	**8**
3	**Organic brain syndrome**	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.	❑	❑	**8**
4	**Visual disturbance**	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates, or hemorrhages in the choroid, optic neuritis, scleritis, or episcleritis. Exclude hypertension, infection, or drug causes.	❑	❑	**8**
5	**Cranial nerve disorder**	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.	❑	❑	**8**
6	**Lupus headache**	Severe, persistent headache: may be migrainous, but nonresponsive to narcotic analgesia.	❑	❑	**8**

SELENA-SLEDAI					
Check “Present” if descriptor is present at the time of visit or in the preceding 30 days.					
#	Descriptor	Definition	Present	Absent	Weight
7	**CVA**	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.	❑	❑	**8**
8	**Vasculitis**	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.	❑	❑	**8**
9	**Arthritis**	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).	❑	❑	**4**
10	**Myositis**	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.	❑	❑	**4**
11	**Urinary casts**	Heme-granular or red blood cell casts.	❑	❑	**4**
12	**Hematuria**	> 5 red blood cells per high power field. Exclude stone, infection, or other causes.	❑	❑	**4**
13	**Proteinuria**	> 0.5 protein:creatinine ratio. New onset or recent increase of more than 0.5 on the protein:creatinine ratio. *Note: ALE09 will typically use a spot urine protein:creatinine ratio. If only the 24-hour urine is available, then proteinuria is defined as: “>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.”*	❑	❑	**4**
14	**Pyuria**	> 5 white blood cells per high power field. Exclude infection.	❑	❑	**4**
15	**Rash**	Ongoing inflammatory lupus rash.	❑	❑	**2**
16	**Alopecia**	Ongoing abnormal, patchy, or diffuse loss of hair due to active lupus.	❑	❑	**2**
17	**Mucosal ulcers**	Ongoing, oral or nasal ulcerations due to active lupus.	❑	❑	**2**
18	**Pleurisy**	Classic and severe pleuritic chest pain, or pleural rub, or effusion, or new pleural thickening due to lupus.	❑	❑	**2**
19	**Pericarditis**	Classic and severe pericardial pain, or rub, or effusion, or electrocardiogram confirmation.	❑	❑	**2**
20	**Low complement**	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.	❑	❑	**2**
21	**Increased DNA Binding**	> 25% binding by Farr assay or above normal range for testing laboratory.	❑	❑	**2**
22	**Fever**	> 38°C. Exclude infectious cause.	❑	❑	**1**

SELENA-SLEDAI					
Check "Present" if descriptor is present at the time of visit or in the preceding 30 days.					
#	Descriptor	Definition	Present	Absent	Weight
23	**Thrombocytopenia**	< 100,000 platelets/mm^3 *[equivalent to 100 x10^9/L]*	❑	❑	**1**
24	**Leukopenia**	< 3,000 white blood cells/mm^3 *[equivalent to 3 x10^9/L]* Exclude drug causes.	❑	❑	**1**

Total Score (sum of weights next to descriptors marked present)**:**

SELENA SLEDAI FLARE COMPOSITE	
Mild or Moderate Flare	**Severe Flare**
Change in SLEDAI instrument score of >=3 points from previous visit with a total score <= 12	Change in SLEDAI instrument score >= 1 from previous visit with a total score > 12
New or worse: • Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus • Nasopharyngeal ulcers • Pleuritis • Pericarditis • Arthritis • Fever (SLE)	New or worse: • CNS-SLE • Vasculitis • Nephritis • Myositis • Platelets < 60,000 • Hemolytic anemia: Hemoglobin <70g/L or decrease in Hemoglobin >30 g/L **Requiring:** double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization
Increase in prednisone, but not to >0.5mg/kg/day	Increase in prednisone to >0.5 mg/kg/day
Added NSAID or new prescription of hydroxychloroquine for SLE activiy	New prescription of cyclophosphamide, azathioprine, methotrexate, MMF or any other major immunosuppressive for SLE activity
Increase in PGA of >=1.0 from previous visit with a total PGA <= 2.5	Hospitalization for SLE Activity
	Increase in PGA of > 0 from previous visit with a total PGA>2.5

