C O N F I D E N T I A L

Autoimmunity Centers of Excellence

Protocol # ALE09

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

Short Title: JBT-101 in SLE

BB-IND #132445

Version 4.0: 05 October 2018

IND Sponsor: Division of Allergy, Immunology, and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)

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Protocol: ALE09 **Version/Date: v4.0 / 05 October 2018**

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

Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)

INSTRUCTIONS*: The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to:*

DAIT Regulatory Management Center (RMC)

Pharmaceutical Product Development (PPD)

3900 Paramount Parkway

Morrisville, NC 27560

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

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*)
    - 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

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- 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
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:

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• 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.

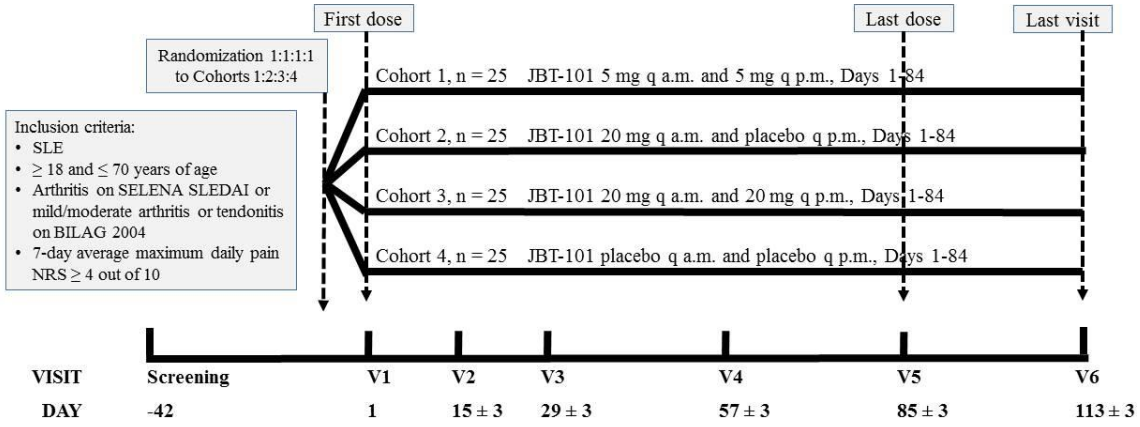
Lay Summary:

One hundred adults with SLE and active joint disease with at least moderate pain will be enrolled in this study to evaluate the safety, efficacy, and mechanisms of action of JBT-101.

JBT-101 is a synthetic endocannabinoid receptor type 2 (CB2) agonist and an activator of the body's normal processes to resolve innate immune responses without immunosuppression. JBT-101 induces a class switch in production of lipid mediators to increase production of "Specialized Pro-resolving lipid Mediators" (SPMs) while reducing production of pro-inflammatory mediators. In turn, SPMs trigger a physiologic network to resolve inflammation and fibrosis, and, when present, increase clearance of pathogens. With return to homeostasis, clinical benefit is expected to occur in people with SLE, for example, in those who have inflammation of the musculoskeletal system and associated pain.

Subjects will be randomized to receive 2 daily oral doses of JBT-101 (three groups of varying doses; JBT-101 10 mg daily, JBT-101 20 mg daily or JBT-101 40 mg daily) or placebo for 84 days and will continue to be followed for an additional 28 days. Subject visits to assess endpoints occur on Day 1, then every 2 weeks twice, then every 4 weeks three times, for six total visits after randomization. The study will compare changes over time in daily measures of the maximum pain NRS in treated groups compared to the placebo group after 12 weeks of treatment. Studies are also planned to evaluate tolerability and inflammation.

FLOW DIAGRAM OF PROTOCOL



ABBREVIATIONS

βHCG	β Human Chorionic Gonadotropin
ACE	Autoimmunity Centers of Excellence
ACR	American College of Rheumatology
ADCT	Autoimmune Diseases Clinical Trials
AE	Adverse event
ARCI-M	Addiction Research Center Inventory-Marijuana
AUC	Area under the curve
b.i.d.	Twice a day
BILAG	British Isles Lupus Activity Group
BP	Blood pressure
CB1	Cannabinoid type 1 receptor
CB2	Cannabinoid type 2 receptor
CBC	Complete blood count
CFR	Code of Federal Regulations
Cmax	Concentration maximum
Corbus	Corbus Pharmaceuticals Holdings, Inc.
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DEA	Drug Enforcement Administration
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FIMR	Feinstein Institute for Medical Research
GCP	Good Clinical Practice
HED	Human equivalent dose
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IFN	Interferon
IL	Interleukin
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-to-Treat or Intent-to-Treat
IVRS	Interactive voice-response system
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
NRS	Numerical rating scale

NSAIDs	Non-steroidal anti-inflammatory drugs
P	Pulse
PBMC	Peripheral blood mononuclear cells
PI	Principal Investigator
PP	Per Protocol
PPD	Purified protein derivative
PK	Pharmacokinetic
PROMIS	Patient-Reported Outcomes Measurement Information System
q.d.	Once per day
QTc	Corrected QT
R	Respiratory rate
RhoFED	Rho Federal Systems Division, Inc.
RMANOVA	Mixed models repeated measures analysis of variance
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SELENA	Safety of Estrogen in Lupus: National Assessment
SID	Subject identification number
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SP	Safety Population
SPMs	Specialized Pro-resolving Lipid Mediators
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TEAE	Treatment emergent adverse event
TNFα	Tumor necrosis factor α
ULN	Upper Limit of Normal

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1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Disease Background

1.1.1 Description and Epidemiology of Disease

Systemic lupus erythematosus (SLE) is a chronic and serious illness that has no cure and for which current therapeutic strategies have limited efficacy and significant toxicities.

SLE is a prototypical autoimmune disease with a wide array of clinical manifestations, including rash, photosensitivity, oral ulcers, arthritis, pleuritis, pericarditis, kidney problems, seizures and psychosis, and blood cell abnormalities [1]. Patients with SLE have an increased frequency of related autoimmune problems, such as Sjögren's syndrome and antiphospholipid syndrome (i.e., clotting problems, strokes, fetal loss) that require additional treatments. SLE may occur with other autoimmune conditions, such as thyroiditis, hemolytic anemia, and idiopathic thrombocytopenia purpura. Accelerated atherosclerosis among SLE patients is responsible for premature mortality [2, 3].

The musculoskeletal system is the most commonly involved system in SLE, with reported incidences of 69-95% in different series [4-6]. Arthritis is the most commonly reported of all 11 American College of Rheumatology (ACR) criteria for the diagnosis of SLE [1]. In addition, arthritis is the first manifestation of SLE in about 60-70% of patients [1, 7]. After five years of disease, joint involvement affects about 85% of patients [1]. Tendon inflammation, manifesting as tendonitis, tenosynovitis or tendon rupture, has been well described in SLE, occurring in 23-44% of patients [8-10]. A small percentage of SLE patients develop Jaccoud's arthropathy due to recurrent episodes of inflammation resulting in ligamentous laxity and joint subluxation. In addition to joint symptoms, generalized myalgia is frequently associated with SLE, occurring in as many as 80% of SLE cases [10]. This myalgia characteristically affects the deltoids and quadriceps and occurs during disease flares.

Musculoskeletal involvement in SLE is associated with pain. Chronic pain is a common entity for most SLE patients, resulting in a significant reduction in quality of life and productivity [11-14]. In focus groups of SLE patients, pain was the most frequently identified health issue, occurring in > 85% of patients [15]. Indeed, SLE patients have higher visual analogue pain scores than patients with rheumatoid arthritis [16]. Satisfaction of SLE patients with their medical care is inversely related to their level of pain [17].

In addition to pain caused by active musculoskeletal inflammation, SLE patients may experience pain from concurrent fibromyalgia. About 16-32% of SLE patients also meet criteria for fibromyalgia [18].

Improvement in patient-reported pain in SLE is associated with improvement in patient overall health [19]. Pain responders have greater improvement in Medical Outcome Study

Short Form-36 Survey scores, patient global health assessment scores, and Physician's Global Assessment, compared to non-responders [19].

1.1.2 Immunopathogenesis of Systemic Lupus Erythematosus

SLE is a disease characterized at a molecular level by loss of tolerance resulting in autoreactive B and T cells, abnormally primed dendritic cells, autoantibody production [20, 21], generation of immune complexes, and their deposition in tissues. The characteristic serologic feature of SLE is autoantibodies against one's own nucleic acid or DNA- or RNA-binding nuclear proteins [22]. These immune complexes have been shown to activate innate immune responses through toll-like receptors, Fcγ receptors and complement [23-25].

Chronic activation of innate immune responses by immune complexes in SLE can lead to production of pro-inflammatory cytokines such as type 1 interferons (IFNs), with subsequent local activation of dendritic cells, presentation of self-antigen, and perpetuation of autoimmunity. Interferons, particularly the type 1 IFNα, are implicated in the pathogenesis of SLE [26]. Many patients with SLE display up-regulation of type 1 IFN-inducible genes, referred to as the "type 1 IFN gene signature", and some have elevated serum levels of IFNα [27-29]. Elevated serum and tissue levels of multiple other pro-inflammatory cytokines, including IFNα, interleukin (IL)-1, IL-2, IL-6, IL-10, IL-12, IL-18, IFNγ, BAFF and tumor necrosis factor α (TNFα) have been implicated in the immune-pathogenesis of SLE [30-34]. These molecules mediate tissue destruction and contribute to breaking tolerance through effects on further B cell activation, auto-antibody production and expression of costimulatory molecules on lymphocytes[30, 35, 36] . Specifically, plasma levels of IL-6 have been correlated with lupus arthritis [37].

This self-amplifying cycle of ongoing activation of innate immune responses and subsequent perpetuation of autoimmunity underpins the immunopathogenesis of SLE. As a consequence, SLE is a disease characterized at the tissue level by chronic inflammation, which causes local pain, tissue damage, and organ dysfunction. This immune pathology can translate clinically to ongoing joint and periarticular inflammation with chronic musculoskeletal pain [38].

1.1.3 Current Treatment of Active Musculoskeletal Involvement in Systemic Lupus Erythematosus

Treatments approved by the FDA specifically for the treatment of SLE include only hydroxychloroquine, corticosteroids, aspirin, and most recently, belimumab [39, 40]. As an indicator of the dearth of new treatments for SLE, belimumab was the first treatment approved for SLE in 50 years [39].

Traditional treatment strategies for active joint involvement in SLE generally begin with the use of non-steroidal anti-inflammatory drugs (NSAIDs), anti-malarial drugs, and non-narcotic analgesic drugs, then escalate with symptom severity to include corticosteroids or other immunosuppressive drugs and narcotic analgesic drugs [41]. These therapies can be limited in their efficacy and associated with toxicities [42-44]. Nonsteroidal anti-inflammatory drugs are relatively contraindicated in SLE patients with renal disease.

Potential toxicities of NSAIDs, including enhanced photosensitivity, aseptic meningitis, gastrointestinal irritation, ulcers, bleeding and renal toxicity limit their use in SLE patients. Hydroxychloroquine, an antimalarial agent which modulates the innate immune system, is commonly used to limit exposure to corticosteroids and to target constitutional and musculoskeletal features of disease. While its safety profile is relatively non-toxic and there is evidence that it decreases organ damage and prolongs states of remission, the acute therapeutic effect of hydroxychloroquine is mild [45].

Corticosteroids and/or immunosuppressive agents are used for joint involvement in SLE patients that is refractory to NSAIDs and anti-malarial treatments [46], even though the patients are at risk for developing cumulative toxicities from exposure to these drugs. For example, avascular necrosis is an extremely painful and debilitating problem that is associated with corticosteroid use and occurs in approximately 37% of SLE patients [47]. Other potentially devastating side effects of corticosteroids include infection, weight gain, osteoporosis, cataracts, and diabetes. The pro-atherogenic effects (hypertension, dyslipidemia, metabolic syndrome) of steroids are particularly disturbing, given the accelerated atherosclerosis associated with SLE [2, 3]. Immunosuppressive medications such as azathioprine, methotrexate, mycophenolic acid, leflunomide, cyclophosphamide, cyclosporine used to treat joint involvement in SLE are associated with multiple toxicities. Common toxicities include infections (some with fatal outcomes), hepatic, bone marrow and renal impairment, and infertility. Infection is a major contributor to morbidity and mortality in SLE [48-51].

Narcotic analgesia can afford relief of pain from joint involvement, but complications of narcotic analgesics, including somnolence, constipation, addiction/dependence, fatigue and nausea, can be formidable. There is a rapidly increasing awareness of the dramatic rise in opioid-related abuse, addiction and overdose-related deaths [52].

Directly relevant to the treatment of active musculoskeletal disease in SLE are four recent treat-to-target recommendations in SLE from an international task force [53]. In redacted version, these four recommendations are: the treatment target should be remission of organ manifestations; factors such as pain that negatively influence health-related quality of life should be addressed; maintenance treatment should aim for the lowest glucocorticoid dose needed to control disease; and relevant therapies adjuvant to any immunomodulation should be considered to control comorbidity in SLE.

Clearly, there is a significant unmet need for improved treatment of joint involvement and associated pain in patients with SLE who are refractory to NSAIDS and anti-malarial therapy, to resolve joint inflammation, improve pain, and avoid or reduce the risk of infection and the need for systemic corticosteroid therapy, immunosuppressive medications, and/or chronic narcotic analgesia.

1.2 Rationale for JBT-101

1.2.1 Specialized Pro-resolving Lipid Mediators Induce Resolution of Inflammation, Infection, and Fibrotic Processes

Inflammation normally resolves. Physiologic resolution of innate immune responses occurs when naturally-occurring counter-regulatory processes are sufficient to overcome the pro-inflammatory milieu [54-57]. The key up-stream event in resolution of innate immune responses is "class switch" of bioactive lipid mediators from pro-inflammatory mediators, such as leukotriene B4 and prostaglandin E2, to specialized pro-resolving lipid mediators (SPMs), including lipoxins, resolvins, maresins, and protectins [58]. The SPMs initiate resolution of innate immune responses, including resolution of inflammation, bacterial infection, and fibrotic processes, thereby restoring homeostasis [54-57].

Resolution of innate immune responses is an active and orchestrated process that is not the same as anti-inflammation or immunosuppression [54]. Resolution of immune responses incorporates multiple pathways to restore homeostasis [54-57] including:

- Increase in production of SPMs and anti-inflammatory eicosanoids, with a concomitant decrease in production of pro-inflammatory eicosanoids [54-57]
- Increase in production of IL-10 [59], an anti-inflammatory cytokine, coupled with a decrease in production of pro-inflammatory cytokines [60, 61], pro-fibrotic growth factors [62, 63], and extracellular matrix [64]
- Increase in influx of non-inflammatory macrophages [65, 66], with a decrease in influx and accumulation of inflammatory cells and pro-fibrotic myofibroblasts [63, 65, 67] in inflamed tissues. This includes inhibition of adhesion molecule expression, chemokine production, and migration of inflammatory cells into tissues [67-70]
- Increase in apoptosis of inflammatory cells, including neutrophils [70-72] and pro-fibrotic cells, including fibroblasts [73], in involved tissues
- Increase in autophagy in inflammatory cells [60]
- Increase in clearance of apoptotic cells and cellular debris by non-inflammatory macrophages [67, 70, 72]
- Increase in bacterial clearance. SPMs stimulate production of bactericidal peptides [74], enhance phagocytosis and killing of bacteria by neutrophils and macrophages [71, 75-77] and enhance the antibacterial effects of antibiotics [78]
- Subsequent increase in migration of non-inflammatory macrophages out of previously inflamed tissues through efferent lymph [67], completing the return to homeostasis

The cumulative effect is that class switch of eicosanoids to increase production of SPMs results in activation of a naturally occurring, broad-reaching, physiologic network that resolves innate immune responses, including inflammation, infection, and fibrotic processes, restoring homeostasis without immunosuppression.

1.2.2 Proposed Mechanism of Action of JBT-101, a Synthetic CB2 Agonist

JBT-101, a fully synthetic endocannabinoid-mimic, is proposed to activate the resolution machinery of innate immune responses, through cannabinoid type 2 receptor (CB2)-mediated responses. The endocannabinoid system consists of endocannabinoids, CB receptors, and the machinery dedicated to endocannabinoid synthesis, cellular uptake, and degradation. The resolution machinery of innate immune responses and the endocannabinoid system have many common characteristics. Both are naturally occurring, primitive, and conserved biologic networks whose inherent purpose is to restore homeostasis following times of stress [79-82]. Receptors and natural ligands in both systems can be expressed on demand upon cell activation. Both systems use ligands that are synthesized from membrane phospholipids such as arachidonic acid and docosahexaenoic acid during calcium-activated biosynthetic pathways [83, 84]. Ligands for both systems act in an autocrine and paracrine fashion [85, 86].

There are two main endocannabinoid receptor subtypes: cannabinoid receptor type 1 (CB1), mainly expressed in the central and peripheral nervous system, and CB2, mainly distributed throughout immune and hematopoietic cells [87-89]. Cell surface expression of CB2 is rapidly up-regulated on multiple immune cell types during immune responses [90-92]. Expression of CB2 on immune cells is 10-100 times greater than CB1 expression [88].

JBT-101 is a full agonist of CB2, with limited ability to cross the blood-brain barrier [93] and activate CB1 in the brain, through which psychoactivity of cannabinoids is mediated. The composition of JBT-101 that will be used in this trial has a 12 times greater affinity for CB2 than CB1 [94].

Based on human and animal model data and other pre-clinical studies, JBT-101 is proposed to be an upstream activator of the resolution machinery of innate immune responses inducing a class switch in production of bioactive eicosanoids to favor SPMs. This class switch in eicosanoids is expected to initiate a naturally-occurring, physiologic biologic network that will resolve chronic inflammation, without immunosuppression. Clinical benefit is expected with return of homeostasis, including improvement in signs and symptoms of active SLE, including multiple measures of active musculoskeletal inflammation, and a reduction in disease flares. Because its proposed mechanism of action does not include immunosuppression or narcotic analgesia, treatment with JBT-101 is expected to be safe enough and well tolerated for long-term use in SLE. To our knowledge, there are no other therapies in development for SLE at this time that are designed to induce class switch of bioactive eicosanoids to increase SPMs and resolve inflammation in SLE, emphasizing the uniqueness of JBT-101 as a potential treatment for SLE. In addition to its expected clinical benefit based on this novel mechanism of action, JBT-101 is expected to have an acceptable safety profile, based in part on its relative specificity for CB2, limited penetration of the blood-brain barrier penetration, and lack of psychoactivity associated with CB1/ tetrahydrocannabinol agonists/mimetics. As of January 2017, JBT-101 has been tested in a clinical trial in Systemic Sclerosis (SSc), and there are two ongoing clinical trials in inflammatory myositis and cystic fibrosis. No serious adverse events attributed to JBT-101 in these 3 clinical trials have been reported. There is no reason to suspect that a SLE population

will be at greater risk for potential JBT-101 toxicity than any of these 3 immune-compromised populations.

1.2.3 Summary of Biologic Effects of JBT-101

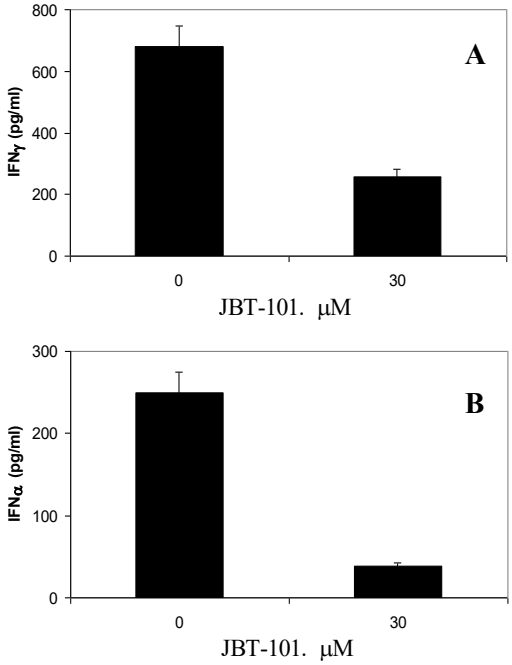
The biologic effects of JBT-101 that are relevant to the treatment of SLE are outlined here, and data in support of these effects can be found in more detail in the Investigator's Brochure (IB) for JBT-101. In humans, human cells, and/or animal models of inflammation, JBT-101 increases production of the SPM lipoxin A4 and anti-inflammatory eicosanoids such as PGD2 and PGJ2, while decreasing production of pro-inflammatory eicosanoids and pro-inflammatory cytokines that have been implicated in SLE, including IFNα, IL-6, and IL-1β [62, 63, 95-101]. In other animal models of disease, JBT-101 inhibits tissue inflammation and edema, as well as tissue damage caused by inflammation [62, 63, 95, 96, 98, 101]. Of significance, JBT-101 inhibits lung inflammation and fibrosis, when administered in both preventative and therapeutic manners in rodent models [63, 102]. In one animal model of prolonged and excessive lung inflammation induced by persistent infection, JBT-101 restores resolution of lung inflammation to normal, improves bacterial clearance, lessens associated weight loss, and improves survival, without immunosuppression [102]. JBT-101 also prevents development of inflammation and fibrosis in the skin in animal models [62, 101]. JBT-101 has direct effects on fibroblasts that may reduce fibrosis, including inhibition of TGFβ and collagen production [62, 63].

The human equivalent dose (HED), based on body surface area, of effective/ active doses in rodent models were between about 0.5 - 60 mg per day total daily dose, with a median HED of about 5 mg per day (difficulties in translating doses in animal models to human equivalent doses are acknowledged).

