Official Title: A Phase II, Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of GDC-0853 in Patients With Moderate to Severe Active Systemic Lupus Erythematosus

NCT Number: NCT02908100

Document Date: Protocol Version 3: 09-February-2018

PROTOCOL

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PROTOCOL NUMBER:	GA30044
VERSION NUMBER:	3
EUDRACT NUMBER:	2016-001039-11
IND NUMBER:	130,011
TEST PRODUCT:	GDC-0853 (RO7010939)
MEDICAL MONITOR:	[redacted], M.D., MPH
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 27 June 2016
DATE AMENDED:	Version 2: 12 May 2017 Version 3: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	09-Feb-2018 22:54:12

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized as follows and are reflected as applicable in the protocol:

- The Medical Monitor has been updated.
- The study design figure has been modified without changes to the overall design (Figure 1).
- The British Isles Lupus Activity Group (BILAG) and Physician's Global Assessment (PGA) components of the SRI-4 have been removed from the secondary endpoints because those components are not standalone endpoints. The reduction of at least 4 points from baseline in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K remains an exploratory endpoint because it is the only component within the SRI-4 that shows clinical improvement (Section 2).
- The endpoint to evaluate SRI-4 response at Week 48 with and without oral corticosteroid (OCS) taper to evaluate patients with high plasmablast signature levels to have an enhanced clinical response to GDC-0853 relative to patients with low levels remains a secondary endpoint. The other corresponding endpoints to evaluate SRI-4 response at Week 24 with and without OCS taper have been re-categorized as exploratory endpoints (Section 2, Section 6.4.2, and Section 6.4.3).
- To better characterize the progression of lupus in patients on trial and provide other endpoints that may be less sensitive to placebo response, the BILAG-based Composite Lupus Assessment (BICLA) and SRI-6 endpoints have been re-categorized from exploratory to secondary endpoints (Section 2).
- Pharmacokinetic (PK) objectives and endpoints have been updated to clarify that the stated analysis will be conducted solely on pharmacokinetic data generated from the current study. PK analyses that incorporate data from multiple clinical studies (potentially including GS39684), including population PK analyses using models that incorporate pooled data, may be conducted separately (Section 2).
- The length of the study has been updated from 62 to 61 weeks to reflect the sum of the 5-week screening period, 48-week study conduct period, and 8-week safety follow-up period (Section 3.2.1).
- Language has been added to clarify the reference for nonclinical efficacy data for the BTK inhibitor GDC-0834 (Section 3.3.1).
- The minimum SLEDAI-2K score requirement for subjects to enroll in the study has been increased from a 6 to an 8 to ensure severity of lupus is appropriate for the study (Section 4.1.1).
- The requirements for at least one standard oral treatment for SLE within the dose ranges specified in the inclusion criteria have been clarified. Additional SLE treatments do not need to be above the lower limits of doses listed (Section 4.1.1).

- The maximum doses of mycophenolate mofetil and mycophenolic sodium have been increased to allow for patients with stable renal function or patients with more active lupus disease to be included in the study (Section 4.1.1).
- The lupus nephritis exclusion criteria have been updated to allow for patients with mild renal dysfunction, similar to other recent lupus trials, to enrich for patients with more serologic activity who might be expected to respond better to study treatment (Section 4.1.2).
- The exclusion criterion regarding history of anti-phospholipid antibody syndrome has been further clarified to explain that low doses of aspirin or clopidogrel for anti-coagulation are not excluded but should follow local regulations (Section 4.1.2).
- Language has been added to clarify tuberculosis exclusion criteria (Section 4.1.2).
- Time-specific medications that cannot be taken prior to screening have been clarified from days to weeks (Section 4.1.2).
- Language has been added to clarify how sites should document study drug administration (Section 4.3.2.2).
- Language has been added to clarify that anti-malarial doses should remain stable on study (Section 4.3.2.3.1).
- Steroid burst treatment and tapering requirement language has been clarified (Section 4.3.2.3.3).
- Clarification has been provided for steroid doses that are considered escape therapy (Section 4.3.2.3.4).
- Language has been added to clarify that low doses of aspirin may not be taken at the same time as anti-platelet agents (Section 4.4.1.5).
- Anti-platelet agents have been removed from the list of prohibited therapies as there have been no bleeding events to date and there does not appear to be an increased risk from anti-platelet agents (Section 4.4.2).
- Leflunomide, penicillamine, and sulfasalazine were primarily considered exclusionary since they affect the progression of rheumatoid arthritis (another indication being assessed with GDC-0853). Since these medications are unlikely to be used in lupus, they have been removed from the prohibited medications list (Section 4.4.2).
- IV and IM steroids (except as escape therapy) have been added to the prohibited therapies section (Section 4.4.2).
- The CYP3A drug-drug interaction section was updated based on new data from clinical pharmacology studies (Section 4.4.2.2).
- Clarifying language has been added to patient preparation for electrocardiograms (Section 4.5.10.2).
- The hepatotoxicity language has been updated to clarify the expected AST/ALT values required for eligibility on study do not depend on creatinine kinase (CK), aldolase, and lactate dehydrogenase (LDH) values obtained at screening (Section 5.1.1.6).