13.4 BILAG-2004 Index Scoring

- scoring based on the principle of physician's intention to treat

Category	Definition
A	**Severe disease activity requiring any of the following treatment:** **1. systemic high dose oral glucocorticoids (equivalent to prednisolone > 20 mg/day)** **2. intravenous pulse glucocorticoids (equivalent to pulse methylprednisolone ≥ 500 mg)** **3. systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis)** **4. therapeutic high dose anticoagulation in the presence of high dose steroids or immunomodulators** **eg: warfarin with target INR 3 - 4**
B	**Moderate disease activity requiring any of the following treatment:** **1. systemic low dose oral glucocorticoids (equivalent to prednisolone ≤ 20 mg/day)** **2. intramuscular or intra-articular or soft tissue glucocorticoids injection (equivalent to methylprednisolone < 500mg)** **3. topical glucocorticoids** **4. topical immunomodulators** **5. antimalarials or thalidomide or prasterone or acitretin** **6. symptomatic therapy** **eg: NSAIDs for inflammatory arthritis**
C	**Mild disease**
D	**Inactive disease but previously affected**
E	**System never involved**

CONSTITUTIONAL

Category A:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly
Anorexia

Category B:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly
Anorexia

BUT do not fulfil criteria for Category A

Category C
Pyrexia recorded as 1 (improving) **OR**

One or more of the following recorded as > 0:

Weight loss
Lymphadenopathy/Splenomegaly
Anorexia

BUT does not fulfil criteria for category A or B

Category D
Previous involvement

Category E
No previous involvement

MUCOCUTANEOUS

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - severe
Angio-oedema - severe
Mucosal ulceration - severe
Panniculitis/Bullous lupus - severe
Major cutaneous vasculitis/thrombosis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - mild
Panniculitis/Bullous lupus - mild
Digital infarcts or nodular vasculitis
Alopecia - severe

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Angio-oedema - mild
Mucosal ulceration - mild
Alopecia - mild
Periungual erythema/chilblains
Splinter haemorrhages

Category D
Previous involvement

Category E
No previous involvement

NEUROPSYCHIATRIC

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Aseptic meningitis
Cerebral vasculitis
Demyelinating syndrome
Myelopathy
Acute confusional state
Psychosis
Acute inflammatory demyelinating polyradiculoneuropathy
Mononeuropathy (single/multiplex)
Cranial neuropathy
Plexopathy
Polyneuropathy
Status epilepticus
Cerebellar ataxia

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Seizure disorder
Cerebrovascular disease (not due to vasculitis)
Cognitive dysfunction
Movement disorder
Autonomic disorder
Lupus headache - severe unremitting
Headache due to raised intracranial hypertension

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

MUSCULOSKELETAL

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Severe Myositis
Severe Arthritis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Mild Myositis
Moderate Arthritis/Tendonitis/Tenosynovitis

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Mild Arthritis/Arthralgia/Myalgia

Category D
Previous involvement

Category E
No previous involvement

CARDIORESPIRATORY

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Myocarditis/Endocarditis + Cardiac failure
Arrhythmia
New valvular dysfunction
Cardiac tamponade
Pleural effusion with dyspnoea
Pulmonary haemorrhage/vasculitis
Interstitial alveolitis/pneumonitis
Shrinking lung syndrome
Aortitis
Coronary vasculitis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Pleurisy/Pericarditis
Myocarditis - mild

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

GASTROINTESTINAL

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Peritonitis
Lupus enteritis/colitis
Intestinal pseudo-obstruction
Acute lupus cholecystitis
Acute lupus pancreatitis

Category B
Any Category A feature recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Abdominal serositis and/or ascites
Malabsorption
Protein losing enteropathy
Lupus hepatitis

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

OPHTHALMIC

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Orbital inflammation/myositis/proptosis
Keratitis - severe
Posterior uveitis/retinal vasculitis - severe
Scleritis - severe
Retinal/choroidal vaso-occlusive disease
Optic neuritis
Anterior ischaemic optic neuropathy

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Keratitis - mild
Anterior uveitis
Posterior uveitis/retinal vasculitis - mild
Scleritis – mild

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Episcleritis
Isolated cotton-wool spots (cytoid bodies)

Category D
Previous involvement

Category E
No previous involvement

RENAL

Category A
Two or more of the following **providing 1, 4 or 5 is included**:

1. Deteriorating proteinuria (severe) defined as

   (a) urine dipstick increased by ≥ 2 levels (used only if other methods of urine protein estimation not available); **or**

   (b) 24 hour urine protein > 1 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio > 100 mg/mmol that has not decreased (improved) by ≥ 25%; **or**
   (d) urine albumin-creatinine ratio > 100 mg/mmol that has not decreased (improved) by ≥ 25%

2. Accelerated hypertension
3. Deteriorating renal function (severe) defined as

   (a) plasma creatinine > 130 μmol/l and having risen to > 130% of previous value; **or**
   (b) GFR < 80 ml/min per 1.73 m^2 and having fallen to < 67% of previous value; **or**
   (c) GFR < 50 ml/min per 1.73 m^2, and last time was > 50 ml/min per 1.73 m^2 or was not measured.