Potentially relevant to the treatment of SLE and inflammatory arthritis in SLE, preliminary studies done by the Protocol Chairs and collaborators have demonstrated that JBT-101 reduces production of IFNα and IFNγ by peripheral blood mononuclear cells (PBMC) from healthy volunteers and from patients with SLE ex vivo. In summary, the results showed:

- JBT-101 reduced release of IFNα and IFNγ from PBMC from both healthy volunteers and five SLE patients, when those PBMC were stimulated with CpG DNA (for IFNα production) or phytohemagglutinin (for IFNγ production), $p < 0.05$ (see Figure 1).
- In a dose-dependent manner, JBT-101 reduced levels of IFNα mRNA in PBMC from an SLE patient, when those PBMC were stimulated with CpG DNA, $p < 0.05$ [101].
- When added to SLE PBMC stimulated with CpG DNA *ex vivo*, 30 μM JBT-101 reduced IFNα production in 7/9 (78%) of subjects, with inhibition in those seven subjects ranging from 42% to 97%. Similarly, when added to SLE PBMC stimulated with phytohemagglutinin *ex vivo*, 30 μM JBT-101 reduced IFNγ production in 5/6 (83%) of subjects, with inhibition in those five subjects ranging from 48% to 85%. Suppression of both IFNα and IFNγ production was independent of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores [101].

Figure 1. JBT-101 decreases IFN production by ex vivo stimulated PBMC from SLE patients



Legend: Panel A. PBMC were isolated from five SLE patients and stimulated with phytohemagglutinin without or with 30 uM JBT-101. IFNγ release from these PBMC was reduced 63.5 +/- 13.9% (mean +/- SD) by addition of JBT-101 (p = 0.001 versus untreated, stimulated control cells by student t test).

Panel B. PBMC were isolated from five SLE patients and stimulated with CpG DNA without or with 30 uM JBT-101. IFNα release from these PBMC was reduced by JBT-101 (p < 0.001 vs untreated, stimulated control cells by student t test).

In support of these findings in PBMC from SLE patients, JBT-101 decreased production of IFNα by PBMC from dermatomyositis patients [100].

In addition, in support of potential benefit of JBT-101 in musculoskeletal inflammation in SLE, JBT-101 at doses equivalent to 0.5 mg every other day in humans inhibited adjuvant-induced arthritis in rodents, with prevention of pannus formation, bone destruction, and joint ankylosis, accompanied by a significant improvement in a composite clinical score that included joint swelling and pain [96]. JBT-101 also inhibited the development of serositis induced by toll-like receptor activation of cells within the mouse peritoneal cavity [98].

1.3 Summary of Pre-Clinical and Clinical Studies

See the IB for JBT-101 for details of design and findings in non-clinical and previous clinical studies. Certain information relevant to safety and trial design is summarized below.

1.3.1 Animal and Human Biomaterials Safety Data

A nonclinical safety program was designed to support the development of JBT-101 and consisted of safety pharmacology, general toxicology, reproductive and developmental, and genotoxicity studies conducted with JBT-101.

Safety pharmacology and general toxicology studies up to 6 and 9 months' duration in rats and dogs identified central nervous system/neurobehavioral effects in rats and/or dogs. JBT-101-related convulsions were observed in rat and dog studies, but this adverse finding was considered to be related to procedures during animal handling and dosing, and the JBT-101 systemic exposure by C_{max} at No-Observed Adverse Effect Levels in these studies were determined to be ≥5× in rats and ≥1.7× in dogs related to clinical exposure at a human dose

of 20 mg (b.i.d.) JBT-101. Specifically, the lowest dose where seizures were observed in rats was 4 mg/kg/day. The highest dose being used in this study is approximately 0.67 mg/kg/day. In addition, JBT-101 did not have any effect on seizure threshold in animals. There were no other treatment-related clinical, macroscopic or microscopic findings indicating organ toxicity in any of the repeat dose studies. In the in vitro human ether a-go-go (hERG) assay, the approximate half maximal inhibitory concentration (IC_{50}) value for inhibition of the potassium current by JBT-101 was 7 μM (2800 ng/mL), 5× higher than clinical C_{max} exposure value at a human dose of 20 mg (b.i.d.) JBT-101. In addition, there were no adverse cardiovascular effects occurred in vivo in anaesthetized dogs, or on cardiovascular parameters in dogs after repeat administration of JBT-101 up to 10 mg/kg BID for 9 months. In a physical dependence rat study, JBT-101 did not exhibit drug dependence lability. Furthermore, JBT-101 was not teratogenic in the rat embryofetal development study and a pilot rabbit embryofetal development study (i.e., Segment 2 studies). In a reproductive and developmental rat study (i.e., Segment 1), JBT-101 had no effect on male and female fertility. JBT-101 was not mutagenic or clastogenic in in vitro or in vivo genotoxicity studies.

1.3.2 Animal Toxicokinetic Results

Toxicokinetic results from the 2-week once a day (q.d.) dose studies in rats and dogs and the 2-week and 13-week studies of the rat three times a day and dog b.i.d. studies demonstrated that:

- JBT-101 exposure increased in a linear fashion with increases in dose.
- JBT-101 exposure was comparable in males and females in both species.
- JBT-101 exposure was comparable after the first and 14th doses in the 2-week q.d. dose studies, indicating an absence of accumulation or time-dependency to pharmacokinetic (PK) measurements. In the 13-week study in rats, no change in C_{max} was observed between days 14 and 98 of treatment, whereas there was between a 10-20% accumulation of JBT-101 based on AUC between days 14 and 91 of treatment. In the 13-week study in dogs, there was no change in C_{max} observed between days 14 and 91 and no change in JBT-101 AUC levels was observed between days 14 and 98 of treatment.

1.3.3 Animal Metabolism

Studies of metabolism in animals have shown that:

- JBT-101 binds tightly to plasma proteins, with binding of ≥ 97% in rat, dog, and human plasma.
- JBT-101 undergoes limited metabolism. The percent of unchanged JBT-101 remaining after a 2-hour incubation in vitro was 103%, 90%, 86%, and 83% for rat, dog, monkey, and human hepatocytes, respectively.

- JBT-101 is not a substrate for cytochrome P450 and displayed no inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 at concentrations of up to 50 µM. Because the half maximal inhibitory concentration values for JBT-101 were greater than 50 µM for all P450 isozymes, there appears to be no cytochrome P450 inhibition at pharmacological study product levels.

1.3.4 Clinical Studies

As of January 2017, 117 healthy volunteers and 19 subjects with neuropathic pain have received JBT-101 through participation in two Phase 1 clinical trials, three mechanism of action studies, and one Phase 2 clinical trial in refractory neuropathic pain under different Investigational New Drug Applications (INDs) and sponsors (no longer active), for indications/investigational purposes not being considered in this IND. Subjects received up to 240 mg total daily dose and were dosed up to seven days in total, up to three times a day. Subjects were ages 18-77 years of age. Details of the study designs can be found in the IB for JBT-101.

As of April 2017, 42 subjects (27 JBT-101, 15 placebo) with diffuse cutaneous systemic sclerosis (SSc) were enrolled in trial JBT101-SSc-001, and 36 of 38 subjects that completed double blind treatment enrolled in the one-year open-label extension. Eighty-five subjects with cystic fibrosis (61 JBT-101, 24 placebo) were enrolled in trial JBT101-CF-001. Twenty-two subjects (~11 JBT-101, 11 placebo) with skin-predominant dermatomyositis are actively being enrolled in trial JBT-101-DM-001.

All of the data used for analyses of the pharmacokinetic and metabolism studies and safety measures was derived from the completed Phase 1 (CT-3-01, CPL7075-001-01) and Phase 2 studies (CPL7075/102/02/02/001.1, JBT101-SSc-001).

Details of pharmacokinetic and metabolism findings in the completed Phase 1 and Phase 2 clinical trials can be found in the IB for JBT-101. Key pharmacokinetics and metabolism findings include:

- JBT-101 was rapidly absorbed from the gastrointestinal tract.
- Mean C_{max} values increased approximately proportional to the increase in dose for single doses from 10 to 240 mg and multiple doses from 20 to 80 mg per day.
- Mean $AUC_{0\text{-}inf}$ values also increased approximately proportional to the increase in dose for single doses from 10 to 240 mg. For multiple doses from 20 to 80 mg per day, $AUC_{0\text{-}24h}$ values increased slightly greater than the increase in dose. The mean ± SD $AUC_{0\text{-}INF}$ for JBT-101 was 35,025 ± 5784 ng·hr/ml for 80 mg three times a day.
- Subjects ≥ 65 years old had an average $AUC_{0\text{-}24h}$ about 15% greater than that of the younger subjects.
- The fraction absorbed, mean clearance divided by fraction absorbed, and volume of distribution tended to increase slightly with dose in multiple dose studies.
- For multiple doses, T_{max} occurred at around 3 hours.

- The average half-life ranged from 3.7 to 5.6 hours for single doses.
- There were no effects of the fed state at 20 and 40 mg doses.
- Following JBT-101 administration at 20-40 mg b.i.d. for 7 days in humans, the only observable plasma metabolite of JBT-101 was a glucuronide metabolite [103], which represented 9% of total JBT-101 present in the plasma.

The safety findings in each completed individual clinical trial can be found in detail in the IB for JBT-101. In summary, key safety findings from the two Phase 1 trials (CT-3-01, CPL7075-100-01) and two Phase 2 trials (CPL7075/02/01/001.1, JBT101-SSc-001) are:

- Maximum Tolerated Dose is 180 mg total daily dose
- No deaths and no serious, severe or unexpected AEs related to JBT-101 occurred in any of the studies
- One of 27 (3.7%) JBT-101-treated subjects in the SSc trial (JBT101-SSc-001) withdrew due to a TEAE of moderate dizziness.
- Mild to moderate AEs consistent with CB1/CB2 agonists occurred at higher doses, especially ≥ 150 mg/day total daily dose
- In pooled safety data, TEAEs that occurred in ≥ 5% of 88 JBT-101-treated subjects who received doses within the estimated therapeutic range of ≤ 60 mg total daily dose were dizziness (n = 10, 11%), dry mouth (n = 5, 5.6%), arthralgias (n = 6, 6.8%), GI disturbances (n = 6, 6.8%) and fatigue (n=9, 10.2%). Note that the majority of subjects with GI complaints (6/6), fatigue (8/9) and arthralgias (6/6) were in the SSc trial and all of these symptoms are common in SSc.
- In pooled safety data of all trials (n = 150 total) and all doses of JBT-101, which included 71 subjects who received JBT-101 at doses higher than the estimated therapeutic range, TEAEs that were observed in two or more subjects ≥ 5% of the time included mild dizziness (21.3%), moderate dizziness (10%), mild somnolence (6%), mild nausea (12%), mild dry mouth (8%), and mild fatigue (5.3%) (Table 27 of the Investigator Brochure for JBT-101). These AEs were consistent with CB1/CB2 agonist class effects and showed a dose-response. Most AEs occurred in the highest frequency in subjects who received ≥ 150 mg total daily dose of JBT-101. Adverse events that were reported in ≥ 5% of placebo-treated subjects were headache (5.7%).There were no AEs or laboratory abnormalities that indicated immunosuppression or an increase in rate of infection.
- Changes from baseline in blood pressure (BP) and pulse rate (P) in subjects treated with JBT-101 were generally similar to those treated with placebo, although in multiple dosing studies in healthy volunteers, BP recordings that were considered intermittent hypotension occurred more frequently subjects ≥ 65 years of age than in subjects ≥ 18 and ≤ 45 years of age (4/6 versus 0/18, respectively).
- No clinically relevant changes in physical examination findings were observed.

- No clinically relevant changes in electrocardiograms (ECGs) or QT/corrected QT interval (QTc) intervals were observed. In the multiple dosing studies, subjects ≥ 18 and ≤ 45 years of age had no abnormal ECG findings and no differences in mean changes in QTc intervals between subjects treated with JBT-101 versus placebo. In subjects who received high doses (≥ 180 mg total daily dose JBT-101) and were ≥ 65 years of age, three of six subjects who received JBT-101 had prolongation of QTc intervals ≥ 30 msec from baseline on Day 1, with no prolongation exceeding 39 msec and no QTc exceeding 500 msec. The maximum QTc observed was 487 msec. None of these changes were considered clinically significant. The longest prolongation of QTc, as of July 2017, with JBT-101 has occurred in a healthy subject who received placebo.
- There were no notable changes in hematology or chemistry values from baseline. Individual changes in liver and renal function tests were few and small in magnitude. No food or age effects were observed in the laboratory hematology and chemistry values.

In formal testing, there was no psychoactivity, effect on mood, or effect on attention/cognition at doses up to 80 mg total daily dose. The efficacy findings in the completed Phase 2 trials (CPL7075/02/01/001.1, JBT101-SSc-001) as of July 2017 can be summarized as follows:

  - JBT-101 reduced neuropathic pain significantly compared to placebo [104]

- In JBT101-SSc-001, evidence of efficacy was observed across multiple outcomes, including the Combined Response Index in diffuse cutaneous SSc, the modified Rodnan Skin Score, Physician Global Assessment, Patient Global Assessment, the Health Assessment Questionnaire-Disability Index, a systemic sclerosis skin symptom questionnaire, and the 5D-Itch questionnaire
- In JBT101-SSc-001, multiple different glucuronide metabolites of JBT-101 were observed in the plasma at < 10% with one glucuronide metabolite present at >10% at all doses. An open-label extension to the JBT101-SSc-001 study is ongoing, with 36 subjects enrolled as of July 2017. All subjects in the open-label extension receive JBT-101 20 mg once or twice per day, for up to 12 months. As of July 2017, total duration of double blind placebo controlled and open-label extension dosing with JBT-101 was median 234 days (range 28, 295 days). All 36 subjects had at least one open-label extension visit ≥ 28 days post baseline. Adverse events (AEs, n = 88) occurred in 28/36 (78%) subjects in the open-label extension. Most AEs were mild (55/88, 62%) or moderate (30/88, 34%) in severity and unrelated to JBT-101 (75/88, 85%). The AEs that occurred in ≥ 10% of subjects (n, % of subjects) were mild fatigue (5, 14%) and mild/moderate upper respiratory tract infection (4, 11%).

Study JBT101-CF-001 is a double-blind, placebo-controlled, randomised Phase 2 study conducted at 21 centres in the US and Europe. JBT-101 was administered at 1 mg once per day or 5 mg once per day for 28 days, escalating to 20 mg once per day or 20 mg twice per

day for an additional 56 days in subjects with cystic fibrosis. Eight-five subjects were dosed with study medication, the last subject has completed the trial, and it is estimated that ~61 subjects received JBT-101 and ~24 subjects received placebo throughout the trial. Safety data is summarized as follows:

- The majority of spontaneously reported adverse events were mild to moderate in JBT-101 treated subjects. The most frequent adverse event reported during JBT-101 treatment was mild dry mouth.
- Four of 61 (6.6%) of JBT-101 subjects withdrew following a TEAE, of which two were considered related to JBT-101 including mild lack of cognitive clarity, and a moderate feeling unmotivated. One of 24 (4.2%) of the placebo subjects withdrew following mild difficulty focusing, mild lack of cognitive clarity
- Triplet ECGs with QT/QTc interval measurements were done throughout the trial and showed no significant changes from baseline and similar findings in subjects who received JBT-101 and placebo.
- Overall, changes from baseline in the ARCI-M were similar in subjects who received JBT-101 and placebo.

JBT-101-treated subjects exhibited clear reductions in inflammatory biomarkers in the sputum including total cells, neutrophils, eosinophils, macrophages, lymphocytes, interleukin-8, neutrophil elastase, and IgG in sputum. The number of new pulmonary exacerbations (commencement of new systemic antibiotic) per individual per 12 weeks (event rate) was 0.28 for JBT-101 vs. 0.60 for placebo (54% reduction). The event rate per 12 weeks of new pulmonary exacerbations treated with IV antibiotics was 0.09 for JBT-101 (all doses combined) vs. 0.26 for placebo (65% reduction) and was lowest with JBT-101 20 mg b.i.d. (80% reduction).No unexpected SAEs were reported; most SAEs are acute infectious pulmonary exacerbation of cystic fibrosis.

Study JBT101-DM-001 is a double-blind, placebo-controlled, randomised Phase 2 study being conducted at one centre in the US. JBT-101 or placebo is administered at 20 mg once per day for 28 days, escalating to 20 mg twice per day for an additional 56 days in subjects with skin-predominant dermatomyositis. As of July 2017, 22 subjects have been dosed with study product, and it is estimated that ~11 subjects received JBT-101 and ~11 subjects have received placebo. Safety data are summarized as follows:

- The study has not completed enrolment and remains blinded.
- Following their review of blinded safety data, a Safety Monitoring Committee recommended no change to the protocol or safety monitoring plan.
- There have been no serious, severe, or unexpected AEs. Most AEs have been mild in severity.

An open label extension of the study has started and as of July 2017, 11 patients have enrolled.

1.4 Current Licensing of JBT-101

JBT-101 has not been approved for any indication.

1.5 Known and Potential Risks and Benefits of JBT-101

1.5.1 Potential Risks

Expected AEs in clinical studies with JBT-101 include those related to active SLE, JBT-101, and common events in the general population. Expected AEs related to active SLE include any new or worsening signs and symptoms of mucocutaneous disease, serositis, musculoskeletal disease, peripheral or central nervous system disease, renal disease (and accompanying systemic hypertension and reduction in renal function), hematologic cytopenias (autoimmune hemolytic anemia, leukopenia, thrombocytopenia), depression and anxiety and/or signs of constitutional disease such as lymphadenopathy, fever and weight loss. Other expected AEs related to active SLE also include mild to severe infections related either to disease or immunosuppressive medications, medically significant elevations in acute phase reactants such as total globulins, CRP, sedimentation rate, and anti-dsDNA or other antibody levels, medically significant reductions in complement levels, and mild normocytic anemia. Additional anticipated risks of JBT-101 specific to SLE patients would include worsening xerostomia in patients with dry mouth from associated sicca syndrome. Many patients with SLE also demonstrate cognitive impairment and/or depression that may worsen or become apparent during a disease flare.

Expected AEs related to JBT-101 are via CB receptors. CB1/CB2 agonists can produce AEs in humans, and many of these may be caused by the activation of central CB1 rather than of CB2 or peripheral CB1. Adverse effects most often observed, at least in other published clinical trials, have been dizziness/light-headedness, dry mouth, tiredness/fatigue, muscle weakness, myalgia (muscle pain) and palpitations [105]. Other less frequently reported side effects of CB1/CB2 agonists include disorientation, feeling of drunkenness, ‘high sensation’, mental clouding and/or altered time perception, impairment of memory or ability to concentrate, tremor, balance impairment or lack of coordination, nausea/feeling sick, vomiting, hypotension, blurred vision, constipation or diarrhea, confusion, dysphoria/depression, disorientation, paranoia and hallucinations [105]. Any of these AEs potentially could be seen with JBT-101 exposure.

As of July 2017, a number of the AEs associated with CB1/CB2 agonists have been reported in subjects exposed to JBT-101 and future subjects are at risk for these same AEs. As seen in pooled safety data from the 2 Phase 1 studies and 2 Phase 2 completed clinical trials, AEs that occurred in ≥ 5% of JBT-101 treated subjects were fatigue, dry mouth, arthralgias, dizziness, nausea and vomiting. Many of the other AEs listed as class effects of CB1/CB2 agonists have been reported by JBT-101-treated subjects, albeit at frequencies lower than 5% as of July 2017 (see Tables 17, 18 and 20 in the Investigator Brochure for JBT-101). JBT-101 is a full agonist of CB2, with little evidence of psychotropic activity at likely therapeutic doses, because of limited ability to cross the blood-brain barrier and reduced affinity for

CB1. Psychotropic activity of JBT-101 will be tested formally with the ARCI-M questionnaire [106].

Prolongations of QTc interval to less than 500 msec total and up to 39 msec prolongation from pre-treatment baseline were observed in a previous Phase 1 study, and all of these prolongations were judged not clinically significant. They were observed in some subjects ≥ 65 years of age exposed to JBT-101 at a total daily dose greater than or equal to 180 mg for seven days. The QTc changes were also observed on ECGs not done using standard techniques to measure QT/QTc intervals. For this reason, to ensure safety of subjects, the QT/QTc interval will be measured at time points before, during and after treatment, and maximum doses of JBT-101 to be tested in this study will not exceed 40 mg/day (given as 20 mg b.i.d.). In the JBT101-SSc-001 study, assessment of ECGs and corrected QT intervals using standard techniques revealed no clinically significant prolongation of corrected QT intervals or other significant electrocardiogram findings.

Studies of human reproduction have not been performed with JBT-101. It is not known if JBT-101 can cause fetal harm when administered to pregnant women or if it can negatively affect reproductive capacity. Women of childbearing potential should avoid becoming pregnant and should not be breastfeeding at the start of the study, during the study, and for 28 days after the last dose of study drug.

Expected AEs in a general population include events such as mild changes in vital signs, sore throats, mild skin, upper or lower respiratory tract, or genitourinary infections requiring topical or oral antibiotics, asymptomatic bacteriuria, headaches, nausea, mild rashes, and minor accidents. Mild abnormalities in laboratory testing of CBC testing, platelets, differential cell counts, metabolic panels including liver function tests and electrolytes, and urinalyses are expected to occur in a general population.

Abrupt discontinuation of treatment with JBT-101 has not been shown to cause any harmful effects in previous studies; therefore, study product may be stopped without tapering or adding additional treatments. If a subject has received clinical benefit from JBT-101, then his/her disease activity may or may not worsen after discontinuation of JBT-101. To reduce this risk of disease flare, subjects will continue their standard-of-care medication throughout the study and during the follow-up period. Subjects will have follow-up safety evaluation and testing of disease activity 28 ± 3 days after the end of the planned active treatment period or after withdrawal or discontinuation of study product.

Subjects will be instructed to call the site investigator or treating physician if they experience an AE (whether or not they determine it to be related to the study) and may be evaluated for potential toxicity at an unscheduled visit.

Please see the IB for JBT-101 for further information about risk.

1.5.2 Potential Benefits

No physical, psychological, social, legal, or any other benefits are claimed for individual SLE subjects who chose to participate in this study. Based on biologic effects of JBT-101 and other preferential CB2 agonists in *in vitro* and *in vivo* models of inflammation and various diseases, it is reasonable to test JBT-101 for evidence of efficacy in SLE in this study. The information that will come from this study will address effects of JBT-101 on efficacy, safety, tolerability, and biomarkers of inflammation in SLE subjects. This information will be used in decision making about whether to progress JBT-101 to future pivotal clinical studies, as a step toward approval by regulatory agencies for treatment of SLE.