- Language has been revised to account for the fact that some sites may not allow follow-up on partner pregnancies (Section 5.4.3.2).
- Language has been updated to clarify the analysis method for the primary endpoint (Section 6.4.1).
- Language has been revised to clarify the PK analysis details (Section 6.6).
- Language has been added to clarify that the Sponsor will review all protocol deviations as per the Sponsor's Standard Operating Procedures, and prospective requests to deviate from the protocol are not allowed (Section 9.2).
- The Web site URL for the "Roche Global Policy on Sharing of Clinical Trials Data" has been corrected (Section 9.5).
- Height measurement has been added to the Week 48 visit to align with the open-label extension study and to allow for comparison to baseline (Appendix 1).
- CK, aldolase, and LDH have been added to the Week 48 visit to align with the open-label extension study and to allow for comparison to baseline (Appendix 1).
- T, B, and natural killer cells (TBNK) has been added at screening to allow the adjudication committee to review CD19 count during screening (Appendix 1).
- The blood sample for pharmacodynamics (PD) RNA, PD biomarker serum and plasma, exploratory urinary biomarker collection, and peripheral blood mononuclear cells (PBMC) will no longer be collected at the early termination visit in order to reduce study procedure related burden for patients as these samples are not necessary for safety follow-up (Appendix 1).
- The Systemic Lupus International Collaborating Clinics (SLICC) Damage Index has been updated to the 1997 version including pancreatic insufficiency and tendon rupture (Appendix 7).
- Appendix 19 has been updated based on new clinical pharmacology data.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS**
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SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the contact provided to the investigator at study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS**
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PHASE:	Phase II
INDICATION:	Systemic Lupus Erythematosus
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of GDC-0853 compared with placebo in patients with moderately to severely active systemic lupus erythematosus (SLE). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the clinical efficacy of GDC-0853 in combination with SOC	• SRI-4 response at Week 48
Secondary Efficacy Objectives:	
• To evaluate the clinical efficacy of GDC-0853 over time using the SRI-4 as a standardized disease activity measure	• SRI-4 response at Week 48 with a sustained reduction of OCS dose to <10 mg/day and $\leq$ Day 1 dose during Week 36 through Week 48 • SRI-4 response at Week 24 with a sustained reduction of OCS dose to <10 mg/day and $\leq$ Day 1 dose during Week 12 through Week 24 • SRI-4 response at Week 24
• To evaluate if patients with high plasmablast signature levels have an enhanced clinical response to GDC-0853 relative to patients with low levels	• *SRI-4 response at Week 48* • *SRI-4 response at Week 48 with a sustained reduction of OCS dose to <10 mg/day and $\leq$ Day 1 dose during Week 36 through Week 48*
• *To evaluate the clinical efficacy of GDC-0853 over time using BICLA and SRI-6 as standardized disease activity measures*	• *SRI-6 response at Weeks 24 and 48* • *BICLA response at Weeks 24 and 48*