4. Active urinary sediment
5. Histological evidence of active nephritis within last 3 months
6. Nephrotic syndrome

Category B
One of the following:

1. One of the Category A feature

2. Proteinuria (that has not fulfilled Category A criteria)
   (a) urine dipstick which has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); **or**

   (b) 24 hour urine protein ≥ 0.5 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥ 25%; **or**
   (d) urine albumin-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥ 25%

3. Plasma creatinine > 130 μmol/l and having risen to ≥ 115% but ≤ 130% of previous value

Category C
One of the following:

1. Mild/Stable proteinuria defined as

   (a) urine dipstick ≥ 1+ but has not fulfilled criteria for Category A & B (used only if other methods

of urine protein estimation not available); **or**
(b) 24 hour urine protein > 0.25 g but has not fulfilled criteria for Category A & B ; **or**
(c) urine protein-creatinine ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B; **or**
(d) urine albumin-creatinine ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B

2. Rising blood pressure (providing the recorded values are > 140/90 mm Hg) which has not fulfilled criteria for Category A & B, defined as

(a) systolic rise of ≥ 30 mm Hg; **and**
(b) diastolic rise of ≥ 15mm Hg

Category D
Previous involvement

Category E
No previous involvement

Note: although albumin-creatinine ratio and protein-creatinine ratio are different, we use the same cut-off values for this index

HAEMATOLOGICAL

Category A
TTP recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any of the following:

Evidence of haemolysis and Haemoglobin < 8 g/dl
Platelet count < 25 x 10^9/l

Category B
TTP recorded as 1 (improving) **OR**

Any of the following:

Evidence of haemolysis and Haemoglobin 8 - 9.9 g/dl
Haemoglobin < 8 g/dl (without haemolysis)
White cell count < 1.0 x 10^9/l
Neutrophil count < 0.5 x 10^9/l
Platelet count 25 - 49 x 10^9/l

Category C
Any of the following:

Evidence of haemolysis and Haemoglobin ≥ 10g/dl
Haemoglobin 8 - 10.9 g/dl (without haemolysis)
White cell count 1 - 3.9 x 10^9/l
Neutrophil count 0.5 - 1.9 x 10^9/l
Lymphocyte count < 1.0 x 10^9/L
Platelet count 50 - 149 x 10^9/l
Isolated Coombs' test positive

Category D
Previous involvement

Category E
No previous involvement

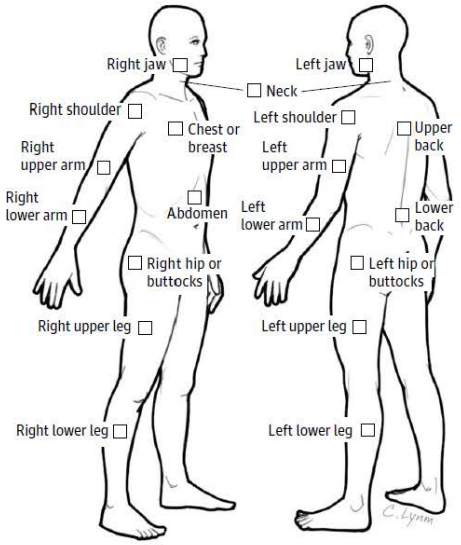
13.5 Fibromyalgia Symptom Scale

ALE09 FIBROMYALGIA SYMPTOM SCALE
REQUIRED SOURCE DOCUMENT
Rave EDC Page: Fibromyalgia Symptom Scale

PARTICIPANT ID: _____ **DATE OF ASSESSMENT:** _____
(dd/mon/yyyy)

Patient Self-report Survey for the Assessment of Fibromyalgia

(1) Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Check the boxes in the diagram for each area in which you have had pain or tenderness.



(2) For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.
- **No problem**
- **Slight or mild problem:** generally mild or intermittent
- **Moderate problem:** considerable problems; often present and/or at a moderate level
- **Severe problem:** continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

(3) During the **past 6 months** have you had any of the following symptoms?