1.6 Rationale for the Study

There remains significant unmet medical need for the treatment of active musculoskeletal disease in SLE that is refractory to treatment with NSAIDS and anti-malarial agents and necessitates the addition of corticosteroids, immunosuppressive medications and/or narcotic analgesia. A double-blind, randomized, placebo-controlled design will be used to reduce bias in assessment of safety, tolerability, and efficacy of JBT-101 in SLE subjects with active musculoskeletal disease. JBT-101 and placebo will be administered in addition to current standard of care that the subject is receiving, to reduce risk of precipitating disease flares by stopping standard-of-care treatments. There is limited metabolism of JBT-101, and JBT-101 has no impact on multiple cytochrome P450 systems, an observation that reduces the likelihood of adverse drug-drug actions in SLE patients on complex treatment programs.

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. JBT-101 is expected to decrease production of pro-inflammatory cytokines implicated in the pathogenesis of SLE, such as IFNα, IL-6, and IL-1β. Further, JBT-101 is expected to activate apoptosis in activated immune cells and induce clearance of apoptotic cells (efferocytosis) and cellular debris by non-inflammatory macrophages. Through these mechanisms, JBT-101 is expected to provide efficacy in active musculoskeletal inflammation in SLE, without immunosuppression.

For the primary efficacy analysis, inflammatory pain will be measured daily using the maximum pain numerical rating scale (NRS), and longitudinal changes will be evaluated after 12 weeks (end of treatment). Other efficacy outcomes include categorical change in pain (improvement, no change, worsening), the number (%) of subjects achieving a 30% (or 50%, 75% or 100%) reduction in maximum pain from baseline to end of treatment, and SLE disease activity measures, including number of tender and swollen joints on 66/68 joint count, presence versus absence of arthritis by Safety of Estrogen in Lupus: National Assessment (SELENA) SLEDAI and score in the musculoskeletal domain of the British Isles Lupus Activity Group (BILAG) 2004, the SLE Responder Index and its domains (SELENA SLEDAI assessment, BILAG 2004 assessment, and Physician's Global Assessment), and disease flares. Efficacy also will be assessed with patient-reported outcomes [Lupus Activity Patient Global Assessment and Patient-Reported Outcomes Measurement Information

System (PROMIS)-29 Short Form, PROMIS Item Bank v2.0 - Cognitive Function test, and Treatment Satisfaction Survey]. Changes from baseline in secondary efficacy outcomes are expected to occur and be in the direction of improvement, although the changes are not expected to reach statistical significance at $p < 0.05$ after 84 days exposure in this first trial in relatively small numbers of SLE patients. In contrast, changes in the metabolipidomic profile and stimulated whole blood cytokine expression are expected within days, and changes in biomarkers of inflammation, such as C-reactive protein (CRP) and type I IFN gene expression, are expected to happen within a few weeks.

Safety assessments include patient-reported AEs, vital signs, physical examinations, complete blood count (CBC) with cell differential, metabolic panel, urinalysis, and 12-lead ECGs for QT/QTc intervals. Blood for JBT-101 concentrations and metabolites, biomarkers of inflammation, metabolipidomic profiles, cytokine expression in serum and stimulated whole blood, and analysis of type 1 IFN gene expression will also be collected. Confirmation of the lack of psychotropic properties of oral JBT-101 will be done using the Addiction Research Center Inventory-Marijuana (ARCI-M) questionnaire.

The mechanism of action of JBT-101 will be evaluated by measuring metabolipidomic profiles, to determine whether JBT-101 increases SPMs, especially lipoxin A4, and anti-inflammatory eicosanoids, both in absolute amounts and relative to pro-inflammatory eicosanoid mediators. The downstream consequences of this activity on biologic pathways relevant to disease pathology in SLE will be tested, looking for decreased expression of cytokines and gene transcripts that are elevated during inflammation in SLE.

This is a first-in-SLE study of JBT-101. The data from this study will provide information on whether the benefit: risk profile in SLE supports further clinical development and progression to future pivotal clinical testing. The data will support selection of optimal dose and dose regimen of JBT-101 in future SLE studies.

1.6.1 Rationale for the Inclusion and Exclusion Criteria

The target population is adults with SLE who have active musculoskeletal disease (arthritis or tendonitis) with significant inflammatory pain, despite treatment with an anti-malarial drug unless intolerant of an anti-malarial drug, and who are on stable doses of prednisone ≤ 10 mg daily or equivalent for at least 14 days prior to dosing with study product. To reduce risk to subjects in this first-in-SLE study, subjects will be excluded who have severe organ damage, severe disease activity and/or require > 10 mg day oral prednisone or equivalent for treatment. Additionally, patients with a recent or current history of substance abuse or those with chronic pain requiring narcotic analgesia will be excluded in order to limit confounding effects of these substances on our endpoints. Subjects will be ≥ 18 and ≤ 70 years of age at the time of signing the Informed Consent Form. Adults are selected as the target population, because neither toxicology studies in juvenile animals nor safety or efficacy assessments in children with SLE have been done yet.

Subjects with fibromyalgia are not excluded from the study. Given that up to about one-third of SLE patients have concomitant fibromyalgia, exclusion of SLE subjects with fibromyalgia

from this study is impractical and would delay and jeopardize completion of study enrollment. Multiple steps have been included in the trial design to account for the potential impact of pain from fibromyalgia on study results. To ensure that a significant component of the subjects daily pain NRS score is from inflammatory pain from joint/tendon involvements, subjects will be required to have arthritis and/or tendonitis on SELENA SLEDAI assessment or B score in the musculoskeletal domain of the BILAG 2004 assessment. The presence or absence of fibromyalgia and its severity will be assessed using the Fibromyalgia Symptom Score [107]. The absence versus presence of fibromyalgia (Fibromyalgia Symptom Score < 13 versus ≥ 13 at Screening) will be used as a stratification variable at randomization and in subset analyses of the efficacy outcomes.

1.6.2 Rationale for the Treatment Arm

The JBT-101 doses selected for this study are within the range of doses that were well tolerated in previous Phase 1 and 2 studies and in a recently completed clinical trial in SSc, all sponsored by Corbus Pharmaceuticals Holdings, Inc. The JBT-101 oral doses selected for this study are 5 mg b.i.d., 20 mg q.d., and 20 mg b.i.d. Parallel dose assignment to JBT-101 in doses up to 20 mg b.i.d. is supported by a previous multiple ascending dose study and a Phase 2 study in humans in which JBT-101 doses up to 40 mg b.i.d. showed acceptable safety profiles and were well-tolerated. In a recently completed study of JBT-101 in systemic sclerosis and ongoing studies in dermatomyositis and cystic fibrosis (sponsored by Corbus) using similar doses to those proposed in this clinical trial (5 mg-40 mg daily), JBT-101 has been well tolerated with no severe AEs attributable to JBT-101. Each dose is expected have an acceptable safety profile, be well-tolerated, and provide clinical benefit, based on previous animal or human testing and the nature of the inflammatory components of SLE. Based on preclinical data and early higher dose clinical data, it is expected that any safety risk and clinical efficacy of JBT-101 in humans will be related to exposure. Based on extrapolation from animal models of inflammation, 5 mg q.d. was estimated to be about the median dose required for efficacy in humans. However, information from the cystic fibrosis study and from a cutaneous model of E. coli- induced inflammation [101] suggests that 5 mg b.i.d. may be more effective than the 5 mg q.d. dose:

- The 5 mg q.d. dose has some but more limited effects than 20 mg b.i.d. on biomarkers in the sputum in cystic fibrosis patients, with biologic effects of 20 mg b.i.d. ≥ 20 mg q.d. and > 5 mg q.d. doses
- In a human model of innate immune responses (E. coli- induced cutaneous inflammation) the 5 mg b.i.d. dosing demonstrates the expected mechanism of action by enhancing resolution of inflammation. Some activities such as induction of Specialized Pro-resolving lipid Mediators are less with 5 mg b.i.d. than with 20 mg b.i.d. whereas other activities such as inhibition of neutrophil infiltration in the skin are equal

Since the 5 mg b.i.d. dose does not pose any safety issues, we plan to use 5 mg b.i.d. as the low dose arm. The JBT-101 20 mg dose is expected to provide maximal or near maximal levels of clinical benefit, and the JBT-101 20 mg b.i.d. dose is expected to provide maximal/plateau levels of clinical benefit. Inclusion of the JBT-101 20 mg q.d. and 20 mg

b.i.d. doses is expected to maximize opportunity to detect clinical efficacy, safety signals, evidence of biologic activity, and effects on biomarkers in this study. Finally, the availability of data from three different doses of JBT-101 will facilitate the exploratory modeling of relationships between plasma concentrations of JBT-101 and efficacy outcomes, SAEs, biomarkers of inflammation, and levels of certain SPMs.

The 84 days duration of dosing is supported by findings in 13-week toxicology studies in rats and dogs. This study will provide data on safety, tolerability, plasma concentrations, and clinical efficacy of JBT-101 over a longer exposure than in a shorter study.

In support of oral administration q.d. or b.i.d. without regard to fed/fasted state, JBT-101 is well absorbed from the gastrointestinal tract and exhibits dose proportional PK at the doses to be tested in this study. Based on PK results in previous clinical trials, Tmax is expected to be between 2.7 to 3.5 hours for the 5 and 20 mg doses in the current trial, which supports the timing of 3 hours post dosing as an estimate of time of maximal plasma concentrations. The average terminal chemical half-life of JBT-101 in subjects who received 10 mg or 20 mg q.d. in previous studies ranges from 3.7 to 4.4 hours and the biologic effects of JBT-101 are longer, which supports q.d. and b.i.d. testing. Doses to be tested in this study have not shown a significant food effect in a prior clinical study, which supports dosing without regard to fed state.

1.6.3 Rationale for the Control Arm

Inclusion of a placebo cohort in this study is important to control for variations in disease activity and AEs that occur commonly in SLE as a result of their disease, co-morbid illness and/or adverse effects of prescribed medications. Because of the relatively short duration of the study and maintenance of the subject's existing medications for musculoskeletal disease activity and pain, the inclusion of a placebo cohort does not impose undue risk on these subjects. To limit risk of increasing disease activity in a placebo-controlled trial, patients with a BILAG A in any organ system at Screening or Visit 1 (Day 1) will be excluded, because those individuals should receive a new treatment for that severely active organ system. Subjects will be maintained on their SLE medications from Screening throughout Visit 6 (Day 113), to reduce a risk of disease flare precipitated by discontinuation of medications to meet entry criteria. Stopping rules will limit the risk of AEs due to severe increases in disease activity.

1.6.4 Rationale for Mechanistic Studies

The rationale for the mechanistic studies is to validate the preclinical studies and investigate the *in vivo* effects of JBT-101 on pathways that promote ongoing inflammatory responses and those that promote resolution of inflammation. Pre-clinical studies done *in vitro* using healthy control and SLE PBMC and in animal models suggest that the drug's anti-inflammatory properties are mediated by inhibition of pro-inflammatory cytokines such as IL-1β, IL-6, IFNα and IFNγ and by increased production of prostaglandins and other bioactive lipids that facilitate the resolution of inflammation. All of these cytokines have been implicated in the pro-inflammatory milieu that is associated with SLE. Additionally,

although JBT-101 has not been demonstrated previously to have an effect on TNFα we plan to verify this in the planned mechanistic studies, which will be completed using stored specimens should the clinical results warrant further study. In addition to supplying more information that will enhance our understanding of the mechanism of action, it is possible that the mechanistic studies will identify a surrogate biomarker for response that is more sensitive and specific than currently accepted disease activity measures. This has significant potential importance for the design of a Phase III study.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Primary Objective(s)

The primary objective of this trial is to evaluate efficacy of JBT-101 for treatment of inflammatory pain related to active musculoskeletal disease in SLE.

For evaluation of this objective, the primary efficacy analysis will compare longitudinal changes in daily measures of the maximum pain NRS in treated groups compared to the placebo group after 12 weeks of treatment.

2.2 Secondary Objective(s)

The secondary objectives are to:

1. Evaluate efficacy of JBT-101 in active musculoskeletal disease in SLE
2. Evaluate efficacy of JBT-101 in overall disease activity in SLE
3. Evaluate efficacy of JBT-101 in patient-reported outcomes in SLE
4. Evaluate the safety and tolerability of JBT-101 in subjects with SLE
5. Evaluate the effects of JBT-101 on biomarkers of inflammation in SLE
6. Evaluate the effects of JBT-101 on bioactive lipids in SLE
7. Evaluate JBT-101 plasma concentrations and metabolites in SLE

2.3 Exploratory Objectives

The exploratory objectives of this trial are:

1. Explore impact of JBT-101 on symptoms of fibromyalgia
2. Explore relationships between JBT-101 plasma concentrations and efficacy, SAEs, biomarkers of inflammation, and certain SPMs, including lipoxin A4

3 STUDY DESIGN

3.1 Description of Study Design

This study is a randomized, double-blind, placebo-controlled, multi-center clinical trial to test the efficacy, safety, and tolerability of JBT-101 compared to placebo for the treatment of SLE, to evaluate JBT-101's impact on SPMs and biomarkers of inflammation in SLE, and to determine JBT-101 plasma concentrations and metabolites in SLE subjects. The target population is SLE subjects ≥ 18 and ≤ 70 years of age with active musculoskeletal disease (arthritis and/or tendonitis) and 7-day average of maximal daily pain NRS score ≥ 4 of 10 (at least moderate pain) at Screening. If applicable, subjects must be on stable doses of corticosteroids ≤ 10 mg daily prednisone or equivalent prior to assessment of screening daily pain NRS score and non-increasing doses of other immunosuppressive medications for at least 3 months. Additionally, subjects must be on a stable dose of any anti-malarial drug for at least 3 months prior to screening or have a history of intolerance, contraindication, or unwillingness to take an anti-malarial drug.

One hundred eligible subjects will be randomized in a 1:1:1:1 ratio to one of four cohorts to receive assigned study treatment (see Table 1 below). On Days 1-84, study product (JBT-101 or matching placebo) will be self-administered orally b.i.d., with at least 8 hours between doses and without regard to fed state. Randomized eligible subjects will take the 1st dose of study medication in the clinic at Visit 1 (Day 1) (See Section 5.3, *Administration of Study Product*).

Table 1. Randomization 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

Written informed consent must be obtained prior to the subject undergoing any study-related procedure, including screening tests and washout periods for prohibited medications, when applicable. During the screening period, subjects will be evaluated by the site investigator or qualified designee to assess eligibility for randomization into the study. Screening will take place over multiple days. The subject must report maximum daily pain NRS scores for seven days following the initial visit in the clinic, to ascertain whether eligibility criteria are met with a 7-day average of maximum daily pain NRS score ≥ 4 of 10.

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 maximum daily pain NRS score,

including directions for recording scores at about the same time every day, preferably before bedtime. Subjects who are found to be eligible after the screening evaluation will return for Visit 1 (Day 1) within 42 days of the initial screening visit. Subject eligibility will be confirmed prior to randomization. Randomized subjects will be instructed to continue to record their maximum daily pain NRS score through Visit 6 (Day 113).

There will be six additional study visits; Visits 1-6 on Days 1, 15 ± 3, 29 ± 3, 57 ± 3, 85 ± 3 and 113 ± 3, respectively. Treatment occurs from Visits 1-5 (Days 1-85), and Visit 6 (Day 113) is a follow-up visit 28 ± 3 days after treatment ends. The 3 day window at Visits is included in case of holidays or unusual circumstances, and it is expected that most if not all visits will be on the targeted day. Vital signs, AEs, prior/concomitant medications, and blood for laboratory safety tests will be evaluated at Visits 1-6 (Days 1-113). On Visit 1 (Day 1), Visit 3 (Day 29), Visit 4 (Day 57), Visit 5 (Day 85) and Visit 6 (Day 113), subjects will also have a physical exam, urinalysis, and other assessments for evaluation of disease status including patient reported outcomes. Psychoactivity of JBT-101 will be assessed using the ARCI-M questionnaire at Visit 1 (Day 1), Visit 3 (Day 29) and Visit 5 (Day 85). Twelve-lead ECGs and QT/QTc intervals will be assessed at Screening and at Visit 1 (Day 1) and Visit 5 (Day 85). At Visit 1 (Day 1), the ARCI-M questionnaire and QT/QTc intervals will be assessed both before and 2.5 to 3.5 hours after the first dose of JBT-101, when plasma concentrations of JBT-101 should be about maximal. Study personnel will record the subject's interval medical history, assess AEs and medication use, and collect samples for safety, pharmacokinetic, and mechanistic assessments (see *Flow Diagram of Protocol* and Section 6, *Assessments of Safety and Efficacy*; Table 3, *Schedule of Events* for the specific assessment schedule). Subjects will return study drug bottles for a pill count, and new bottles will be dispensed, as appropriate.

For therapeutic stability, subjects should remain on their current treatment regimen for SLE from Screening through Visit 6 (Day 113), unless the site investigator or other treating physician judges that a change in therapy is needed to provide best medical care for the subject. If a subject experiences an increase in disease activity of SLE during participation in the study, he/she should be treated with standard of care for that increase in activity. If medically appropriate, some drugs that would interfere with evaluation of efficacy should be withheld for specified durations prior to certain study visits. See Section 5.6, *Prohibited Medications* for details.

Concomitant therapies taken for the long term treatment of pre-existing conditions other than SLE may be continued during the study provided they are in accordance with the exclusion criteria (Section 4.2, *Exclusion Criteria*). It is preferred that these medications be stabilized before entry and continued wherever practical without variation of dose or regimen during the study. Concomitant medications and new medications should be administered at the discretion of the site investigator or treating physician in order to provide the subject with the best possible medical care. Because of the unavailability of toxicology data or clinical experience of JBT-101 in combination with many therapeutic agents, it is recommended that changes in ongoing treatments or introduction of new therapies are kept to a minimum. The benefit: risk to the subject should be carefully assessed and consideration given to the timing of any necessary introductions of new medications.

Because this is an early study and no efficacy has been demonstrated in SLE, there are no plans to provide the subject with open-label JBT-101 after the study period. If they so choose, subjects may continue to be seen in the site investigator's clinical practice.

About 150 individuals will be screened to identify 100 eligible subjects, for a screen failure rate of about 33%. The number of subjects enrolled may be expanded by up to nine additional subjects, if these additional eligible subjects have signed the Informed Consent Form and are actively engaged in the screening process at the time 100 subjects have been randomized into the study.

About 15 sites in the United States will participate in this trial. The target enrollment of 100 eligible subjects will take place over about 24 months, for a recruitment rate of about 0.28 subjects per site per month. The feasibility of this plan is judged acceptable, based on expert input from the Protocol Chairs and their collaborators.

The planned total duration of an individual subject's participation in the study is about 112 Days (84 days treatment and 28 days follow-up), plus Screening, unless the subject withdraws prematurely. (See Section 5.8, *Treatment Discontinuation and Subject Withdrawal*.) Once 80% of planned sites are activated, the entire study is expected to take 24-30 months to complete.

3.1.1 Stratification, Randomization, and Blinding

Eligible subjects will be randomized in a 1:1:1:1 ratio to one of four cohorts: 5 mg JBT-101 b.i.d., 20 mg JBT-101 q.d., 20 mg JBT-101 b.i.d., or placebo (see Section 3.1, *Description of Study Design*, Table 1). Subjects will be stratified by 7-day average of maximum daily pain NRS score ≤ 6 versus > 6 and Fibromyalgia Symptom Scale Score < 13 versus ≥ 13 at Screening.

To maintain the study blind, JBT-101 and placebo capsules and their packaging will be identical. All subjects will receive b.i.d dosing to maintain blinding to treatment assignment. In general, clinical staff, including the investigators, will be blinded to the treatment assignments until completion of the study. In addition, they will not have access to any mechanistic data, and mechanistic laboratory staff will not have access to any clinical results until completion of the study. The success of blinding will be formally tested using a Treatment Satisfaction Survey that asks each study subject and corresponding site investigator to guess the study group assignment for that subject at the end of active treatment and then comparing these responses to what would be expected by chance.

Unblinding must be approved by the study Medical Monitor unless an immediate life threatening condition has developed and the Medical Monitor is not accessible. The site investigator will notify the protocol chair(s) and the DAIT- Statistical and Clinical Coordinating Center (SACCC) of the unblinding event on the next business day. The emergency unblinding will also be reported to the Data and Safety Monitoring Board (DSMB).

A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the Medical Monitor and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

An individual's treatment assignment will be unblinded if the subject experiences a suspected adverse reaction that is serious and unexpected (see Section 7.2.1, *Adverse Event* and Section 7.2.1.1 *Suspected Adverse Reaction* and Section 7.2.2, *Unexpected Adverse Event*) or other protocol-specific event(s) determined by DAIT/NIAID to warrant unblinding.

3.1.1.1 Subject Completion and Replacement

A subject is considered to have completed the study if he/she has completed Visit 6 (Day 113).

Randomized subjects who never initiate treatment may be withdrawn and will not count towards the accrual of 100 eligible subjects.

3.2 Description of Endpoints

See Section 6, *Assessment of Safety and Efficacy,* for detailed descriptions of endpoint measures, and Section 8, *Statistical Considerations and Analytical Plan*, for planned analyses.

3.2.1 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.

3.2.2 Secondary Efficacy Endpoints

1. The 7-day average of maximum daily pain NRS scores prior to Visits 1, 3, 4, 5, and 6 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*)
    - 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).

3.2.3 Safety Endpoints

Safety will be evaluated by describing incidence of treatment-emergent adverse events (TEAEs) from Visit 1 (Day 1) through 6. TEAEs will be identified by monitoring subject-reported AEs, vital signs, medical history, physical exams, blood and urine safety tests, 12-lead electrocardiograms, and the ARCI-M. 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.
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

3.2.4 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 cytokine 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)

3.2.5 Exploratory Endpoints

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

4 SELECTION OF SUBJECTS

The target population is adults with SLE who have active musculoskeletal disease (arthritis or tendonitis) with significant inflammatory pain, despite treatment with an anti-malarial drug unless intolerant of an anti-malarial drug, and who are on stable doses of prednisone ≤ 10 mg daily or equivalent for at least 14 days prior to assessment of 7-day average of maximum daily pain NRS score at Screening and 42 days prior to Visit 1 (Day 1).