Objectives (cont'd)	Corresponding Endpoints (cont'd)
Exploratory Efficacy Objectives:	
• To evaluate the clinical efficacy of GDC-0853 over time with multiple standardized disease activity measures	• SRI-5, *7, and* 8 response at Week 48 • SRI-5-8 response at Week 48 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 36 through Week 48 • SRI-5, *7, and* 8 response at Week 24 • SRI-5-8 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24
• To evaluate the ability of GDC-0853 to prolong the time to first SLE flare	• Time to first SLE Flare as defined by the SFI • Time to first SLE Flare as defined by the BILAG
• To evaluate the ability of GDC-0853 to decrease the number of total SLE flares	• Total number of SLE flares as defined by the SFI • Total number of SLE flares as defined by the BILAG
• *To evaluate the clinical efficacy of GDC-0853 over time based on the individual components of the SRI*	• *Reduction of ≥ 4 points from baseline in the SLEDAI-2K at Weeks 24 and 48*
• *To evaluate if patients with high plasmablast signature levels have an enhanced clinical response to GDC-0853 relative to patients with low levels*	• *SRI-4 response at Week 24* • *SRI-4 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24*
• To evaluate the ability of GDC-0853 to improve cutaneous manifestations of SLE	• Change in CLASI Total Activity Score at Week 24 and Week 48 relative to baseline (i.e., Day 1) • ≥ 50% improvement in CLASI score in patients with at least moderate skin involvement (baseline CLASI ≥ 10)
• To evaluate the ability of GDC-0853 to *prevent* systemic damage	• Change in SLICC/*ACR Damage Index* at Week 24 and Week 48 relative to baseline
• To evaluate the ability of GDC-0853 to improve arthritis	• Change in joint involvement at Week 24 and Week 48 relative to baseline using the 28-Joint Count assessment • ≥ 50% improvement in the 28 Joint Count assessment for patients with ≥ 8 swollen or tender joints at baseline
• To evaluate the ability of GDC-0853 to improve fatigue	• Change in FACIT-Fatigue score at Week 24 and Week 48 relative to baseline
• To evaluate the ability of GDC-0853 to improve Patient's Global Assessment	• Change in Patient's Global Assessment of disease activity at Week 24 and Week 48 relative to baseline
• To evaluate if GDC-0853 is steroid sparing	• Change in cumulative steroid dose at Week 24 and Week 48 relative to baseline • Glucocorticoid toxicity at Weeks 12, 24, 36, and 48 relative to baseline using the GTCI • *A*chieving a corticosteroid dose of < 10 mg/day among patients at ≥ 10 mg/day at baseline

Objectives (cont'd)	Corresponding Endpoints (cont'd)
Safety Objective:	
• To evaluate the safety of GDC-0853 in combination with SOC therapy in patients with moderate to severe active SLE	• The nature, frequency, severity, and timing of adverse events using the NCI CTCAE scale to grade adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results following GDC-0853 administration
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of GDC-0853 in patients	• *Plasma concentrations of GDC-0853 at specified timepoints*
Exploratory Pharmacokinetic Objectives:	
• To evaluate the relationship between measures of drug exposure and pharmacodynamic effect, efficacy, and safety of GDC-0853	• Exploratory biomarker measures in Table 3 • SRI-4 response and other measures of efficacy or clinical activity • The nature, frequency, severity, and timing of adverse events • Changes in vital signs, ECGs, and clinical laboratory results following GDC-0853 administration
• To evaluate the impact of selected covariates on measures of GDC-0853 exposure and/or response	• Gender, age, body weight, and other patient demographics • *GDC-0853 PK* • SRI-4 and other measures of efficacy or clinical activity
• To evaluate the impact of genetic polymorphisms on measures of GDC-0853 exposure	• Presence of genetic polymorphisms and/or genotype(s) • *GDC-0853 PK*
Exploratory Biomarker Objectives:	
• To evaluate the relationship of GDC-0853–induced changes in biomarkers (see Table 3) and efficacy	• Primary and secondary endpoints at mentioned above • Biomarker endpoints (see Table 3)
• To evaluate whether biomarkers (e.g., but not limited to plasmablasts, autoantibodies and other inflammatory biomarkers) measured at baseline may identify patients with enhanced clinical response to GDC-0853	• Primary and secondary efficacy endpoints as noted above • Time to first SLE Flare as defined by the SFI • Time to first SLE Flare as defined by the BILAG • Total number of SLE flares as defined by the SFI and BILAG
• To evaluate whether the levels of the aforementioned biomarkers associate with disease progression	• Primary and secondary efficacy endpoints as noted above

AUC_{0-t} = area under the concentration–time curve from time 0 to time t; BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Activity Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CL/F = apparent clearance; C_{max} = maximum concentration observed; CTCAE = Common Terminology Criteria for Adverse Events; C_{trough} = steady-state concentration at the end of a dosing interval; ECG = electrocardiogram; FACIT = Functional Assessment of Chronic Illness Therapy; GTCI = Glucocorticoid Toxicity Change Index; NCI = National Cancer Institute; OCS = oral corticosteroids; PK = pharmacokinetic; QOL = quality of life; SLEDAI $-2K = Systemic$ Lupus Erythematosus Disease Activity Index 2000; SFI = $SELENA\text{-}SLEDAI\ SLE$ Flare Index; SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus; SOC = standard of care; SRI = Systemic Lupus Erythematosus Responder Index; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration.