A. Pain or cramps in lower abdomen	☐ No	☐ Yes
B. Depression	☐ No	☐ Yes
C. Headache	☐ No	☐ Yes

(4) Have the symptoms in questions 2-3 and pain been present at a similar level for at **least 3 months**?
☐ No ☐ Yes

(5) Do you have a disorder that would otherwise explain the pain?
☐ No ☐ Yes

Participant Initials: _____ **Date survey completed:** _____
(dd/mon/yyyy)

13.6 Lupus Activity Patient's Global Assessment

ALE09: JBT-101 in SLE | REQUIRED Source Document | Manual of Procedures

LUPUS ACTIVITY PATIENT'S GLOBAL ASSESSMENT
(100 mm VAS)
REQUIRED SOURCE DOCUMENT
Rave EDC Page: Lupus Activity Patient Global Assessment

Participant ID:_____ **Date of Assessment:** _____
(dd/mon/yyyy)

Patient Instructions: Please answer the question by placing a vertical (|) mark to indicate your response. Please initial and date this form. After you have finished, return the document to the ALE09 Study Coordinator.

Considering all the ways lupus affects you, mark a vertical line at the spot on the horizontal line to describe your disease activity within the last week.

0 100

Not Active Extremely Active

Participant Initials: _____ **Date:** _____

---------- **For Site Coordinator Use Only** ----------

Site Coordinator Directions: Use a metric ruler and measure (in millimeters) from the "0" to the horizontal line placed by the patient. Enter the distance in millimeters below next to "Length of line" and then transfer the information onto the "Lupus Activity Patient Global Assessment" CRF page. You should also measure the total length of the line from 0 to 100 and write this information below and enter into Rave EDC. Place this document with the subject's research record.

Length of line *(from 0 to vertical assessment line)* _____ mm *(round to the nearest mm)*

Total Length of line _____ mm

Initials of site personnel measuring the line: _____ **Date:** _____

ALE09: Lupus Activity Patient's Global Assessment | Page **1** of **1** | 02 June 2017

13.7 ARCI-M Questionnaire

ALE09 ADDICTION RESEARCH CENTER INVENTORY – MARIJUANA (ARCI-M)
POST-DOSE DATA COLLECTION WORKSHEET
REQUIRED SOURCE DOCUMENT
Rave EDC Page: ARCI-M Questionnaire

PARTICIPANT ID: _____

1. Things around me seem more pleasing than usual.
   - ❑ True
   - ❑ False
2. I feel as if something pleasant had just happened to me.
   - ❑ True
   - ❑ False
3. I have difficulty in remembering.
   - ❑ True
   - ❑ False
4. I feel a very pleasant emptiness.
   - ❑ True
   - ❑ False
5. My mouth feels very dry.
   - ❑ True
   - ❑ False
6. Some parts of my body are tingling.
   - ❑ True
   - ❑ False
7. I have a weird feeling.
   - ❑ True
   - ❑ False
8. My movements seem slower than usual.
   - ❑ True
   - ❑ False
9. I notice that my heart is beating faster.
   - ❑ True
   - ❑ False
10. My thoughts seem to come and go.
    - ❑ True
    - ❑ False
11. I notice my hand shakes when I try to write.
    - ❑ True
    - ❑ False
12. I have an increasing awareness of bodily sensations.
    - ❑ True
    - ❑ False

Participant Initials: _____ **Date survey completed** *(dd/mon/yyyy)*: _____
Assessment Time: ____:____ **AM/PM** *(Circle one)*

13.8 PROMIS-29 Short Form

PROMIS–29 Profile v2.0

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.0

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.0

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

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13.9 PROMIS Item Bank v2.0 - Cognitive Function Short Form 8a

PROMIS® Item Bank v2.0 – Cognitive Function- Short Form 8a

Cognitive Function- Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
PC2r	My thinking has been slow.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC35r	It has seemed like my brain was not working as well as usual.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC36r	I have had to work harder than usual to keep track of what I was doing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC42r	I have had trouble shifting back and forth between different activities that require thinking	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC8r	I have had trouble concentrating	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC25r	I have had to work really hard to pay attention or I would make a mistake	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC1r	I have had trouble forming thoughts	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC5r	I have had trouble adding or subtracting numbers in my head	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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13.10 Treatment Satisfaction Survey (Participant)

ALE09: JBT-101 in SLE | REQUIRED Source Document | Manual of Procedures

ALE09 TREATMENT SATISFACTION SURVEY (PARTICIPANT)
REQUIRED SOURCE DOCUMENT
Rave EDC Page: Treatment Satisfaction Survey

PARTICIPANT ID: _____ **DATE OF ASSESSMENT:** _____
(dd/mon/yyyy)

To be completed by the participant at the last visit prior to interaction with study staff, other than checking in.