Women and minorities will be recruited. Based on the demographics of this disease and the sites that will be used, it is anticipated that approximately 90% of the study population will be women and 60-75% will be African American and Hispanic or Asian. Urban sites will be included, to increase opportunities to enroll minority subjects. Pregnant and lactating women will be excluded from the study because of the unknown effects of JBT-101 on the fetus. Subjects < 18 years of age will be excluded, because there are no toxicology studies in juvenile animals and no safety, tolerability, and efficacy data in adults with SLE.

4.1 Inclusion Criteria

Individuals who meet **ALL** of the following criteria at Screening are eligible for enrollment:

1. Fulfill the updated ACR 1997 Revised Criteria for the Classification of Systemic Lupus Erythematosus [108]
2. ≥ 18 and ≤ 70 years of age at the time the Informed Consent Form is signed
3. At least 3 months treatment with an anti-malarial drug such as hydroxychloroquine or a history of intolerance, contraindication, or unwillingness to take an anti-malarial drug
4. Meets the SELENA SLEDAI definition of arthritis [109] or moderate arthritis or tendonitis that has not improved over the last month (i.e. BILAG B on the updated BILAG 2004 [110])

5. Seven-day average of maximum of daily pain NRS scores ≥ 4 out of 10 during screening with continued reporting of pain NRS scores on at least 67% of days between the Screening visit and randomization.
6. Overlap with polymyositis, systemic sclerosis, Sjögren's syndrome, or rheumatoid arthritis is allowed, if, in the site investigator's judgment, the predominant clinical features are those of SLE
7. Not expected by the site investigator to require a change in potential disease-modifying treatments for SLE from Screening through Visit 6 (Day 113)
8. Willing to not start or stop any NSAIDs or potential disease-modifying medications or supplements for SLE from Screening through Visit 6 (Day 113), unless a change is recommended by the site investigator or other treating physicians
9. Willing not to use any legal or illegal cannabinoids, including FDA-approved cannabinoids or cannabinoid-mimic drugs, or any illegal substance of abuse from Screening through Visit 6 (Day 113)
10. If a woman of child-bearing potential, willing to use one of the highly effective (failure rate < 1% per year) birth control method from Screening through Visit 6 (Day 113) or for 28 ± 3 days after the last dose of study product (See Appendix A: Reproductive Potential and Effective Methods of Contraception)
11. Willing to follow instructions, complete study procedures and attend study visits as required by this protocol

4.2 Exclusion Criteria

Individuals who meet **ANY** of the following criteria are not eligible for enrollment:

1. Severe or unstable SLE, such as any one of the following:
   a. A BILAG A score in one or more BILAG domains at Screening
   b. Treatment with any intraarticular, intravenous, or intramuscular systemic corticosteroids within 14 days of Screening
   c. Treatment with oral prednisone > 10 mg per day or > 20 mg every other day (or equivalent dose of another corticosteroid) within 14 days of Screening
   d. Increased dose of systemic corticosteroids in the 14 days prior to Screening
   e. Treatment with cyclophosphamide or anti-TNFα biologic agents within 3 months before Visit 1 (Day 1)
   f. Treatment with B cell-depleting monoclonal antibodies (rituximab, Ocrelizumab, anti-CD-22) within 6 months before Visit 1 (Day 1)
   g. Treatment with methotrexate, mycophenolate, azathioprine, leflunomide, cyclosporine, belimumab, tacrolimus, or any other immunosuppressive agent not included in 1b.-f. above, when the dose of that immunosuppressive agent has increased within 3 months before Visit 1 (Day 1). Concurrent treatment with any of

these medications is allowed as long as the doses have been stable for at least 3 months before Visit 1 (Day 1)

h. Actively listed on an organ transplantation list or have received an organ transplant other than a corneal transplant

2. Significant diseases or conditions other than SLE that may influence response to the study product or safety, such as:
   a. Active bacterial or viral infection requiring systemic antibiotic or anti-viral treatment within 14 days before Visit 1 (Day 1)
   b. Acute or chronic hepatitis B or C infection
   c. Human immunodeficiency infection
   d. History of active tuberculosis or positive tuberculosis skin or blood test without: 1) completing a course of appropriate treatment; or 2) having received at least one month of appropriate treatment prior to Visit 1 (Day 1) and continuing to receive appropriate treatment during the study
   e. No elective surgery should be planned from Visit 1 (Day 1) through Visit 6 (Day 113)
   f. A history of cancer. Except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy greater than one year before Visit 1 (Day 1)
   g. Significant heart disease as defined by:
      i. Uncontrollable congestive heart failure, unstable angina, unstable atherosclerotic cardiovascular disease, significant arrhythmia requiring chronic therapy, pulmonary arterial hypertension with dyspnea, disability rated as New York heart Association Grade III or higher, severe systemic hypertension or severe peripheral vascular disease
      ii. Marked baseline prolongation of QT/QTc interval (i.e. repeated demonstration of a QTc interval $\geq$ 450 msec for males and $\geq$ 470 msec for females)
      iii. History of risk factors for torsade de pointes (e.g., heart failure, hypokalemia)
      iv. Clinically significant confirmed abnormality, as determined by the site investigator or qualified designee, on 12-lead ECG at Screening
3. History of chronic pain requiring treatment with narcotic analgesia for more than 30 days total within 6 months (183 days) of baseline. This does not include self-limited pain associated with identifiable events such as surgery
4. Current evidence of alcohol abuse (defined as 4 or more drinks per day on at least 4 days of the week) or history of abuse of illegal and/or legally prescribed drugs such as barbiturates, benzodiazepines, amphetamines, cocaine, or opioids during the 1 year prior to Screening
5. Currently pregnant, breast-feeding, or lactating

6. Any investigational agent within 30 days or five therapeutic half-lives of that agent whichever is longer, before Visit 1 (Day 1)
7. Any of the following values for laboratory tests at Screening:
    a. A positive pregnancy test (also at Visit 1 (Day 1))
    b. A newly positive QuantiFERON® blood test for tuberculosis, without: 1) completing a course of appropriate treatment; or 2) having received at least one month of appropriate treatment prior to Visit 1 (Day 1) and continuing to receive appropriate treatment during the study. If the subject has a previous documented positive tuberculosis skin, then this testing does not need to be repeated. If the subject has a documented negative test result within the last year, testing does not need to be repeated, at the discretion of the site investigator
    c. Hemoglobin < 8 g/dL
    d. Neutrophils < 1.0 x 10^9/L
    e. Platelets < 75 x 10^9/L
    f. eGFR < 50 ml/min according to Cockcroft-Gault equation
    g. AST, ALT, or alkaline phosphatase > 2.0 x upper limit of normal
8. Any other conditions that, in the opinion of the site investigator, are clinically significant and may put the subject at greater safety risk, influence response to study product, or interfere with study assessments. When in doubt, the site investigator or qualified designee should discuss the situation with the Protocol Chairs.

4.3 Co-enrollment Guidelines

Enrolled subjects are allowed to continue participation in observational research studies that do not dictate treatment. Co-enrollment in another research study that dictates treatment in any way is not allowed from Screening through Visit 6 (Day 113).

4.4 Strategies for Recruitment and Retention

The target enrollment is 100 eligible subjects. Most subjects will be recruited from specialized academic outpatient SLE clinics run by the site investigators or at which the site investigators participate. A need to advertise for subjects outside the sites is not anticipated, although it is acceptable. If it becomes necessary to advertise, DAIT/NIAID will review and approve such advertisements to make sure they meet FDA requirements. Children, pregnant females, prisoners and other vulnerable populations will not be recruited. The clinical trial will be listed on clinicaltrials.gov and possibly other relevant websites to make information about this trial easily accessible on the internet.

To encourage retention in the study, every effort will be made to be respectful of the subject's time. The total time required from the subject will vary with the visit and the efficiency of each site and is expected to be 11-15 hours across all visits plus travel time. Absent any safety reason to withdraw from the study, subjects will be encouraged to stay in

the study at each visit by study personnel and reminded of the date and time of their next visit.

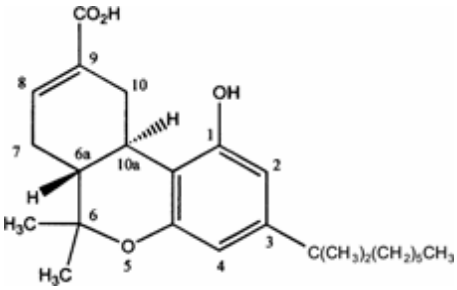
5 TREATMENT OF SUBJECTS

5.1 Description of Study Product

5.1.1 Product Description

Active Product: JBT-101 is (6aR, 10aR)-3-(1,1-dimethylheptyl)- Δ8-tetrahydro-cannabinol-9-carboxylic acid (see Figure 2), also known as Lenabasum, anabasum, resunab, ajulemic acid, CT-3, IP751 and CPL7075. It is a dimethylheptyl structural analogue of tetrahydrocannabinol-11-oic acid, designed and selected on the basis of cannabinoid structure-activity features associated with limited penetration of the blood-brain barrier, to reduce unwanted psychoactivity. JBT-101 has preferential binding to CB2 versus CB1 and exhibits preferential cellular activation through CB2 (Tepper et al., 2014). Detailed study product information can be found in the IB for JBT-101. The structure of JBT-101 is shown in Figure 2.

Figure 2. Structure of JBT-101



Molecular Formula: $C_{25}H_{36}O_4$

Molecular Weight: 400.55

CAS Number: 137945-48-3

Appearance: White to tan powder

JBT-101 is manufactured by Corbus Pharmaceuticals Holdings, Inc.

Comparator Product: Placebo is microcrystalline cellulose (no active ingredient), formulated to have an appearance and weight similar to JBT-101.

5.1.2 Packaging and Labeling of Study Product

JBT-101 5 mg and 20 mg and placebo are powder-in-capsule preparations packaged in identical no. 2 gelatin capsules. JBT-101 and placebo will be packaged in coded bottles of 35 capsules each that will be labeled in accordance with regulatory requirements. The bottles will be made of high density polyethylene with polypropylene child-resistant caps and an induction seal. Each bottle will contain a canister that absorbs oxygen.

Study product will be supplied in kits of two bottles per kit. Each bottle will be numbered to match the kit. Each kit will contain a 28-day supply of study product plus packaged overage

that is enough for another seven days of treatment, in case the next visit is delayed. In each kit, one bottle will be labeled for the morning dose and the other bottle will be labeled for evening dose, with written directions for morning or evening dosing and with visual clues about the time of dosing. Different kits will be manufactured to meet the needs of the study and will contain one of the following:

- Cohort 1 Kit: One bottle of JBT-101 5 mg for a.m. dose and one bottle of 5 mg for p.m. dose
- Cohort 2 Kit: One bottle of JBT-101 20 mg for a.m. dose and one bottle of placebo for p.m. dose
- Cohort 3 Kit: One bottle of JBT-101 20 mg for a.m. dose and one bottle of JBT-101 20 mg for p.m. dose
- Cohort 4 Kit: One bottle of placebo for a.m. dose and one bottle of placebo for p.m. dose

The bottles will be indistinguishable from each other in appearance, and the kits will be indistinguishable from each other in appearance.

JBT-101 will be dispensed to study subjects in the original packaging with a label clearly indicating that the contents are for investigational purposes only. The label will include conditions for storage, a unique drug ID, and other pertinent information such as Sponsor and caution statement. Neither JBT-101 nor placebo should be used after the expiration date unless a written notification of an expiration date extension is provided by the manufacturer.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the pills or bottles, it should not be used. The study drug in question should be quarantined at the study site and the problem immediately reported to DAIT/NIAID or their representative.

5.1.3 Storage and Handling of Study Product

DAIT, NIAID will provide the investigational product for the conduct of this protocol and will be responsible for the disposal of unused product.

The investigational product will be stored at the site pharmacy or in the site investigator's locked storage cabinet/safe. Study product will to be stored at room temperature away from temperature and humidity extremes. Storage conditions must be appropriate for small quantities of Controlled Drugs Act Schedule 1 substances. The study product that is returned by the subjects to the site also will be stored under conditions appropriate for small quantities of Controlled Drugs Act Schedule 1, until disposal.

The site pharmacist, site investigator or qualified designee is responsible for investigational product accountability, maintaining accurate logs of study product received, dispensed, returned or destroyed, and ensuring the appropriate amount of study drug is kept on site and that it is used for research purposes only. He/she will perform drug accountability procedures

such as checking drug shipments against the shipping contents form, maintaining a log of the amount of study drug provided to individual subjects, and reconciling used and unused drug supply by subjects and the study unit.

Upon completion of the study, any unused investigational product(s) at the study sites will be returned to the drug distributor, as requested by DAIT/NIAID.

5.2 Dosage Regimen

The JBT-101 doses selected for this study are 5 mg b.i.d., 20 mg q.d., and 20 mg b.i.d. for oral administration without regard for fed/fasted state. JBT-101 will be administered orally b.i.d. on Days 1-84, with at least 8 hours between doses. (See Section 3.1, *Description of Study Design*; Table 1.)

5.3 Administration of Study Product

JBT-101 will be self-administered orally b.i.d., with at least 8 hours between doses and without regard to fed state. See Section 3.1, *Description of Study Design*; Table 1 for morning and evening dosing for the 4 cohorts. The first dose of JBT-101 at Visit 1 (Day 1) will be taken in the clinic, and the subjects will be observed in the clinic for at least 30 minutes after this dose or longer, until, in the opinion of the investigator, vital signs and clinical symptoms are acceptable for the subject to leave the clinic. After this observation period, subjects must still be available for additional assessments 2.5 to 3.5 hours after administration of the study product.

JBT-101 should be taken in the following way:

- JBT-101 and placebo capsules should be swallowed whole, with liquid as helpful, and should not be broken, chewed or opened. Morning and evening doses should be at least 8 hours apart.
- If a dose of JBT-101 or placebo is missed, it should be taken as soon as possible on the same day, as long as the other dose that day can be timed to be at least 8 hours separate from the time of the missed dose. If it is missed for the entire day, it should not be made up.
- Doses can be taken without regard to fed state.

Subjects who take more than the prescribed dose of JBT-101 or placebo should be instructed to seek emergency medical care, if needed, and to contact the study staff as soon as possible.

5.4 Management Plan for Potential Risks

As of July 2017, no severe AEs have been found to be definitely related to JBT-101. As such, the plans detailed in the section are proposed as general precautions for potential risks.

Expected AEs related to JBT-101 are via CB receptors. As of July 2017, a number of the AEs associated with CB1/CB2 agonists have been reported in subjects exposed to JBT-101, such as fatigue, dizziness, decreased concentration, feeling “weird”, lightheadedness,

asthenia, somnolence, nausea, vomiting, mild orthostatic hypotension, and dry mouth. Patients in the study will be monitored closely for all of these side effects as well as for potential toxicities including psychotropic, gastrointestinal and cardiovascular effects. They are scheduled to be seen frequently during the treatment period (on study Days 1, 15, 29, 57 and 85) and on day 113 for safety follow-up. The ARCI-M scale will be used to assess psychotropic effects of the drug. The Lupus Activity Patient Global Assessment, PROMIS-29 Short Form and PROMIS Item Bank v2.0 - Cognitive Function will be used to assess fatigue and quality of life. The IVRS e-diary for the NRS scale will be used to record pain on a daily basis. Disease activity will be evaluated using patient history, physical exams, hematologic, blood chemistries, urinalyses and serologies pertinent to the SLEDAI (C3, C4 and anti-dsDNA antibodies).

Prolongations of QTc interval to less than 500 msec total and up to 39 msec prolongation from pre-treatment baseline were observed in a previous Phase 1 study, and all of these prolongations were judged not clinically significant. They were only observed in some subjects ≥ 65 years of age exposed to JBT-101 at a total daily dose of up to 180 mg for seven days. For this reason, to ensure safety of subjects, the QT/QTc interval will be measured throughout the study, and maximum doses tested will not exceed 40 mg/day (given as 20 mg b.i.d.).

If a subject develops a grade 3 or higher NCI-CTCAE (version 4.0) adverse event that is deemed by the blinded site investigator to be possibly related, probably related, or related to study drug, the subject will be discontinued from treatment but will continue to be monitored at the scheduled follow-up visits unless consent is withdrawn.

There will be no dose modification in this study, other than temporary or permanent discontinuation of study drug and there is no rescue treatment.

5.4.1 Prevention of Potential Risks to Study Product

The Inclusion/Exclusion criteria have been designed to exclude subjects with significant other illnesses or conditions that would increase safety risks during the trial. Subjects with chronic pain requiring ongoing treatment with narcotic analgesia are also excluded. Subjects will additionally be reminded to call their study physician in the event that they develop any adverse event (whether or not they determine it to be related to the study) and may be evaluated for potential toxicity at an unscheduled visit.

5.4.2 Management of Potential Risks to Study Product

Severe symptoms related to the potential risks of JBT-101 may necessitate stopping study drug. Stopping study drug is not a reason for withdrawal from the study, but a subject may be withdrawn at the discretion of the PI if deemed it is in the subject's best interest.

For subjects who experience potential CB1/CB2 mediated AEs (fatigue, dizziness, decreased concentration, feeling "weird", lightheadedness, asthenia, somnolence, GI disturbances such as nausea or vomiting, or dry mouth), treatment for symptoms should be prescribed as needed, and study treatment may be withheld at discretion of PI.

5.5 Concurrent Medications and Therapy

The intent is that each subject is maintained on all his/her medications for SLE from Screening through Visit 6 (Day 113), unless the site investigator or other treating physicians judge that a change in therapy is needed to provide best medical care for the subject. Information about the concomitant medications and treatments will be collected at each Visit. All concomitant medications given to the subject during the study will be recorded on the eCRF.

Concomitant therapies taken for the long term treatment of pre-existing conditions other than SLE may be continued during the study provided they are in accordance with the exclusion criteria. It is preferred that these medications be stabilized before entry and continued wherever practical without variation of dose or regimen during the study.

During the study, concomitant medications and new medications should be administered at the discretion of the site investigator or treating physician in order to provide the subject with the best possible medical care. Because of the unavailability of toxicology data or clinical experience of JBT-101 in combination with many therapeutic agents, it is recommended that changes in ongoing treatments or introduction of new therapies are kept to a minimum. The benefit: risk to the subject should be carefully assessed and consideration given to the timing of any necessary introductions of new medications.

Permitted concomitant medications for SLE during the study include stable doses, including stable doses of as needed (prn) medication, of any of the following:

- Anti-malarial medications
- Systemic corticosteroids ≤ 10 mg q.d. or ≤ 20 mg every other day oral prednisone or equivalent corticosteroid
- Methotrexate, mycophenolate, azathioprine, leflunomide, belimumab, cyclosporine, or tacrolimus
- Topical therapies, such as topical corticosteroids, antibiotics, anti-viral agents, artificial tears, ophthalmic ointments
- NSAIDS, dosing must be held within 12 hours of certain study Visits (see Table 2 below)
- Non-narcotic and narcotic analgesic, dosing of must be held within 6 or 12 hours, based on half-life of the analgesic, of certain study Visits (see Table 2). Narcotic analgesics are permitted only for prn use for acute events not related to SLE disease activity
- Other medications not specifically included in this list of allowed concomitant medications for SLE are allowable, based on the judgment of the investigator and provided they are not included in the list of disallowed medications (Table 2)

5.6 Prohibited Medications

A list of disallowed medications is provided in Table 2.

Table 2. Disallowed medications and conditions

Drug Class	Requirements
Analgesics with half-life < 6 hours	Prohibited for **6 hours** prior to study assessments at Visits 1, 3, 4, 5, and 6
NSAIDS and analgesics with half-life ≥ 6 hours	Prohibited for **12 hours** prior to study assessments at Visits 1, 3, 4, 5, and 6
Systemic corticosteroids > 10 mg per day or > 20 mg every other day oral prednisone or equivalent corticosteroid or increase in dose of systemic corticosteroid	To accommodate the occasional use of extra corticosteroids by patients for reasons not associated with SLE flares, 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. These short increases in dose may not be accompanied by a documented SLE disease flare. However, use is prohibited for **14 days** prior to study visits for Screening.
Intraarticular, intravenous, or intramuscular systemic corticosteroids	Prohibited for **14 days** prior to study visits for Screening and during the study
Any cannabinoid, cannabinoid-mimic (except JBT-101), or illegal substance of abuse	Prohibited from **Screening** through Visit 6 (Day 113)
Cyclophosphamide or anti-TNFα biologic agents	Prohibited for **3 months** before Visit 1 (Day 1) and during the study
Rituximab, ocrelizumab, anti-CD22 monoclonal antibody	Prohibited for **6 months** before Visit 1 (Day 1) and during the study
Other investigational agents	Prohibited for **30 days** or 5 half-lives before Visit 1 (Day 1), whichever is longer and during the study

5.7 Procedures for Monitoring Subject Compliance

The number of capsules of study product returned to the site will be counted and recorded on Visits 2 (Day 15), 3 (Day 29), 4 (Day 57), and 5 (Day 85). Note that at Visit 2, the study drug capsules will be counted to evaluate compliance, but the bottles will be returned to the subject for dosing until Visit 3.

5.8 Treatment Discontinuation and Subject Withdrawal

5.8.1 Interruption of Dosing and Study Treatment Discontinuation

Interruption of continued dosing in individual subjects may occur for safety reasons and at the discretion of the site investigator, if it is felt that interruption of dosing is in the best interest of the subject. Other than in urgent situations, it is 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 are permitted, as necessary in the judgment of the investigator for safety purposes.

Study treatment will be discontinued permanently for any individual subject under the following conditions:

1. At any time during the study at the request of the subject or subject's guardian
2. If investigators or the DAIT/NIAID Medical Monitor determine(s) that the subject's health, safety, and/or well-being are threatened
3. Study treatment will be discontinued for any subject who experiences any of the following:
   - A severe flare by the SELENA SLEDAI Flare Index or a BILAG A in any domain except musculoskeletal
   - Starting a medication that is prohibited during the study (See Table 2 in Section 5.6, *Prohibited Medications*)
   - Increases in doses of methotrexate, mycophenolate, azathioprine, leflunomide, belimumab, cyclosporine, or tacrolimus above stable baseline doses
   - 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
   - Pregnancy. (See Section 7.6, *Pregnancy Reporting*)

Abrupt discontinuation of treatment with JBT-101 is not known to cause any harmful effects; therefore, study product will be stopped without tapering or adding additional treatments. All remaining study product will be returned to the study staff.

There will be no dose modification in this study, other than temporary or permanent discontinuation.

5.8.1.1 Procedures for Discontinuation of Protocol-Specified Treatment Requirements

Whenever possible, subjects who have been discontinued from study treatment should complete all scheduled study visits including all exams, procedures, assessments, and tests for the duration of the study. Furthermore, if discontinuation is due to safety concerns, subjects will be given appropriate care under medical supervision beyond the last scheduled study visit, if necessary, until the symptoms of any AE resolve or the subject's condition becomes stable. If the site Principal Investigator (PI) determines that completion of these visits is not clinically appropriate for the subject or if the subject or subject's guardian elects

not to complete these visits, the subject will be withdrawn from the study per the guidelines in Section 5.8.2.1, *Procedures for Subject Withdrawal from the Study*.

5.8.2 Subject Withdrawal from the Study

When a subject is withdrawn from the study, protocol-specified treatment requirements are discontinued, and study-related visits, exams, procedures, assessments, tests and data collection are terminated. Individual subjects will be withdrawn from the study under the following conditions:

- The subject or subject's guardian withdraws consent
- If the subject elects to participate in any other sort of study or clinical trial (excluding observational registries or cohorts), the subject may be withdrawn at the discretion of the DAIT/NIAID
- Subject non-compliance with treatment regimens or failure to keep appointments

5.8.2.1 Procedures for Subject Withdrawal from the Study

All withdrawn subjects will have a follow-up visit after study product is discontinued for final safety monitoring. The timing of the Early Withdrawal Visit in this study is 28 ± 3 days after study product is discontinued. Assessments will be the same for subjects who withdraw before completing all dosing and those who complete all dosing. Subjects who withdraw consent will be asked to complete the Early Withdrawal Visit; however, they will not be required to complete the visit.

Subjects who are withdrawn due to pregnancy will be followed according to the procedures outlined in Section 6.1.9, *Pregnancies.*

5.8.3 Safety Stopping Guidance

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews or emergency meetings. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. The DSMB will have the discretion to recommend actions regarding study conduct and continuation as a consequence of any planned or unplanned monitoring activity.

In addition to the planned safety reviews, the DSMB will be informed of the following events as they occur:

- Any immediately life threatening event or death that occurs in the study that is at least possibly related to study intervention
- Two or more subjects with QT-prolongations defined as QTc prolongation > 500 msec total duration and > 60 msec from Visit 1 (Day 1) QTc interval prior to study drug administration

In addition, 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.
- 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

In the event of a temporary halt in enrollment, no new subjects will be consented or start on therapy with JBT-101 or placebo; and subjects already on JBT-101 or placebo will continue on therapy unless they are the focus of the DSMB review. Subjects in the screening phase of the study may continue to undergo minimal risk procedures (e.g., blood tests), but more than minimal risk procedures should be deferred. Randomization will not occur until the DSMB review is complete. The FDA will be notified of any halt in enrollment. After careful review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

6 ASSESSMENT OF SAFETY AND EFFICACY

6.1 Assessments of Eligibility and Safety

The following laboratory safety tests will be done at regularly scheduled intervals: hematology (CBCs with cell differential and platelet count); chemistry (complete metabolic panel including electrolytes, renal function, and liver function tests); urinalysis with microscopic examination; and pregnancy testing in women with childbearing potential.

Medical history, physical examination, and prior medications will be completed at Screening, for purposes of eligibility. Physical examination results, adverse events, and concomitant medications will be recorded as per Table 3, *Schedule of Events*.

Psychoactivity of JBT-101 will be assessed using the ARCI-M questionnaire at Visit 1 (Day 1) and follow-up visits per Table 3, *Schedule of Events*. Twelve-lead ECGs and QT/QTc intervals will be assessed at Screening and at Visit 1 (Day 1) and Visit 5 (Day 85). Both ARCI-M questionnaire and QT/QTc intervals will be assessed on Visit 1 (Day 1) prior to treatment and between 2.5 and 3.5 hours after the first dose of JBT-101, when plasma concentrations of JBT-101 should be about maximal.

Blood and urine laboratory safety tests, CRP, anti-DNA antibody tests, C3 levels, C4 levels, and urine protein/creatinine measurements will be done in central laboratories. A central reading center will be used to determine QT/QTc intervals.

6.1.1 Medical History and Use of Contraception

At Screening, a medical history will be performed and include subject demographics, history of SLE including current symptoms and past and present organ involvement, and current treatment for SLE. The medical history assessment will include concurrent illnesses, other current medications, past medical history, and review of systems. Child-bearing potential, last menstrual period and use of effective methods of contraception will be assessed for all women at Screening (See Appendix A: Reproductive Potential and Effective Methods of Contraception). Date of last menstrual period will be assessed for all women of childbearing potential at Visits 1 (Day 1) and follow-up visits per Table 3, *Schedule of Events*. Concurrent illnesses, current medications, and review of body systems will occur at Visits 1 (Day 1) and follow-up visits per Table 3, *Schedule of Events*. Changes from Visit 1 (Day 1) that constitute adverse events should be reported (See Section 7.4, *Grading and Attribution of Adverse Events*).

6.1.2 Concomitant Medication and Treatment History

A list of current prescription and over-the-counter medications, supplements, and treatments for SLE will be obtained. Assessment of eligibility should include a review of permitted and prohibited medications. Concomitant medications will be recorded on the concomitant medication eCRF from Screening through Visit 6 (Day 113). The medication, dose, frequency, route, start date, stop date, and indication will be captured.

6.1.3 Physical Examination

At Screening, a physical examination is performed to assist in determining the subject's eligibility for the study. Physical examinations also will be performed at Visits 1 (Day 1) and follow-up visits per Table 3, *Schedule of Events*. Physical examinations will include the following assessment: alertness and orientation, general appearance, skin, head, eyes, ears, nose, and throat, lungs, heart, peripheral pulses, abdomen, musculoskeletal examination including tender, swollen, and painful joints, reflexes and lymph nodes. Breast and genitourinary examinations are not required. The Visit 1 (Day 1) physical examination will be used as baseline.

6.1.4 Vital Signs, Height and Weight Measurements

Weight, systolic and diastolic BP, pulse (P), respiratory rate (R), and temperature will be recorded on Screening and all Visits. Weight will be measured with outerwear, such as coats and jackets, and footwear removed. The systolic and diastolic BP will be measured with the patient seated and will be recorded after at least 5 minutes of rest. The same arm will be used for the measurement throughout the study. Pulse will also be measured with the subject seated at rest for at least 5 minutes. Body temperature will be measured on the skin or in the

mouth. These vital sign measurements should be obtained prior to taking samples for the laboratory testing at the applicable study visits. Standing height is to be measured at Visit 1 (Day 1) with footwear removed.

6.1.5 Disease Flares for Safety Assessment

The original lupus instruments to assess disease flares included 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 investigator believes it is indicated.

6.1.5.1 SELENA SLEDAI (28 day assessment)

The SELENA SLEDAI is a validated measure of global disease activity in SLE and was modified from the original SLEDAI for the SELENA clinical trial in 1997. The original SLEDAI was developed in 1992; it includes both subjective reports from patients and objective findings from physicians and laboratory data [111]. The SELENA SLEDAI modification of the original SLEDAI changed some of the item definitions in order to clarify attribution and change in disease activity. These included changes to definitions of seizure activity, strokes, serositis, visual disturbances and proteinuria [109, 112].

The SELENA SLEDAI is a one page assessment that contains 24 items covering 9 organs systems and items are scored as either present or absent. Each item is assigned a weighted score. 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. Scores range from 0–105 points. A score of 6 is considered clinically important and may affect the decision to treat. The original SLEDAI captured disease activity within the 10 days prior to assessment; however, this time period was extended to include the previous 30 days [113, 114].

The SLEDAI does not record improving or worsening, and does not include severity within an organ system. The sensitivity to change is less for the SLEDAI than other commonly used outcome measures in SLE [115].

6.1.5.2 BILAG 2004

The purpose of the BILAG is to assess organ-specific SLE activity based upon the “intent-to-treat” premise. The updated version (BILAG 2004) was published in 2005 and is a validated measure of disease activity [110]. BILAG 2004 assesses 97 clinical signs, symptoms and laboratory parameters important in SLE across nine organ systems. Each symptom is scored with respect to severity over the previous 28 days (0 = not present, 1 = improving, 2 = same, 3 = worse, and 4 = new). The BILAG provides a more sensitive measure of change than the SLEDAI [115].

As above, each question is recorded as 0, 1, 2, 3, or 4. The BILAG 2004 scoring algorithm categorizes disease activity into 5 different levels from A–E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent)

dose of > 20 mg daily or high-dose anti-coagulation. Grade B represents moderate disease activity prompting consideration of a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarial drugs, or nonsteroidal anti-inflammatory drugs. Grade C indicates mild stable disease, while grade D implies no disease activity but the system had previously been affected. Grade E indicates no current or previous disease activity.

6.1.5.3 **Flare Definitions**

Disease flares will be defined using SELENA SLEDAI Flare Index and BILAG 2004 assessments. See Section 3.2.3, *Safety Endpoints* and Section 7.4.1, *Grading Criteria* for definitions and severity grading requirements.

The SELENA SLEDAI Flare Index categorizes disease flares as mild/moderate or severe, based on the highest categories of clinical features recorded or by treatment recommendations by the physician.

SELENA SLEDAI and BILAG 2004 disease flares will be identified centrally at the DAIT-SACCC.

6.1.6 **Blood and Urine Laboratory Safety Tests**

Blood and urine laboratory safety tests will be performed throughout the study. The results of all tests will be reviewed by the investigator or qualified designee, who will make judgments on the medical significance of any new or worsening abnormal value. The results of clinical laboratory tests at Screening will assist in identifying subjects who are not suitable for the study due to some biochemical or hematological abnormalities.

The results of clinical laboratory tests at Visit 1 (Day 1) prior to study drug administration will provide a baseline reference against which any fluctuations in these test results during the treatment phase of the trial can be compared. Abnormal tests will be reported as adverse events if they meet grading and reporting criteria (See Section 7.4, *Grading and Attribution of Adverse Events*).

All laboratory safety tests will be performed in licensed clinical laboratories, according to the study schedule. The majority of the laboratory safety tests will be done centrally.

6.1.7 **Electrocardiograms and QT/QTc Intervals**

Twelve-lead ECGs are to be recorded in triplicate at Screening and Visits 1 (Day 1) and 5 (Day 85). They will be evaluated for medically significant abnormalities and QT/QTc intervals. The QT/QTc intervals will be measured at Visit 1 (Day 1) before administration and between 2.5 and 3.5 hours after administration of study product in the clinic, at the time of maximum JBT-101 concentration in the blood.

The triplet twelve-lead ECGs are to be recorded at least 5 minutes apart, with the subject in a rested supine position for at least 10 minutes. Food and drink should not be consumed by the

subject within the 30 minutes before the ECGs are to be recorded. A central reading center will be used to read all ECGs and determine QT/QTc intervals.

Abnormal ECG findings will be reported as adverse events if they meet grading and reporting criteria (See Section 7.4, *Grading and Attribution of Adverse Events*).

6.1.8 ARCI-M Questionnaire

The ARCI-M questionnaire will be completed by subjects at Visits 1 (Day 1), 3 (Day 29), and 5 (Day 85). This is a 12-item yes-no questionnaire developed by the National Institute on Drug Abuse, designed to detect the full range of subjective responses experienced by marijuana users [106]. The ARCI-M questionnaire has been validated by subjects following marijuana smoking. The subject will be asked to fill out the ARCI-M questionnaire prior to other interactions with study staff except for Visit 1 (Day 1). At Visit 1 (Day 1), the ARCI-M questionnaire will be completed at the beginning of the visit, prior to interaction with study staff and between 2.5 and 3.5 hours after administration of study product in the clinic, at the time of maximum JBT-101 concentration in the blood. Evidence of psychotropic effects of the study drug in subjects will be identified by an increase of ≥ 1 in the ARCI-M score assessed longitudinally.

6.1.9 Pregnancies

The effect of JBT-101 in pregnancy is unknown in women who become pregnant while taking JBT-101 or in women who become pregnant by male partners who are taking JBT-101. The effect of semen from men who are taking JBT-101 on pregnancies is unknown. Women subjects of childbearing potential will be instructed to inform the investigator if they become pregnant during the study and within 28 days after taking the final dose of study drug). If the pregnancy occurs during the treatment period, the investigator should discontinue the study drug and instruct the subject to return any unused portion of study drug to the study staff. Male subjects whose partner(s) becomes pregnant while the male subject is on JBT-101 or within 28 days after the male subject's last dose of JBT-101 will be instructed to inform the investigator of the pregnancy. The investigator will counsel male and female subjects about the risks of the pregnancy and the possible effects on the fetus.

See Section 7.6, *Pregnancy Reporting* for instructions on how to report pregnancies.

6.1.10 Tuberculosis Screening

To protect subject safety, subjects should not have untreated tuberculosis during the study with JBT-101. For that reason, tests for tuberculosis infection will be part of screening. Screening for tuberculosis will be consistent with Centers for Disease Control guidelines (http://www.cdc.gov/tb/publications/LTBI/pdf/TargetedLTBI.pdf). All subjects will be tested for tuberculosis using a central QuantiFERON® - TB Gold In-Tube Test (QuantiFERON®), unless they: 1) have a history of a positive tuberculosis screening test and have completed a course of appropriate treatment or have received at least one month of appropriate treatment prior to Visit 1 (Day 1) and will continue to receive appropriate treatment during the study;

or 2) have a documented negative test for tuberculosis within 12 months prior to Visit 1 (Day 1).

- The QuantiFERON® blood test will be run centrally, and that lab will set the cutoff for positive test. If the results of the blood test are indeterminate and the subject is low risk for tuberculosis in the opinion of the investigator, no further testing is needed for eligibility. Otherwise, if a blood test result is indeterminate, the site investigator can repeat a blood test and/or do a PPD skin test.

All subjects with a positive test for tuberculosis are excluded from this study unless they have completed a course of appropriate treatment or have received at least one month of appropriate treatment prior to Visit 1 (Day 1) and will continue to receive appropriate treatment during the study (See Section 4.2, *Exclusion Criteria*).

6.2 Assessments of Efficacy

6.2.1 Primary Efficacy Variable: Maximum Daily Pain NRS Score

Efficacy will be assessed using the maximum daily pain NRS score. The pain 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 numerical rating score 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 will be instructed to 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 will record their maximum daily pain NRS score each day using an IVRS (See Section 3.1, *Description of Study Design*.).

Site personnel will receive daily notifications indicating if subjects have not completed their most recent pain scores and they will be responsible for contacting subjects to ensure pain scores are completed regularly. Sites will also receive monthly reports on overall compliance and data integrity.

6.2.2 Secondary Efficacy Variables

For any individual subject, the same physician should, if possible, assess the 66/68 joint count, physician-reported components of the SELENA SLEDAI and BILAG 2004 score, and the Physician's Global Assessment. The SLE Responder Index, SELENA SLEDAI score, and BILAG 2004 domain scores will all be calculated centrally at the DAIT-SACCC.

6.2.2.1 Response Categories

Improvement will be computed at the % change in the 7-day average of maximum daily pain NRS scores from Visits 1(Day 1) to Visits 3 (Day 29), 4 (Day 57), 5 (Day 85), and 6 (Day 113). Categories for 30%, 50%, 75% and 100% improvement will be evaluated.

6.2.2.2 **Pain Categories**

Change in pain category from baseline will be determined. Categories of pain, as defined by the 7-day average of maximum daily pain NRS, are:

- 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

Changes in categories of pain, as defined by the 7-day average of maximum daily pain NRS are:

- Major improvement: Improvement by at least two pain categories from baseline (Visit 1 (Day 1))
- Improvement: Improvement by one pain category from baseline (Visit 1 (Day 1))
- No change: No change in pain category from baseline (Visit 1 (Day 1))
- Worsening: Worsening by at least one pain category from baseline (Visit 1 (Day 1))

6.2.2.3 **66/68 Joint Count**

Determining the number of swollen joints and tender joints is a key component in the clinical assessment of active musculoskeletal disease in this study. This study will assess swelling and tenderness in 66 and tenderness in 68 joints, which includes joints in the feet. The 66/68 joint count evaluates the following joints: upper—temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal and distal interphalangeal; lower—hip, knee, ankle, tarsus, metatarsophalangeal and interphalangeal.

Swelling and tenderness are measured separately. Joint swelling is soft tissue swelling that is detectable along the joint margins. When a synovial effusion is present, it invariably means the joint is swollen. Neither bony swelling nor deformity of the joints constitutes joint swelling. Fluctuation is a characteristic feature of swollen joints and it may influence the range of joint movement.

Joint tenderness is the presence of pain in a joint at rest with pressure or on movement of the joint, e.g. on movement of the hip joints. Pressure to elicit tenderness should be exerted by the examiner's thumb and index finger sufficient to cause blanching of the examiner's nail bed.

6.2.2.4 **Disease Activity**

See Section 6.1.5.1 and 6.1.5.2 for discussion of the SELENA SLEDAI and BILAG 2004. For each, longitudinal changes in total scores will be evaluated.[109-112, 114-116].

The Physician's Global Assessment utilizes a 0 to 3 visual analogue scale that is anchored by verbal descriptors as follows; 0 = none, 1 = mild, 2 = moderate, 3 = severe. It is widely used in the assessment of disease activity in SLE and provides a simple, broad and accurate assessment from the examiner's perspective [117]. The assessment should be completed as soon as possible after all information including laboratory test results for that visit is available to the physician. An increase of ≥ 0.3 points is considered worsening of the Physician's Global Assessment [118, 119]. Both mean change from Visit 1 (Day 1) and proportion of subjects with worsening of the Physician's Global Assessment will be tested.

The SLE Responder Index is a composite index incorporating both the SELENA SLEDAI and BILAG indices and the Physician's Global Assessment [119].

6.2.3 Patient-reported Outcomes

All patient-reported outcome questionnaires should be completed by the subject prior to any other study-related procedures.

6.2.3.1 Lupus Activity Patient Global Assessment

The Lupus Activity Patient Global Assessment is performed with a visual analogue scale (0 – 100) in which the subject is asked to indicate how active she/he thinks her disease is. The visual analogue scale is anchored by two descriptors; "not active" (score of 0) and "extremely active" (score of 100). The recall period is one week.

6.2.3.2 PROMIS Forms

The PROMIS-29 Short Form, Version 2.0, will be used to assess patient-reported state of health. The NIH established PROMIS (www.nihpromis.org) to create a standardized and uniformly scored set of patient-reported-outcomes instruments. The PROMIS network developed item (question) banks and short forms in more than 20 health domains, as well as, a set of global health items and 29-, 43-, and 57-item profile measures. The seven domains specifically relate to physical, mental and social health and cover the most relevant areas of self-reported health for the greatest majority of people with chronic illness: pain, fatigue, depression, anxiety, sleep and physical function. The PROMIS-29 includes four items each from these seven core PROMIS domains as well as one 10-point rating scale for pain intensity. Norm-based scores have been calculated for each domain, such that a score of 50 represents the mean of the general population (standard deviation = 10). High scores represent more of the domain being measured. Thus, on symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, sleep disturbance, and pain interference), higher scores represent worse symptomatology. On the function-oriented domains (physical functioning and social role), higher scores represent better functioning.

The PROMIS-29 includes a single-item pain NRS, which is a segmented numerical version of the visual analogue scale in which the respondent selects a whole number (0-10 integers) that best reflects the intensity of their pain. The numerical rating score 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 recall period is 7 days.

The PROMIS Item Bank v2.0 - Cognitive Function instrument is part of PROMIS. The PROMIS v2.0 Cognitive Function item bank contains 32 questions to assess adult patient-perceived functional abilities with regard to cognitive tasks.

6.2.3.3 **Fibromyalgia Symptom Scale**

The Fibromyalgia Symptom Scale is a modification of the ACR 2010 criteria (Modified 2011) for fibromyalgia that allows use of the ACR 2010 criteria without the requirement for an examiner[107]. The criteria are simple to use and administer. The Widespread Pain Index and the Symptom Severity Scale comprised the ACR 2010 criteria. The Symptom Score was modified by eliminating the physician's estimate of the extent of somatic symptoms and substituting the sum of 3 specific self-reported symptoms. Then, a 0–31 Fibromyalgia Symptom Scale was created by adding the Widespread Pain Index to the modified Symptom Severity Scale. The criteria properly identify diagnostic groups based on fibromyalgia severity variables. A Fibromyalgia Symptom Scale score = 13 best separates criteria positive and criteria negative patients, classifying 93.0% correctly, with a sensitivity of 96.6% and a specificity of 91.8%.

6.2.4 **Treatment Satisfaction Survey**

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

6.3 Mechanistic Studies

6.3.1 **Biomarkers of Inflammation**

Specimens for evaluation of biomarkers of active inflammation in SLE (detailed below) will be collected at Visits 1 (Day 1) and follow-up visits per Table 3, *Schedule of Events*.

6.3.1.1 **C-reactive Protein**

C-reactive protein levels will be measured in peripheral blood. Elevated CRP levels have been reported in SLE, although levels do not always correlate with disease activity [120].

6.3.1.2 **Pro-Inflammatory Cytokines**

Production of pro-inflammatory cytokines, IFNα, IFNγ, IL-6, TNFα and IL-1β, in peripheral blood will be evaluated in vitro in unstimulated and stimulated cell cultures. Supernatants from cultures with and without stimulant will be frozen and batched for analysis.

6.3.1.3 **Type 1 IFNα gene signature**

Type 1 IFNα gene signature will be assessed from whole blood RNA. Gene expression will be analyzed using published data for IFNα inducible genes [121] and second generation modular transcriptional repertoire analyses [122].