QUESTION	ANSWER
1) Did you receive clinical benefit from the experimental drug treatment you received during this research study?	❑ Yes ❑ No
2) What treatment do you think you likely received during this study?	❑ JBT-101 ❑ Placebo ❑ Can't tell
3) Would you choose to continue taking the same experimental drug treatment that you received during this research study?	❑ Yes ❑ No

_____ **Participant initials**

_____ **Date survey completed**
(dd/mon/yyyy)

ALE09:Treatment Satisfaction Survey (Participant) Page **1** of **1** 20 December 2017

13.11 Email Documentation of Decision to Add Screening FSS as a Covariate

Lynette Keyes-Elstein

From: Margie Byron
Sent: Monday, February 28, 2022 9:55 AM
To: barbarawhitemd@yahoo.com; sconstantine@corbuspharma.com
Cc: Mackay, Meggan; Ding, Linna (NIH/NIAID) [E]; Welch, Beverly (NIH/NIAID) [E]; Mail ADCT ALE09 Project Management; Lynette Keyes-Elstein; Kati Steinmiller; Amanda Mickey
Subject: RE: [EXTERNAL] Re: ALE09_SAP_Draft_v0.4.docx

Hi Barbara and Scott,

Please see the below response to Barbara's comments on the ALE09 draft SAP:

Thank you for your careful read of the SAP. Although we will be making some of your suggested changes and corrections, we will not able to take your suggestions on some of the issues of most concern to you, because they are inconsistent with the protocol. Below we elaborate on a few points:

1. During protocol development, the team discussed whether to pick a single dose for the primary hypothesis, and the decision was no. The sense at the time was that ALL doses would work, and some on the team believed that the lowest dose might be the best. Hence, the sample size/power calculations for the study design were done using the 3 degree of freedom test, which looks at all 3 active doses vs placebo simultaneously. This test will be followed by three Bonferroni-adjusted 1-df "step-down tests" to compare each active treatment arm with placebo. If, as we originally postulated, all 3 dose groups perform better than placebo, then this approach should have more power than looking at a single dose vs placebo comparison. This is a common analysis plan for studies with multiple dosing groups, and the DSMB agreed it is a reasonable approach for the first study with this drug in this patient population.
2. Because the number of participants is sparse at the majority of study sites, inclusion of site as a covariate in the primary model is not practical. All sites are theoretically similar as they were chosen because of their expertise in lupus trials. Further, since the primary endpoint is patient-reported pain, the potential of a site effect is of less concern than it would be had the endpoint been based on a physician assessment. We could do a post-hoc analysis comparing Meggan's site with all-other-sites pooled if that seems worthwhile.
3. The primary analysis model already includes the average pain score over the 7-days prior to screening as a covariate. We have decided to add the screening Fibromyalgia score as well. These 2 covariates should adequately control for random imbalances of baseline pain between treatment arms. Since this is the first study in this patient population, we have no a priori reason for inclusion of other covariates in the primary model. Also, this is a relatively small study and inclusion of extraneous covariates would use up valuable degrees of freedom and reduce power. We will look at other covariates in secondary analyses.
4. We considered model assumptions in a blinded fashion prior to drafting the SAP, so we are confident these will be OK for the selected models.
5. The team has reviewed concomitant medications to identify use of SLE treatments and prohibited medications. There will be final review prior to data lock.

Thanks,
Margie Byron

Margie Byron
Senior Biostatistician
Rho, Inc.
2635 East NC Highway 54
Durham, NC 27713

Phone: 919-595-6454

From: Barbara White [mailto:barbarawhitemd@yahoo.com]
Sent: Monday, February 7, 2022 8:49 PM
To: Scott Constantine <sconstantine@corbuspharma.com>; Mackay, Meggan <mmackay@northwell.edu>
Subject: [EXTERNAL] Re: ALE09_SAP_Draft_v0.4.docx

Hi all, some substnatial comments from me. I think the approach to primary efficay analysis is wrong. I think the approach to fixed effects won't work. I think the approach to change in immunosuppressive medications has not been thought through in enough detail. There are a bunch of unnecessary analyses that will add a lot of time and expense, but not really add much to data understanding. I feel like the a grump after reading it. but thought I should mention my thoughts.

On Tuesday, January 18, 2022, 08:35:27 PM EST, Scott Constantine <sconstantine@corbuspharma.com> wrote:

Hi Barbara,

As mentioned attached please find the ALE09 SAP.

All the best,

Scott

14. ATTACHMENTS

14.1 PROMIS Adult Profile Instruments