6.3.2 **Metabolipidomic Profile**

Metabolipidomic profiles will be assessed in plasma at Visit 1 (Day 1) and Visit 2 (Day 15). At Visit 1 (Day 1), metabolipidomic profiles will be assessed before and 2.5 to 3.5 hours after study product is administered. The metabolipidomic profiles will include measurement of certain SPMs, anti-inflammatory eicosanoids, and pro-inflammatory eicosanoids. As possible, the blood samples for metabolipidomic profile testing should be collected at least 2 hours after the last solid meal.

6.3.3 **JBT-101 Plasma Concentrations and Metabolites**

Plasma concentrations of JBT-101 and its metabolites will be measured at Visit 1 (Day 1) and Visit 2 (Day 15). At Visit 1 (Day 1), plasma levels of JBT-101 and metabolites will be measured before and 2.5 to 3.5 hours after study product is administered.

JBT-101 plasma concentrations and metabolites will be measured using validated assays [101]. Collection at 3 hours after dosing should provide concentrations near peak plasma concentrations and first pass metabolites.

6.3.4 **Optional Unspecified Future Studies**

If the subject provides written informed consent, extra serum and leftover specimens derived from blood samples, including serum, plasma, mRNA, whole blood cells, and whole blood cells culture supernatants, will be stored for future unspecified studies related to JBT-101, the immune system, or SLE.

In addition, if appropriate consents are given, peripheral blood mononuclear cell (PBMC) samples for future, unspecified, IRB approved studies related to JBT-101, the immune system, or SLE will be collected at Visit 1 (Day 1) and follow-up visits per Table 3, *Schedule of Events*.

6.3.5 **Blood Draw Prioritization**

The volume of blood to be drawn at a given visit is limited under the following situations:

- Should the subject have been experiencing severe anemia (hemoglobin < 8g/dL) or have poor venous access, the blood draw limit is 30 mL.
- Should the subject have been experiencing moderate-severe anemia (hemoglobin 8-9 g/dL), the blood draw limit is 50 mL.

- In any patient whose clinical condition might be adversely affected by removal of the volumes required for this protocol, for example, patients with significant anemia (as noted above) or compromised cardiac output, investigators should consider further limiting the volume of blood withdrawn for research purposes.

The priority of samples to collect is as follows:

NOTE: Whole blood for pro-inflammatory cytokines should always be drawn first in the TruCulture tubes.

- Whole blood: TruCulture tubes, pro-inflammatory cytokines (3 mL)
- Safety draws: chemistries, hematologies, anti-dsDNA, C3, C4, CRP (8-11 mL, depending on visit)
- Blood/plasma: metabolipidomic profile, and JBT-101 plasma concentrations and metabolites (4 mL) (Note: For Visit 1 (Day 1), blood is collected twice; pre-dose and post-dose; the post-dose blood draw can be eliminated if indicated)
- RNA: Type 1 IFNα gene signature (2.5 mL)
- Serum for future use (5 mL; limit to 2 mL if necessary)
- PBMCs for future use (30 mL; omit totally for severe anemia or poor venous access)

6.4 Evaluations by Study Visit

Refer to Table 3, *Schedule of Events* (below) for a complete listing of evaluations by study visit.

6.4.1 Screening Period

This study will be explained in lay language to each potential participant. Each participant will sign an informed consent form before committing to study screening procedures.

Unless otherwise specified, the screening evaluations must be performed within 42 days prior to Visit 1 (Day 1). Screening will take place over multiple days. The 7-day average of maximum daily pain NRS score will be calculated by the IVRS to assess eligibility.

Screening laboratory tests, except HIV, hepatitis, and pregnancy testing, may be repeated to establish eligibility within the 42 day window prior to Visit 1 (Day 1), at the investigator's discretion. Subjects who fail screening may be rescreened at a later date, if the investigator judges it likely that the reason for failing to meet eligibility criteria is no longer present.

The following procedures will be performed during the Screening Period:

- Consent presentation and consent signing
- Consent for optional storage and future use of de-identified left-over blood-derived specimens

- Demographics
- Medical history
- Confirm date of last menstrual period in all women and assess birth control status in women of childbearing potential
- Record prior medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature
- Physical examination
- Physician assessments (all scores will be calculated centrally)
    - SELENA SLEDAI and Flare Index
    - BILAG 2004
    - Physician's Global Assessment
- Patient-reported outcomes
    - Fibromyalgia Symptom Scale
    - Complete the subject registration for the IVRS and give him/her the envelope that includes subject-specific username and password, instructions for daily entries, and information on system support. Each subject should be instructed on the use of the IVRS and competency evaluated before leaving the clinic.
- Blood tests
    - 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)
    - QuantiFERON® blood test for tuberculosis, for subjects who do not have a history of prior positive tuberculosis screening test and optional for subjects who have a documented negative result within 12 months prior to Visit 1 (Day 1)
    - Follicle stimulating hormone, for women > 45 and ≤ 55 years of age with no menses for < 2 years
    - Hematology: CBC with differential cell count and platelets
    - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
    - Anti-dsDNA antibody titers, C3, and C4 levels
- Urine tests
    - Urinalysis: microscopic evaluation, and spot protein/creatinine

- Urine βHCG or blood drawn pregnancy test in women of childbearing potential

- Triplet 12 lead ECGs for medically significant abnormalities and QT/QTc interval.

6.4.1.1 **Evaluation of Eligibility and Randomization**

The subject's average of 7-day maximum daily pain NRS score will be computed by the IVRS and reported to site personnel.

If the average is ≥ 4, and the subject meets other eligibility criteria for enrollment, then proceed as follows:

- Instruct the subject to continue to record maximum daily pain NRS score using the IVRS. Randomization will not be allowed, if compliance with reporting falls below 67% during the Screening period.
- Schedule Visit 1 (Day 1) (within 42 days of 1st Screening assessment)
  - Randomizations must occur at least 7 days prior to Visit 1 to ensure that drug will be available on site for Visit 1.
  - Instruct eligible subjects to hold short-acting analgesics for 6 hours and NSAIDs and long-acting analgesics for 12 hours prior to Visit 1 (Day 1).
- Randomize the subject (ensure sufficient time for shipment of study drug prior to the scheduled Visit 1 (Day 1))

If the subject is not eligible, inform the subject and let them know IVRS will no longer accept daily entries.

6.4.2 **Treatment Period**

6.4.2.1 **Visit 1 (Day 1)**

The following procedures will be performed:

- Verify eligibility criteria
- Patient-reported outcomes, before other interactions with study staff
  - ARCI-M questionnaire (Pre-Dose)
  - Lupus Activity Patient Global Assessment
  - PROMIS-29 Short Form
  - PROMIS Item Bank v2.0 - Cognitive Function
  - Fibromyalgia Symptom Scale
- Confirm date of last menstrual period in women of childbearing potential

- Record prior medications
- Vital signs: Height, weight, blood pressure, pulse, respiratory rate, and temperature
- Physical examination
- Physician assessments (all scores will be calculated centrally)
    - 66/68 joint count
    - SELENA SLEDAI and Flare Index
    - BILAG 2004
    - Physician's Global Assessment
- AE monitoring
- **Before** study product administration
    - Blood tests
        - Hematology: CBC with differential cell count and platelets
        - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
        - CRP
        - Anti-dsDNA antibody titers, C3, and C4 levels
    - Blood draws for mechanistic studies
        - Whole blood: TruCulture tubes; pro-inflammatory cytokines
        - Plasma: metabolipidomic profile, and JBT-101 plasma concentrations and metabolites; sampled ≥ 2 hours after last solid meal, if possible.
        - RNA: Type 1 IFNα gene signature
        - Serum: future use (if subject provided written consent)
        - PBMC: future use (if subject provided written consent)
- Urine tests before study product administration
    - Urinalysis: microscopic evaluation, and spot protein/creatinine
    - Urine βHCG pregnancy test in women of childbearing potential
- Triplet 12 lead ECGs for medically significant abnormalities and QT/QTc interval prior to study product administration
- Dispense study product according to randomization schedule. Women of child bearing potential must have negative urine βHCG pregnancy test prior to dispensing study product
- Administer study product in clinic and record time of dose

- Observe subject for at least 30 minutes in clinic, until stable in the judgment of the investigator
- **2.5 to 3.5 hours after** study product administration
    - ARCI-M questionnaire (Post-Dose)
    - Triplet 12 lead ECGs for QT/QTc interval
    - Blood draws for mechanistic studies
        - Plasma: metabolipidomic profile, and JBT-101 plasma concentrations and metabolites; sampled ≥ 2 hours after last solid meal, if possible
- Reminders:
    - Remind subjects to bring the bottles of study drug with them to their next visit.
    - Remind subject to refrain from taking morning dose before Visit 2. Subjects with visits after 2 PM will be instructed to take their morning dose. This is being done to measure trough plasma concentration of JBT-101 at specified visits.

6.4.2.2 **Visit 2 (Day 15 ± 3 days)**

The following procedures will be performed:

- Record concomitant medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature
- AE monitoring
- Blood tests
    - Hematology: CBC with differential cell count and platelets
    - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
- Blood draws for mechanistic studies
    - Plasma: metabolipidomic profile, and JBT-101 plasma concentrations and metabolites; sampled ≥ 2 hours after last solid meal, if possible
    - PBMC: future use (if subject provided written consent)
- Count and record number of capsules the subject has remaining
- Instruct subjects to hold short-acting analgesics for 6 hours and NSAIDs and long-acting analgesics for 12 hours prior to the assessments at Visit 3 (Day 29) and remind them to bring the bottles of study drug with them to their next visit.

6.4.2.3 **Visit 3 (Day 29 ± 3 days)**

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff
    - ARCI-M questionnaire
    - Lupus Activity Patient Global Assessment
    - PROMIS-29 Short Form
    - PROMIS Item Bank v2.0 - Cognitive Function
- Confirm date of last menstrual period in women of childbearing potential
- Record concomitant medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature
- Physical examination
- Physician assessments (all scores will be calculated centrally)
    - 66/68 joint count
    - SELENA SLEDAI and Flare Index
    - BILAG 2004
    - Physician's Global Assessment
- AE monitoring
- Blood tests
    - Hematology: CBC with differential cell count and platelets
    - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
    - CRP
    - Anti-dsDNA antibody titers, C3, and C4 levels
- Blood draws for mechanistic studies
    - Whole blood: TruCulture tubes; pro-inflammatory cytokines
    - RNA: Type 1 IFNα gene signature
    - Serum: future use (if subject provided written consent)
- Urine tests
    - Urinalysis: microscopic evaluation, and spot protein/creatinine
    - Urine βHCG pregnancy test in women of childbearing potential
- Collect returned study product and count and record number of returned capsules
- Dispense study product according to randomization schedule. Women of child bearing potential must have negative urine βHCG pregnancy test prior to dispensing study product.

- Instruct subjects to hold short-acting analgesics for 6 hours and NSAIDs and long-acting analgesics for 12 hours prior to the assessments at Visit 4 (Day 57) and remind them to bring the bottles of study drug with them to their next visit.

6.4.2.4 **Visit 4 (Day 57 ± 3 days)**

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff
  - Lupus Activity Patient Global Assessment
  - PROMIS-29 Short Form
  - PROMIS Item Bank v2.0 - Cognitive Function
- Confirm date of last menstrual period in women of childbearing potential
- Record concomitant medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature
- Physical examination
- Physician assessments (all scores will be calculated centrally)
  - 66/68 joint count
  - SELENA SLEDAI and Flare Index
  - BILAG 2004
  - Physician's Global Assessment
- AE monitoring
- Blood tests
  - Hematology: CBC with differential cell count and platelets
  - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
  - Anti-dsDNA antibody titers, C3, and C4 levels
- Urine tests
  - Urinalysis: microscopic evaluation, and spot protein/creatinine
  - Urine βHCG pregnancy test in women of childbearing potential
- Collect returned study product and count and record number of returned capsules
- Dispense study product according to randomization schedule. Women of child bearing potential must have negative urine βHCG pregnancy test prior to dispensing study product.

- Instruct subjects to hold short-acting analgesics for 6 hours and NSAIDs and long-acting analgesics for 12 prior to the assessments at Visit 5 (Day 85) and remind them to bring the bottles of study drug with them to their next visit.

6.4.2.5 **Visit 5 (Day 85 ± 3 days)**

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff
  - ARCI-M questionnaire
  - Lupus Activity Patient Global Assessment
  - PROMIS-29 Short Form
  - PROMIS Item Bank v2.0 - Cognitive Function
  - Fibromyalgia Symptom Scale
  - Treatment Satisfaction Survey
- Confirm date of last menstrual period in women of childbearing potential
- Record concomitant medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature
- Physical examination
- Physician assessments (all scores will be calculated centrally)
  - 66/68 joint count
  - SELENA SLEDAI and Flare Index
  - BILAG 2004
  - Physician's Global Assessment
  - Treatment Satisfaction Survey
- AE monitoring
- Blood tests
  - Hematology: CBC with differential cell count and platelets
  - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
  - CRP
  - Anti-dsDNA antibody titers, C3, and C4 levels
- Blood draws for mechanistic studies
  - Whole blood: TruCulture tubes; pro-inflammatory cytokines

  - RNA: Type 1 IFNα gene signature
  - Serum: future use (if subject provided written consent)
  - PBMC: future use (if subject provided written consent)
- Urine tests
  - Urinalysis: microscopic evaluation, and spot protein/creatinine
  - Urine βHCG pregnancy test in women of childbearing potential
- Triplet 12 lead ECGs for medically significant abnormalities and QT/QTc interval
- Collect returned study product and count and record number of returned capsules. If study product is not returned, subjects should be instructed not to take any additional study drug and arrangements should be made for the subject to return the study product as soon as possible.
- Instruct subjects to hold short-acting analgesics for 6 hours and NSAIDs and long-acting analgesics for 12 hours prior to the assessments at Visit 6 (Day 113).

6.4.2.6 **Visit 6 (Day 113 ± 3 days)**

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff
  - Lupus Activity Patient Global Assessment
  - PROMIS-29 Short Form
  - PROMIS Item Bank v2.0 - Cognitive Function
  - Fibromyalgia Symptom Scale
- Confirm date of last menstrual period in women of childbearing potential
- Record concomitant medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature
- Physical examination
- Physician assessments (all scores will be calculated centrally)
  - 66/68 joint count
  - SELENA SLEDAI and Flare Index
  - BILAG 2004
  - Physician's Global Assessment
- AE monitoring
- Blood tests
  - Hematology: CBC with differential cell count and platelets

  - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
  - CRP
  - Anti-dsDNA antibody titers, C3, and C4 levels
- Blood draws for mechanistic studies
  - Whole blood: TruCulture tubes; pro-inflammatory cytokines
  - RNA: Type 1 IFNα gene signature
  - Serum: future use (if subject provided written consent)
  - PBMC: future use (if subject provided written consent)
- Urine tests
  - Urinalysis: microscopic evaluation, and spot protein/creatinine
  - Urine βHCG pregnancy test in women of childbearing potential

6.4.2.7 **Early Withdrawal Visit**

If a subject is withdrawn from the study or discontinues the study on or before Visit 1 (Day 1), no additional procedures should be done. If withdrawal or discontinuation is after Visit 1 (Day 1) and at the time of a scheduled visit, the procedures scheduled for that visit should be done and an Early Withdrawal Visit should be done 28 ± 3 days after the last dose of study product, unless consent is withdrawn. If withdrawal or discontinuation is after Visit 1 (Day 1) and not at the time of a scheduled visit, then an unscheduled visit should be done as soon as possible and include evaluations and laboratory safety testing as appropriate for the reasons for withdrawal or discontinuation, and an Early Withdrawal Visit should be done 28 ± 3 days after the last dose of study product, unless consent is withdrawn.

The following procedures will be performed:

- Patient-reported outcomes, before other interactions with study staff
  - ARCI-M questionnaire
  - Lupus Activity Patient Global Assessment
  - PROMIS-29 Short Form
  - PROMIS Item Bank v2.0 - Cognitive Function
  - Fibromyalgia Symptom Scale
  - Treatment Satisfaction Survey, if withdrawal is prior to Visit 5 (Day 85)
- Confirm date of last menstrual period in women of childbearing potential
- Record concomitant medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature

- Physical examination
- Physician assessments (all scores will be calculated centrally)
    - 66/68 joint count
    - SELENA SLEDAI and Flare Index
    - BILAG 2004
    - Physician's Global Assessment
    - Treatment Satisfaction Survey, if withdrawal is prior to Visit 5 (Day 85)
- AE monitoring
- Blood tests
    - Hematology: CBC with differential cell count and platelets
    - Chemistry: Complete metabolic panel, including electrolytes, renal function, and liver function tests
    - CRP
    - Anti-dsDNA antibody titers, C3, and C4 levels
- Blood draws for mechanistic studies
    - Whole blood: TruCulture tubes; pro-inflammatory cytokines
    - RNA: Type 1 IFNα gene signature
    - Serum: future use (if subject provided written consent)
    - PBMC: future use (if subject provided written consent)
- Urine tests
    - Urinalysis: microscopic evaluation, and spot protein/creatinine
    - Urine βHCG pregnancy test in women of childbearing potential
- Collect any remaining study product and count and record number of returned capsules

6.4.3 Visit Windows

All study procedures should be performed within the designated visit window (i.e., ± 3 days) for each scheduled visit (see Table 3, *Schedule of Events* (below)). Whenever possible, a rescheduled visit should remain within the designated visit window. The coordinating center should be notified if the study procedures for any scheduled visit cannot be performed within the designated window.

6.4.4 Unscheduled Visits

Subjects will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. An unscheduled visit will be made, if necessary, for medical issues that arise between study visits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the site investigator or qualified designee.

If an unscheduled visit is necessary to assess the subject for safety purposes, the following evaluations should be obtained, at a minimum:

- Record concomitant medications
- Vital signs: weight, blood pressure, pulse, respiratory rate, and temperature
- Physical examination as relevant to the reason for the unscheduled visit
- AE monitoring
- Urine βHCG pregnancy test in women of childbearing potential
- Laboratory tests as relevant to the reason for the unscheduled visit

Table 3: Schedule of Events (Screening through Post Treatment)

		Treatment					Post Treatment		
Time Point	**Screening[A]**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Early Withdrawal Visit** *(if needed)*	**Unscheduled Visit**
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 status	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-Marijuana (ARCI-M)		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 Function		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	**Screening[A]**	**1**	**2**	**3**	**4**	**5**	**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 Laboratory Assessments									
Infectious Disease: Hepatitis B and C tests, human immunodeficiency virus[H]	X								
Tuberculosis screening test[I]	X								
Follicle stimulating hormone[J]	X								
Hematology: CBC with differential cell count and platelets	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 protein/creatinine	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 Cytokine Studies (3mL)		X[L]		X		X	X	X	
Plasma: Metabolipidomic profile/JBT-101 plasma concentrations and metabolites (4mL)		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 (if needed)	X (if needed)	

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.

7 SAFETY MONITORING AND REPORTING

7.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 7.5.4, *Reporting of Adverse Events to IRBs*) to the DAIT/NIAID. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 4 : http://ctep.cancer.gov/reporting/ctc.html.

7.2 Definitions

7.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

7.2.1.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

7.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the IND.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

7.2.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor [DAIT/NIAID], it results in any of the following outcomes (21 CFR 312.32(a)):

- Death.
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

7.2.4 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest will be collected and reported to the IND sponsor (NIAID), the NIAID Autoimmune DSMB, and to the manufacturer (Corbus Pharmaceuticals Holdings, Inc.).

- 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

If an event meets any of the above AESI categories, regardless of the relationship of the event to the study drug or severity, the event must be reported to the IND sponsor (DAIT/NIAID) as described in Section 7.5.2, *Reporting of AESIs to DAIT/NIAID* and to Corbus Pharmaceuticals Holdings, Inc. as described in Section 7.5.5, *Reporting of Safety Information (AEs, SAEs and AESIs) to Corbus*.

7.3 Collection and Recording of Adverse Events

7.3.1 Collection Period

AEs of Grade 2 and above will be collected from time of signing of informed consent until the subject completes study participation, or until 30 days after he/she prematurely withdraws (without withdrawing consent), or is withdrawn from the study. See Section 7.4, *Grading and Attribution of Adverse Events* for grading criteria.

7.3.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 7.4, *Grading and Attribution of Adverse Events*.

7.3.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 7.2, *Definitions*) on the appropriate AE eCRF regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, whichever occurs first. End of study participation is the final study visit, either at time of study completion or when a subject prematurely withdraws or is withdrawn.

7.4 Grading and Attribution of Adverse Events

7.4.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Protocol Chairs and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild adverse event.
- Grade 2 = moderate adverse event.
- Grade 3 = severe and undesirable adverse event.
- Grade 4 = life-threatening or disabling adverse event.
- Grade 5 = death.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria (i.e. Grade 0, normal). Similarly, changes from screening to baseline will also be recorded as adverse events, but these are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result. Grade 2 or higher AEs will be reported on the appropriate AE electronic case report (AE eCRF) for this study.

In addition, for this study, BILAG 2004 disease flares will be graded as follows:

- Mild SLE flare (Grade 1): New BILAG 2004 grade C in one or more organ systems
- Moderate SLE flare (Grade 2): New BILAG 2004 grade B in one or more organ systems
- Severe SLE flare (Grade 3): New BILAG 2004 grade A in one organ system
- Life-threatening or disabling SLE flare (Grade 4): A life-threatening or disabling new BILAG 2004 grade A

New BILAG flares of Grade 2 or higher (i.e. B or A) will be reported as AEs. Mild/moderate SELENA SLEDAI flares should be reported as AEs if changes in therapy or monitoring are implemented. Severe SELENA SLEDAI flares should be reported as AEs. Signs, symptoms and laboratory test abnormalities reported as part of a SLE flare will not be reported as separate AEs.

7.4.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 4 (below).

Table 4. Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
Unrelated Categories		
1	Not related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
2	Unlikely Related	The adverse event is unlikely related
Related Categories		
3	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
4	Probably Related	The adverse event is likely related
5	Related	The adverse event is clearly related.

7.5 Reporting of Serious Adverse Events and Adverse Events

7.5.1 Reporting of Serious Adverse Events to DAIT/NIAID

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via the DAIT-SACCC. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events (see Section 7.2.3, *Serious Adverse Event*), regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known

information. As additional details become available, the AE/SAE eCRF will be updated and submitted.

For additional information regarding SAE reporting, contact Rho Product Safety:

Rho Product Safety
6330 Quadrangle Drive, Suite 500
Chapel Hill, NC 27517
Toll-free: 1-888-746-7231
SAE Fax Line: 1-888-746-3293
Email: rho_productsafety@rhoworld.com

7.5.2 Reporting AESIs to DAIT/NIAID

After learning that a participant has experienced an AESI, the investigator or designee is responsible for reporting the AESI via an eCRF within 24 hours of becoming aware of the event. The initial eCRF should include as much information as possible, but at a minimum must include the following:

- AESI term.
- Relationship to study medications.
- Whether or not the event meets serious criteria.
- Supplementary eCRF pages that are current at the time of AESI reporting: medical history, concomitant medications, demographics, study drug administration, death.

As additional details become available, the eCRF should be updated and submitted. Every time the eCRF is submitted, it should be electronically signed by the investigator or sub-investigator.

For additional information regarding reporting, contact the DAIT-SACCC.

7.5.3 Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 7.5.1, *Reporting of Serious Adverse Events to DAIT/NIAID*) is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

7.5.3.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 7.2.1.1, *Suspected Adverse Reaction*, and Section 7.2.2, *Unexpected Adverse Event*).

- Serious and not a suspected adverse reaction (see Section 7.2.1.1, *Suspected Adverse Reaction*).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

7.5.3.2 **Expedited Safety Reporting**

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: Serious and unexpected suspected adverse reaction [SUSAR] (see Section 7.2.1.1, *Suspected Adverse Reaction* and Section 7.2.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome)

2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

Category 2: Any findings from studies that suggests a significant human risk

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or in vitro testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

7.5.4 Reporting of Adverse Events to IRBs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs in accordance with applicable regulations and guidelines. All Safety Reports to the FDA shall be distributed by DAIT/NIAID or designee to all participating institutions for site IRB submission.

7.5.5 Reporting of Safety Information (AEs, SAEs and AESIs) to Corbus

DAIT/NIAID will report safety information (AEs, SAEs and AESI) to Corbus as follows:

- For any safety report that meets all of the following criteria of, (i) serious (ii) unexpected and (iii) suspected adverse reaction, NIAID will provide to Corbus a completed copy of the initial safety report at the time the initial report is submitted to FDA. NIAID will provide follow up information to Corbus at the time the follow up safety report is submitted to FDA.
- NIAID will provide monthly listing of safety information (AEs, SAEs, and AESI) to Corbus on a monthly basis.
- NIAID will provide a copy of the IND annual reports at the same time as the transmission to the FDA.

In addition, NIAID will forward the Clinical Study Report as well as any literature articles that are a result of the study to Corbus.

7.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study subject or a partner of a study subject. Pregnancies in women occurring while the subject is on JBT-101 or within 28 days after the subject's last dose of JBT-101 are considered expedited reportable events. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy.

The investigator shall report all pregnancies to the DAIT-SACCC within 1 business day of becoming aware of the event using the Pregnancy eCRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the DAIT-SACCC when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study subject.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall be submitted to the DAIT-SACCC using the SAE reporting procedures described above.

7.7 Reporting of Other Safety Information

An investigator shall promptly notify the site IRB as well as the DAIT/NIAID when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

7.8 Review of Safety Information

7.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the DAIT-SACCC compiling new and accumulating information on AEs, SAEs, AESI and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the DAIT-SACCC (See Section 7.3, *Collection and Recording of Adverse Events*).

7.8.2 DSMB Review

7.8.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner.

7.8.2.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews or emergency meetings (see Section 5.8.3, *Safety Stopping*

Guidance). The DSMB will have the discretion to recommend actions regarding study conduct and continuation as a consequence of any planned or unplanned monitoring activity.

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Sample Size and Power

A total of approximately 100 eligible subjects (approximately 25 per treatment arm) will participate in the study.

The primary hypothesis will be tested using the 3 degree of freedom (df) contrast comparing the difference in predicted means from Day 1 to Day 84 for each JBT-101 cohort versus placebo, where estimates will be derived from a random regression model (See Section 8.3.2.1, *Primary Efficacy Analysis*). The method of Stroup (1999) [123] was used to estimate power and sample size. To apply the method, we made reasonable assumptions about (1) the covariance matrix for the random effects and the residual variance, and (2) mean changes over time for each treatment group.

Subjects who complete the study will have approximately 84 NRS scores assessed daily. To derive the within-subject covariance matrix, we need the within-subject correlation matrix and the standard deviation. We assume the daily assessments have an AR(1) within-subject correlation structure, which seems reasonable based on preliminary data on 24 subjects assessed on days 1, 14, and 28 [101]. Based on this preliminary data, the correlation coefficient for assessments 1 day apart is very high (estimated as 0.9775). The standard deviation (SD) of the NRS is assumed to be the same for each day and likely to be on the range from 1.3 to 1.6. The range is based on a study by Farrar (2001) [124] that examined data from 10 clinical trials including 2724 patients with a variety of conditions characterized by chronic pain who had baseline pain of ≥ 4 on the NRS. The study suggests that patient's perceptions of pain and improvement is similar and consistent across disease indications. Results of this study influenced the recommendations on clinical importance of treatment effects on pain in clinical trials authored by The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group [125].

The covariance matrix for the 84 repeated NRS measures can be derived assuming an AR(1) correlation matrix (r=0.9775 for a 1 day interval) and a choice of SD; we considered the two extremes in SD = 1.3 and 1.6, as well as the pooled estimate (1.43) across the 10 studies in [124]. The next step was to derive the covariance matrix for the random effects in the random regression model (i.e. the subject-level intercepts and slopes). To this end, we simulated day 0 to 84 data for 10,000 subjects, fit the model with fixed and random subject-level intercepts and slopes, and used the output covariance estimates as parameters for power/ sample size computation. Covariance parameters are displayed in Table 5.

Table 5: Covariance Parameters for the Random Regression Model

	Variance (intercept)	Variance (1-day slope)	Covariance (intercept, slope)	Residual
Pooled (daily NRS SD=1.43)	2.35	0.00063	-0.027	0.49
Best case (daily NRS SD=1.3)	1.93	0.00053	-0.023	0.41
Worst Case (daily NRS SD=1.6)	2.96	0.00081	-0.034	0.62

We considered several scenarios for mean changes over time. The IMMPACT group suggests that on average decrease of 2 points (~30% improvement on average) on the NRS scale is consistent with clinically important improvement from the perspective of an individual patient, but they did not make a recommendation for clinically relevant mean decrease in NRS for a treatment group relative to placebo [125]. Although a mean decrease of 2 points on the NRS for a treatment group would certainly be important clinically, a decrease of a smaller magnitude might also include a substantial number of individual subjects who showed improvement of at least 2 points. As such, we considered mean decreases, d, ranging from 1.5 to 2.0 points over 84 days and assumed no change for placebo. For each value of d, we present power/sample size calculations for 2 scenarios. In Scenario 1, the mean decrease of d is achieved in 1 of the JBT-101 treatment groups. The other 2 JBT-101 groups show mean decreases of 0.5d and 0.25d. In Scenario 2, two of the JBT-101 treatment groups achieve a mean decrease of d, and the third shows a decrease of 0.25d. These scenarios are summarized in Table 6. We also considered a 3rd scenario where all 3 treatment groups achieved a mean decrease of d, but power estimates were nearly identical to Scenario 2, and hence, results are not shown.

Table 6: Treatment Effect Scenarios

	Scenario 1	Scenario 2
Placebo	0	0
JBT-101 group 1	-0.25d	-0.25d
JBT-101 group 2	-0.5d	-d
JBT-101 group 3	-d	-d

Using the covariance parameters for pooled, best and worst cases (Table 5) and treatment effects for Scenarios 1 and 2 (Table 6), we generated non-centrality parameters for the F statistic for evaluating the 3 df test, and computed power according to the method of Stroup (1999). Power estimates for a Type 1 error rate = 0.05 and treatment group sizes of 22 and 25 are displayed in Figure 3. The x axis ranges from 1.5 to 2.0 (i.e. values of d) and represents the maximum difference between treatment versus placebo for 1 JBT-101 treated group in Scenario 1 or 2 treated groups in Scenario 2. The y axis displays associated power.

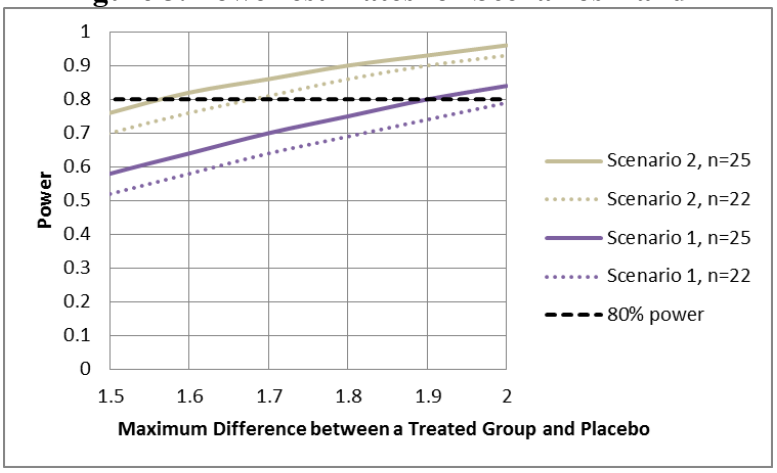
When 2 JBT-101 treated groups achieve the target treatment effect (Scenario 2), power exceeds 80% for treatment effects of at least 1.6 using the pooled SD with 25 per group (Figure 3a). These estimates assume complete data for each subject. Given that this study is of relatively short duration, subject retention is expected to be good with minimal data missing. However, if the sample size drops to 22 per group due to missing data or withdrawals, minimum power is still nearly 80%. If only 1 JBT-101 treated group achieves the target treatment effect (Scenario 1), then a treatment effect of at least 1.9 would be needed for 80% power on the 3 df test.

This analysis does not take into account that the random regression model will include the Screening 7-day average maximum daily pain NRS as a covariate as well as terms for quadratic trends in time, both of which will account for a fraction of the variance in the NRS scores and, hence, may reduce the residual variance and increase power. Figure 3b shows the impact of a small reduction in residual variance from 0.49 to 0.41 (Table 5). For Scenario 2, power exceeds 80% for treatment effects of at least 1.5 with 22 or 25 per group. If only 1 JBT-101 treated group achieves the target treatment effect (Scenario 1), then a treatment effect of at least 1.7 gives power of ~80% or better.

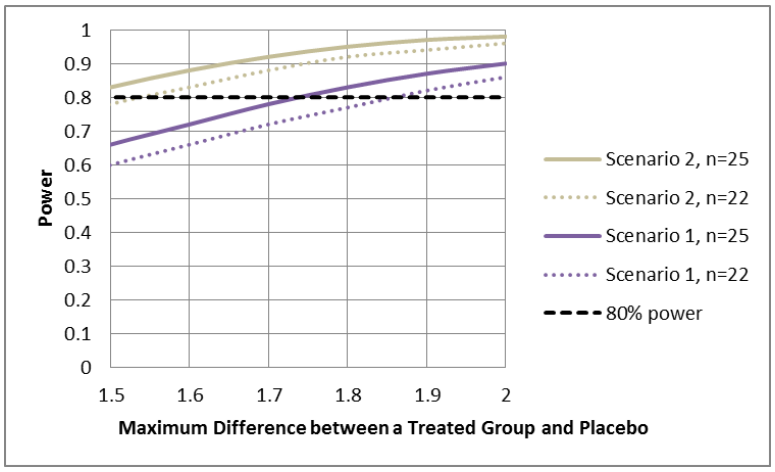
Figure 3c presents a worst case scenario where the variability associated with the NRS scores is high (SD=1.6). All power curves drop by about 10 percentage points compared to Figure 3a. Under this worst case scenario the study would be under-powered except for Scenario 2 for treatment effects exceeding 1.8. However, since results from Farrar suggest that patient's perceptions of pain and improvement is similar and consistent across disease indications, the estimated pooled SD based on over 2000 patients represents a reasonable expectation of the "truth" for our study population [124]. As such, power estimates in Figure 3a are appropriate for this study, and may in fact underestimate power given the enhancements planned for the random regression model as noted above.

In general, power is better when at least 2 of the 3 JBT-101 treatment groups differ meaningfully from placebo. The study will likely be underpowered if only 1 of the JBT-101 treatment groups differs meaningfully from placebo unless that difference is relatively large (1.9 or higher, Figure 3a), for the first Phase 2 study in this patient population, this risk is acceptable. Power is expected to be acceptable with ~22 subjects per arm, but if >12% of subjects who initiate treatment discontinue treatment prematurely, the total sample size may be augmented to ensure adequate power.

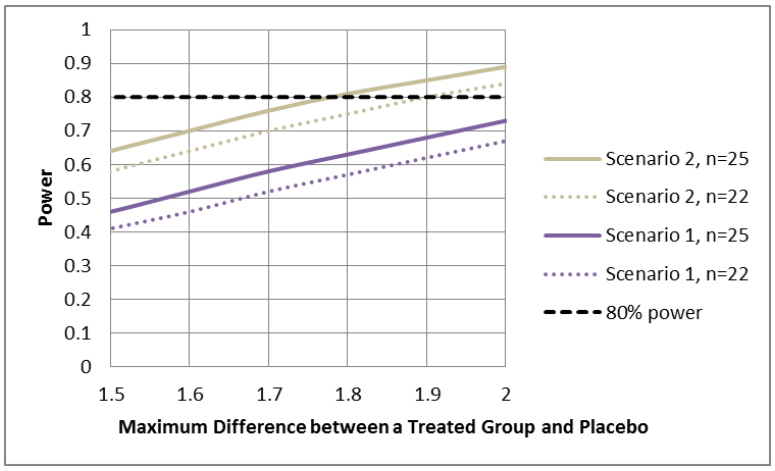
Figure 3. Power estimates for Scenarios 1 and 2



a: Pooled SD of daily NRS = 1.43



b: Best Case- SD of daily NRS = 1.3



c: Worst Case – SD of daily NRS = 1.6

8.2 Analysis Populations

8.2.1 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.

8.2.2 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 effect 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.

8.2.3 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.

8.2.4 PK Population

The PK population will consist of all subjects with at least one valid measure of JBT-101 plasma concentration. Analysis performed on the PK population will be according to the treatment actually received.

8.3 Description of the Analyses

- All data will be provided in data listings sorted by treatment groups, subject number, and visit.
- Summary data will be presented in tabular format by treatment groups.

- Categorical data will be summarized by the number and percentage of subjects in each category.
- Continuous data will be summarized by descriptive statistics including N, mean, standard deviation, median, and range.
- All percentages will be rounded to one decimal place.
- Differences between groups will be calculated as active – placebo and change from baseline (ΔNRS) will be calculated as follow-up visit – baseline.
- The baseline measure will be defined as the last non-missing measure prior to initiation of study product. It is expected that baseline values for efficacy assessments will be measured at Visit 1 (Day 1).
- P-values will be assessed at a 2-sided alpha = 0.05 level for the primary efficacy analysis.
- Secondary analyses are exploratory and intended to deepen our understanding of risks and benefits, to refine hypotheses, and to obtain information from which to design, select doses, and power future pivotal studies. P-values will be presented for secondary efficacy analyses. No adjustments for multiple comparisons are planned for secondary analyses.

8.3.1 Subject Disposition

The disposition of all subjects over the course of the trial will be summarized by cohort and overall. The number and percent of subjects in each analysis population (mITT, PP, safety, and PK) will be displayed. In addition, the presentation will include the number of subjects who completed the study, the number who withdrew prematurely from the study, as well as the reason for withdrawal. In addition, the number of subjects who continued treatment to Visit 5 (Day 85) and who discontinued treatment early will also be summarized along with reasons for discontinuation.

8.3.2 Efficacy Analysis

8.3.2.1 Primary Efficacy Analysis

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 hypothesis to be tested is:

H0: Linear trends from Day 1 to Day 84 are equivalent for each JBT-101 cohort and placebo.
HA: Linear trends from Day 1 to Day 84 are not equivalent across groups.

In addition, pairwise comparisons of each JBT-101 cohort versus placebo are of key interest.

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 random regression approach. 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. Within-subject random effects for intercept and slopes for time and time^2 will be fit using an unstructured covariance matrix assuming the same structure for all treatment groups. In the event of convergence problems, the covariance structure will be simplified by dropping the random effect for time^2. 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, $(\hat{\mu}_{84} - \hat{\mu}_1)_{\text{cohort i}} - (\hat{\mu}_{84} - \hat{\mu}_1)_{\text{placebo}} = 0$ for i=1 to 3.

NRS data up to the day of last dose of study treatment will be included in the analysis for all subjects in the mITT population. Any NRS data entered into the IVRS after discontinuation of study treatment or entered on days when narcotic analgesics were taken will be excluded. If the 3 df test is significant, Dunnett's tests for 1 df pairwise comparisons with placebo are planned. 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.

8.3.2.2 **Secondary Efficacy Analyses**

Secondary analyses of the longitudinally assessed maximum daily pain NRS scores will include:

- A 1 df contrast to compare placebo versus the average across all treated groups
- Analyses to modify the primary analysis model by replacing treatment group with JBT-101 dose, so that dose response may be evaluated
- Modification of the primary random regression model to include interaction terms to evaluate the impact of the Screening 7-day average maximum daily pain NRS on trends over time
- Analyses analogous to the primary analyses using % change in NRS from baseline (i.e. where baseline is the Screening 7-day average maximum daily pain NRS) as the outcome variable
- Evaluation of persistence in trends after treatment is stopped by including data after day 84 in a new random regression model where slopes are allowed to change after this point

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 identify responders whose averages improve by 30% (or 50%, 75% or 100%) over Visit 1 (Day 1) and to evaluate ordinal changes in pain categories (major improvement, improvement, no change, worsening) from Visit 1 (Day 1) to subsequent visits. Relationships between treatment group and each categorical outcome will be evaluated using contingency table analyses. Generalized linear models that account for the correlation structure of the data may be used to further explore any trends that might be suggested by the stratified analyses.

Analyses plans for other categorical secondary endpoints (e.g. presence/absence of arthritis on the SELENA SLEDAI or BILAG scores for the musculoskeletal domain) will be analogous to those noted in the previous paragraph. Generally, mixed models will be used to evaluate disease activity or patient-reported secondary endpoints that are indices or scores assessed at Visits 1 – 5 (Days 1 – 85). Models will be used to compare trajectories and changes in the secondary endpoints over time among the individual JBT-101 groups (Cohort 1, Cohort 2, and Cohort 3) and placebo (Cohort 4). Data transformations will be considered, as appropriate. Larger models may be constructed for these comparisons with consideration of additional covariates that are found to differ between the treatment groups. Covariates may include, but are not limited to: 7-day average of the maximum daily pain NRS score at Visit 1 (Day 1), Fibromyalgia Symptom Score at Visit 1 (Day 1), gender, age, disease duration, and severity.

8.3.3 **Safety Analyses**

8.3.3.1 **Adverse events**

Safety will be assessed primarily by summarizing TEAEs, including treatment-emergent SAEs, and the proportion of subjects with TEAEs and treatment-emergent SAEs in each individual JBT-101 cohort (Cohort 1, Cohort 2, and Cohort 3) to the placebo (Cohort 4).

For placebo and each JBT-101 cohort, the frequency of AEs and SAEs from Screening through Visit 6 (Day 113) will be summarized by system organ class, preferred term, severity (grade), and relationship to study treatment.

Safety endpoint identified in Section 3.2.3, *Safety Endpoints*, will be summarized and listed separately. With the exception of the "psychotropic activity" endpoint, safety endpoints are "events". For each such endpoint, the number of events and numbers and percentages of subjects who experience these events will be summarized for placebo and each individual JBT-101 cohort. No formal statistical testing will be performed to compare safety in different cohorts.

8.3.3.2 **Laboratory safety outcomes**

Results of blood and urine laboratory safety tests, including CBC with cell differential and platelets, metabolic panel, and urine tests will be summarized by visit and time point using descriptive statistics for continuous measures. Changes from Visit 1 (Day 1) will also be summarized. Shift tables will be presented summarizing the shift from Visit 1 (Day 1) to subsequent visits. Results will be presented for placebo and each individual JBT-101 cohort.

8.3.3.3 **Electrocardiograms and QT/QTc intervals**

The QT/QTc intervals and change from Visit 1 (Day 1) to subsequent visits will be summarized by visit using continuous summary statistics for placebo and each individual JBT-101 cohort.

8.3.3.4 **ARCI-M questionnaire**

ARCI-M questionnaire scores will be summarized by visit for Visits 1 (Day 1) (before and after first dose of study drug), 3 (Day 29), and 5 (Day 85), and for change from Visit 1 (Day 1) prior to the first dose of study drug to the visit using continuous summary statistics. The number of subjects with an increase in score by ≥ 1 from Visit 1 (Day 1) prior to study product administration will be presented by visit for Visit 1 (Day 1) after study drug administration, Visits 3 (Day 29) and 5 (Day 85).

8.3.4 **Plasma Concentrations of JBT-101 and Metabolites**

Results of JBT-101 plasma concentrations and metabolites for Visits 1 (Day 1) and Visit 2 (Day 15) will be described, using continuous summary statistics, by visit.

In addition, plasma concentrations will be listed by subject and cohort in a blinded manner, using a mock identification number separate from the subject id, at several times during the trial to determine whether exposure to JBT-101 in the SLE subjects is within the expected

range for the doses administered. Complete analyses of the plasma concentrations and metabolites will be done at the end of the trial.

8.3.5 Mechanistic Analyses

Descriptive statistics and plots (including, but not limited to, those described subsequently) will be used to gain an understanding of the data prior to developing any statistical models. Means, medians, standard deviations, minimums, and maximums will be computed for each continuous mechanistic endpoint at each time point for treatment groups and separately for subjects who do/do not experience clinically significant disease reactivation. For dichotomous mechanistic endpoints, frequencies and percent's will be computed at each time point for treatment. To gain a better understanding of trends over time, summary statistics (e.g., means, medians, or percents) will be plotted versus time at the relevant time points. Plots for individual subjects may also be useful. Complete analyses of the mechanistic endpoints will be done at the end of the trial and will be described in a statistical analysis plan for mechanistic studies.

8.4 Interim Analysis

Interim analyses of data will be reported to the DSMB at planned DSMB meetings and as requested by the DSMB. Planned interim analyses for the DSMB will focus on study conduct and subject safety and may include information on enrollment, randomization, site activation status, major protocol deviations, subject status and demographics, and safety analyses. In addition, the DSMB may review selected efficacy data.

No other interim analyses are planned.

8.5 Other Statistical Considerations

8.6 Covariates

No specific adjustments for covariates are planned for this study.

8.7 Multi-center Studies

No special consideration of site effects is planned. The number of subjects at some study sites is expected to be insufficient (< 5 subjects) for evaluation of site effects. In addition, because the maximum daily pain NRS is patient-reported rather than physician-assessed, site effects would be expected to have a minimal impact on primary endpoint analysis.

8.8 Multiple Comparisons and Multiplicity

The primary analysis for the efficacy of JBT-101 compares the individual trajectories of the 4 cohorts over time. Section 8.3.2 describes the use of Dunnett's test for multiple comparisons against the placebo group. The secondary efficacy analyses will evaluate trends for efficacy, with p-values and confidence intervals presented as descriptive measures of strength of

evidence rather than formal statistical inference. Therefore, no additional multiplicity adjustments are needed for this study.

8.9 Examination of Subgroups

Exploratory subgroup analyses of efficacy endpoints will be done based on subject Screening 7-day average of the maximum daily pain NRS score ≤ 6 versus ≥ 7 and Fibromyalgia Symptom Scale score < 13 and ≥ 13 at Visit 1 (Day 1).

8.10 Changes to the Statistical Analysis Plan

A detailed description of the planned analyses will be provided in a Statistical Analysis Plan that will be completed and signed off prior to database lock. Major changes from this protocol will be noted in the Statistical Analysis Plan. Changes to the Statistical Analysis Plan that are made subsequent to database lock will be documented in the clinical study report.

8.11 Missing Data

For the primary analysis, a longitudinal mixed model is planned, which will include all available data from all subjects in the mITT population regardless of completeness. Because this is a short study, data is expected to be missing at random, but any obvious contradictions to this assumption will be noted and considered. Standard procedures will be used to ensure that data are as complete and accurate as possible. Generally, missing data will not be imputed. Deviations from this approach will be specified in the Statistical Analysis Plan.

9 ACCESS TO SOURCE DATA AND DOCUMENTS

Each participating site will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects participating in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, each site must permit authorized representatives of the IND sponsor(s), the DAIT-SACCC, Corbus Pharmaceuticals Holdings, Inc., and health authorities to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other subject data may be copied (obscuring any personally identifying information). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. Participating sites will normally be notified in advance of auditing visits.

All subject records and study documentation will be kept after the protocol is completed. This will include all documentation of AEs, records of study drug receipt and dispensation, and all IRB correspondence. All study records will be kept for at least two years after the investigation is completed.

10 DATA COLLECTION, QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented. The period of record retention should be consistent with the record retention policies of the sponsoring agency or applicable regulatory agencies. However, in certain instances, documents should be retained for a longer period if required by the applicable regulatory agency or by the National Institutes of Health.

The investigator will report all major protocol deviations to DAIT and the DAIT-SACCC per the instructions in the Autoimmunity Centers of Excellence (ACE) Manual of Procedures. The DAIT-SACCC will forward reports of protocol deviations to the responsible DAIT/NIAID medical officer for review as specified in the Manual of Procedures.

The DAIT-SACCC is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

Data will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, and clinical subject charts. Data from these source materials will be transmitted to the DAIT-SACCC via one of two mechanisms. Data collected electronically at central laboratories will be transferred electronically directly from the laboratory to the DAIT-SACCC using standard secure data transfer procedures. Data collected at the clinical sites will be transmitted to the DAIT-SACCC using an internet-based remote data entry system. Clinical site personnel use an internet browser to key data into eCRFs; each CRF page is submitted to the clinical database electronically as the page is completed. Univariate data validation tests are performed as the data are keyed. The clinical database is backed up nightly; backup tapes are saved in a secure, off-site location. At any time, authorized site personnel may log in to the remote data entry system, review and correct previously entered data, or key additional data. The data will be further validated per the study data validation plan via a series of computerized and manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed and any resulting queries will be resolved with the investigators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

The DAIT-SACCC will periodically visit the participating clinical sites and audit the source documents in order to validate the data in the DAIT-SACCC central database. Data will be provided using the subject's screening or enrollment number, the DAIT-SACCC will not collect personally identifying information such as the subject's name or social security number. Subjects will provide demographic information such as race, ethnicity, and birth date.

Data collected by the DAIT-SACCC will be held in the strictest confidence, and are protected from access that could reveal personally identifying information about any subject in the trial.

11 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

The study will be conducted according to GCP guidelines, U.S. 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards.

11.1 Compliance with Good Clinical Practices

This trial will be conducted in compliance with the protocol, current GCPs recommended by the ICH and the applicable regulatory requirements for participating institutions. These include the tenets of the Declaration of Helsinki and review and approval by the appropriate ethics review committee or IRBs of participating organizations. The DAIT-SACCC will assure compliance through a program of quality assurance audits performed both at participating sites and within the DAIT-SACCC for data quality and adherence to protocol requirements. The DAIT-SACCC is operated by Rho Federal Systems Division, Inc. (RhoFED), Chapel Hill, North Carolina under a cooperative agreement with NIAID.

11.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and associated informed consent documents by an appropriate ethics review committee or IRB. Any amendments to the protocol or consent materials must be approved by the IRB before they are placed into use. In both the United States and in other countries, only institutions holding a current Federal Wide Assurance issued by the Office of Human Research Protection (OHRP) at the Department of Health and Human Services (DHHS) may participate.

The investigator will inform the IRB of serious or unexpected AEs that might occur during the study and are likely to affect the safety of the subjects, or the conduct of the study. The investigators will comply fully with all IRB requirements for both the reporting of AEs, protocol or consent form changes, as well as any new information pertaining to the use of the study medication that might affect the conduct of the study.

11.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki, as well as compliance with all IRB requirements, will be implemented in the study, before any protocol-specified procedures are carried out. A standard consent form for subject participation will be provided with the protocol to each institution. Any modifications to the standard information in the template will require review and approval by DAIT/NIAID. Informed consent will be obtained in accordance with 21 CFR 50.52. Information may be given to subjects in oral, written, or video form by the investigator. All prospective subjects will be given ample time to read the consent form, and ask questions, before signing.

If subjects are to be enrolled who do not speak and read English, the consent materials must be translated into the language appropriate for the enrolling subject. Translated documents

must be certified to contain the complete descriptions provided in the English version of the document. If an interpreter is used to provide or assist in describing the consent materials to an enrolling subject, the interpreter must also sign the consent materials certifying their involvement with the consent process.

After completion, a copy of the signed consent form will be given to the subject. The original signed consent form will be kept on file in the subject's study chart, available for inspection by regulatory authorities, both federal and institutional.

11.4 Data and Safety Monitoring Board

The responsibility for reviewing the ethical conduct of the study and for monitoring reports of evidence of adverse or beneficial effect is assigned to the DAIT Autoimmunity DSMB. The DSMB is an independent group composed of biomedical ethic experts, physicians, and other scientists who are responsible for continuing review of study information. The DSMB makes recommendations to DAIT/NIAID on issues affecting the course and conduct of this clinical study.

11.5 Study Termination

In the event that the study is discontinued, sites will immediately notify subjects to terminate study agent and return for a close-out visit to the site within 30 days.

12 FINANCING AND INSURANCE

Participating institutions must comply with their institution's policies on compensation, insurance, and indemnity. Institutions must have adequate liability insurance coverage to satisfy their local and national requirements for study participation.

13 PUBLICATION POLICY

The Autoimmunity Centers of Excellence (ACE) policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ACE internet website at http://www.rhoworld.com. Study investigators are encouraged to communicate and publish study results with prior notification of DAIT, NIAID, and Corbus Pharmaceuticals Holdings, Inc. The following procedure is suggested:

1. Manuscripts, abstracts, posters and other material for public distribution will be submitted to DAIT, NIAID, and Corbus Pharmaceuticals Holdings, Inc. at least 30 days prior to submission for publication or public presentation.
2. DAIT, NIAID, and Corbus Pharmaceuticals Holdings, Inc. will review and comment on the proposed material within 30 days.
3. DAIT, NIAID, and/or Corbus Pharmaceuticals Holdings, Inc. may ask that confidential information be deleted or redacted in this case where a patent may be filed or where confidential information is involved. Publication or presentation may be delayed up to 60 additional days in order to file a patent application.

14 APPENDICES

14.1 Appendix A: Reproductive Potential and Effective Methods of Contraception

Women are considered to have "no reproductive potential" if they meet any one of the following criteria:

- Hysterectomy
- Bilateral oophorectomy
- Bilateral salpingectomy, or
- Post-menopausal with no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone in the postmenopausal range can be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.

Highly effective methods of birth control are those that result in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly. Examples of highly reliable method of birth control when used consistently and correctly are given:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner

Other acceptable method of birth control:

- Double barrier (male condom with or without spermicide used in combination with a diaphragm or cervical cap with spermicide)
- Sexual abstinence. Abstinence is only acceptable when this is the preferred and usual life style of the individual.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus) and lactational amenorrhea method are not acceptable means of contraception.

14.2 Appendix B: Fibromyalgia Symptom Scale

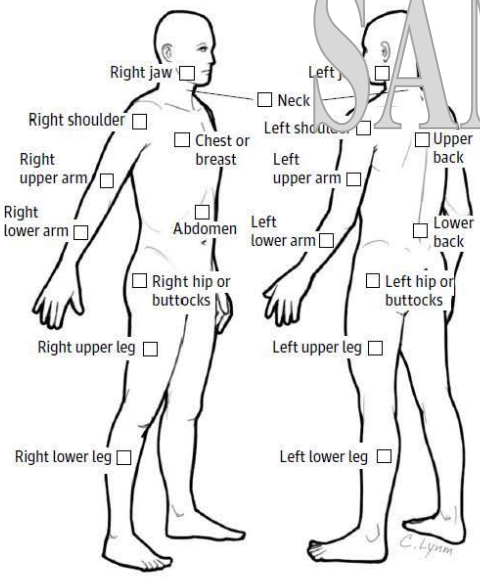
ALE09 FIBROMYALGIA SYMPTOM SCALE
REQUIRED SOURCE DOCUMENT

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 problem; 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)*

14.3 Appendix C: Lupus Activity Patient's Global Assessment

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.

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:** _____

14.4 Appendix D: ARCI-M Questionnaire (Pre-Dose)

ALE09 ADDICTION RESEARCH CENTER INVENTORY – MARIJUANA (ARCI-M)
PRE-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 has 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)*

14.5 Appendix E: ARCI-M Questionnaire (Post-Dose)

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)*

14.6 Appendix F: PROMIS-29 Short Form

PROMIS-29 v2.0

REQUIRED SOURCE DOCUMENT COVER PAGE

Rave EDC Page: PROMIS-29

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

Participant Instructions:

Please complete the attached survey and return it to your ALE09 Study Coordinator.
Please initial and date this form as indicated.

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

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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	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 Soci[illegible] Roles and Activities	**N[illegible]r**	**[illegible]arely**	**Som[illegible]mes**	**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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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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14.7 Appendix G: PROMIS Item Bank v2.0 - Cognitive Function

PROMIS ITEM BANK V2.0 COGNITIVE FUNCTION
REQUIRED SOURCE DOCUMENT COVER PAGE
Rave EDC Page: PROMIS Item Bank v2.0-Cognitive Function

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

Participant Instructions:
Please complete the attached survey and return it to your ALE09 Study Coordinator.
Please initial and date this form as indicated.

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

PROMIS Item Bank v2.0 – Cognitive Function

Cognitive Function

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)**
PC1r	I have had trouble forming thoughts	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC2r	My thinking has been slow.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC3r	My thinking has been foggy.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC5r	I have had trouble adding or subtracting numbers in my head	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC7r	I have made mistakes when writing down phone numbers	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC8r	I have had trouble concentrating.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC10r	I have had trouble finding my way to a familiar place.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC11r	I have had trouble remembering where I put things, like my keys or my wallet	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC12r	I have had trouble remembering whether I did things I was supposed to do, like taking a medicine or buying something I needed.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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PROMIS Item Bank v2.0 – Cognitive Function

	In the past 7 days...	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
PC13r	I have had trouble remembering new information, like phone numbers or simple instructions	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC14r	I have had trouble recalling the name of an object while talking to someone.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC18r	I have had trouble speaking fluently	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC21r	I have walked into a room and forgotten what I meant to get or do there.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC22r	I have needed medical instructions repeated because I could not keep them straight.....	☐ 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
PC26r	I have forgotten names of people soon after being introduced.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC28r	My reactions in everyday situations have been slow.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC30r	Other people have told me I seemed to have trouble remembering information....	☐ 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

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PROMIS Item Bank v2.0 – Cognitive Function

	In the past 7 days...	**Never**	**Rarely (Once)**	**Sometimes (Two or three times)**	**Often (About once a day)**	**Very often (Several times a day)**
PC37r	My thinking has been slower than usual ..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC38r	I have had to work harder than usual to express myself clearly	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC39r	I have had more problems conversing with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC40r	I have had to use written lists m... oft...n than usual so I would not forget th...gs	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC41r	I have had trouble keeping track of what I was doing when interrupted	☐ 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
PC48r	I have hidden my problems with memory, concentration, or making mental mistakes so that others would not notice.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC49r	I have been upset about my problems with memory, concentration, or making mental mistakes.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC50r	My problems with memory, concentration, or making mental mistakes have interfered with my ability to work	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC51r	My problems with memory, concentration, or making mental mistakes have interfered with my ability to do things I enjoy	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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PROMIS Item Bank v2.0 – Cognitive Function

	In the past 7 days...	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
PC53r	My problems with memory, concentration, or making mental mistakes have interfered with the quality of my life.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC-CaPS25r	I have had difficulty multi-ta[illegible]g.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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14.8 Appendix H: Treatment Satisfaction Survey (Participant)

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.

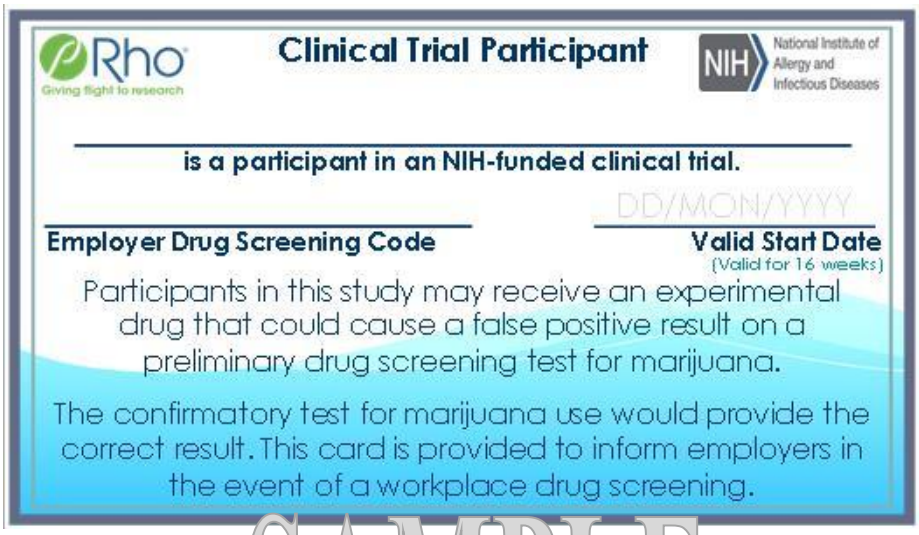
QUESTION	ANSWER
1) Did you receive clinical benefit from the experimental drug treatment you received during this research study?	❑ Yes ❑ No
2) What treatment do you think you likely received during this study?	❑ JBT-101 ❑ Placebo ❑ Can't tell
3) Would you choose to continue taking the same experimental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

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

14.9 Appendix I: Participant Drug Screening Materials

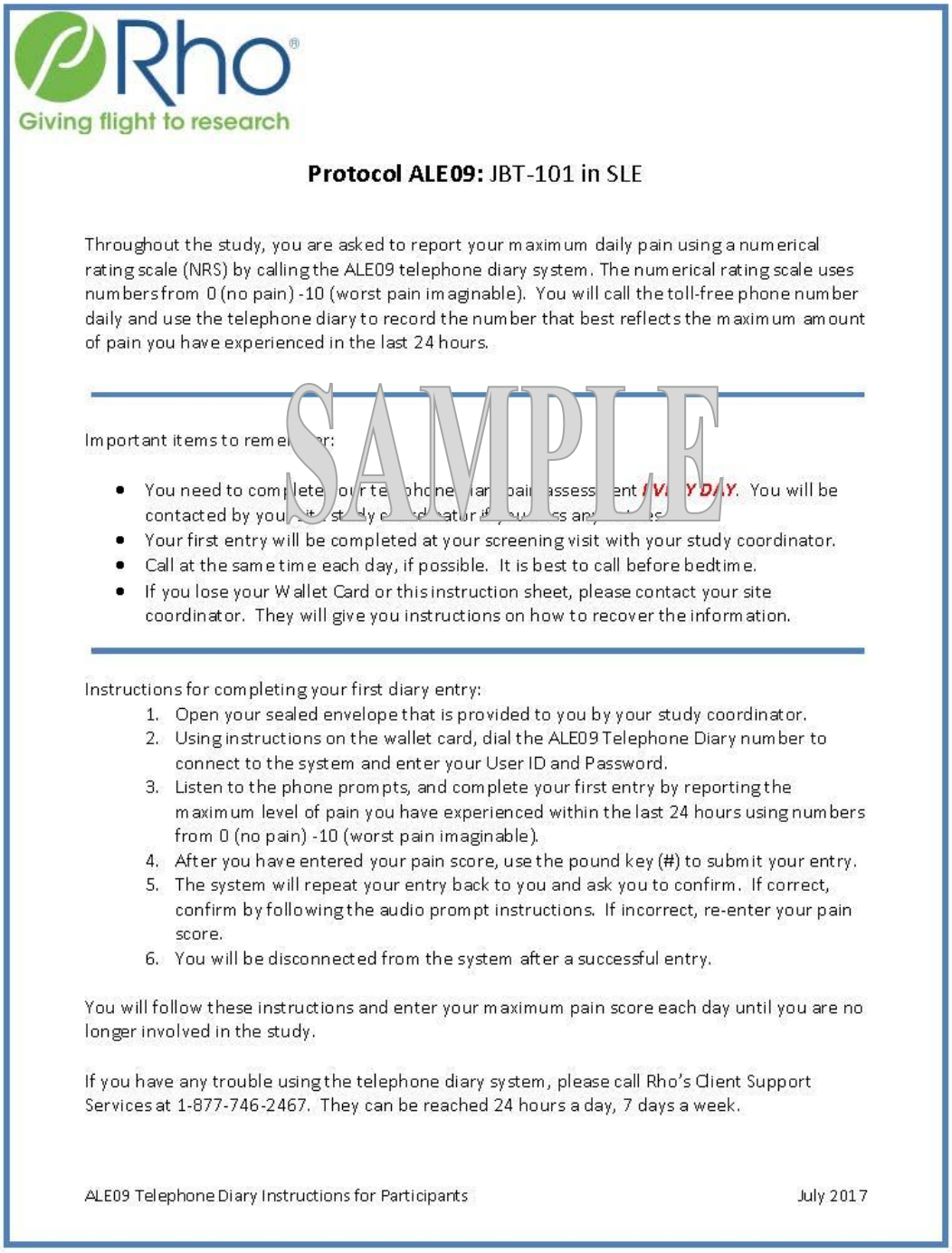
Clinical Trial Participant Identification Card:

Front:



Back:

14.10 Appendix J: Participant Daily Pain NRS Materials



Rho
Giving flight to research

Protocol ALE09: JBT-101 in SLE

Throughout the study, you are asked to report your maximum daily pain using a numerical rating scale (NRS) by calling the ALE09 telephone diary system. The numerical rating scale uses numbers from 0 (no pain) -10 (worst pain imaginable). You will call the toll-free phone number daily and use the telephone diary to record the number that best reflects the maximum amount of pain you have experienced in the last 24 hours.

SAMPLE

Important items to remember:

- You need to complete your telephone diary pain assessment EVERY DAY. You will be contacted by your study coordinator if you miss any entries.
- Your first entry will be completed at your screening visit with your study coordinator.
- Call at the same time each day, if possible. It is best to call before bedtime.
- If you lose your Wallet Card or this instruction sheet, please contact your site coordinator. They will give you instructions on how to recover the information.

Instructions for completing your first diary entry:

1. Open your sealed envelope that is provided to you by your study coordinator.
2. Using instructions on the wallet card, dial the ALE09 Telephone Diary number to connect to the system and enter your User ID and Password.
3. Listen to the phone prompts, and complete your first entry by reporting the maximum level of pain you have experienced within the last 24 hours using numbers from 0 (no pain) -10 (worst pain imaginable).
4. After you have entered your pain score, use the pound key (#) to submit your entry.
5. The system will repeat your entry back to you and ask you to confirm. If correct, confirm by following the audio prompt instructions. If incorrect, re-enter your pain score.
6. You will be disconnected from the system after a successful entry.

You will follow these instructions and enter your maximum pain score each day until you are no longer involved in the study.

If you have any trouble using the telephone diary system, please call Rho's Client Support Services at 1-877-746-2467. They can be reached 24 hours a day, 7 days a week.

ALE09 Telephone Diary Instructions for Participants July 2017

Participant Wallet Card front:

ALE09 Telephone Diary
1-877-208-6060 (toll free)
System User ID & Password
User ID: **«patient_id»**
Password: **«user_password»**

Participant Wallet Card back

ALE09 Telephone Diary
*****Please, call EVERY DAY*****

Questions or issues?
Call Rho Client Support Services at **1-877-746-2467.** They are available 24 hours a day, 7 days a week.

Please keep your Wallet Card and these instructions.

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