Study Design

Description of Study

This is a multicenter, Phase II, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the safety and efficacy of GDC-0853 in combination with SOC therapy in patients with moderate to severe active SLE. Moderate to severe SLE will be defined at screening and baseline (i.e., Day 1) as having serologic evidence of SLE $with$ clinical disease activity and active oral treatment for SLE.

The study will consist of a screening period (up to 35 days) and a 48-week treatment period, followed by either an 8-week safety follow-up visit at Week 56 or possible enrollment into an open-label extension (OLE) study. Approximately 240 patients, meeting all eligibility criteria, will be randomized in a 1:1:1 ratio to one of the following 3 arms:

Arm A: GDC-0853 200 mg twice daily (BID)

Arm B: GDC-0853 150 mg once daily (QD)

Arm C: placebo

All 3 arms will receive blinded study drug in combination with background SOC therapy. Randomization will be stratified by disease activity at screening, entry dose of oral corticosteroids (OCS), and geographic region. All patients will receive blinded study drug twice daily (GDC-0853, placebo, or both to maintain the blind) from baseline to Week 48 and will be assessed at site visits every 4 weeks (including a site-initiated phone call at Week 1) during the treatment period.

Pre-enrollment adjudication by the Medical Monitor and his/her designees will occur for all patients who complete screening prior to their randomization into the study. The Medical Monitor or assigned designee will make the final decision whether or not a patient is eligible for randomization.

Background SOC therapy may consist of an OCS (which must be stable for 2 weeks prior to screening, dose not to exceed 40 mg/day of prednisone or equivalent) and/or certain oral immunosuppression regimens (which must be stable for 2 months prior to screening). All immunosuppressive and anti-malarial medication will be kept stable throughout the trial unless dose reductions are necessary due to toxicity. All patients receiving immunosuppressive treatments are also encouraged to be on supportive therapy (e.g., folic acid, calcium, vitamin D). For patients who are on angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) at study entry, doses of ACE inhibitors or ARBs should be kept stable for at least 10 days prior to randomization and throughout the trial whenever possible. $It\ is\ strongly\ recommended\ that$ ACE inhibitors or ARBs not be initiated during the OCS stability windows.

For patients on an OCS at baseline, there will be two, 12-week, OCS taper windows available to achieve the pre-specified OCS taper of $<$ 10 mg/day prednisone or equivalent. The dose at the end of each OCS-stability window (i.e., the 12-week period immediately following the 12-week OCS taper window) will then be kept stable for an additional 12 weeks.

In the case of increased SLE disease activity, there can be two temporary increases in the corticosteroid dose, called “bursts,” that may be administered if needed. A burst may only be administered during a burst window (defined as the first 10 weeks of each OCS taper window)

and only once per window. A burst is defined as a temporary increase in corticosteroid dose (up to 40 mg/d prednisone or equivalent for Burst Window 1, and up to 20 mg/d prednisone or equivalent for Burst Window 2) with a taper back down to the dose immediately preceding the burst, all within a 2-week period.

If additional treatment is needed beyond the permitted burst therapy because of active SLE, as identified by the investigator, the patient may receive escape therapy; however, such patients will be considered trial-defined non-responders for the purposes of the primary analysis.

During taper, burst, and permitted escape therapies, patients will continue to receive their designated dose of study treatment.

Starting at the screening period, all patients must record their actual OCS use weekly, as instructed by study staff.

An unblinded IMC and Scientific Oversight Committee will be used to monitor multiple safety assessments. In addition, an interim analysis will be conducted after 50-80 patients in each treatment arm have completed 24 weeks of treatment and have been evaluated for SLE Responder Index (SRI)-4 response, in order to conduct a preliminary assessment of the benefit-risk profile of GDC 0853 and potentially enable early stopping for futility and/or safety issues.

Number of Patients

Approximately 240 patients, who meet all eligibility criteria, will be enrolled into the study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years, inclusive
- Able to comply with the study protocol
- Fulfillment of SLE classification criteria according to either the current American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria at any time prior to or at screening
- At least one serologic marker of SLE at screening as follows:
  - Positive antinuclear antibody (ANA) test by immunofluorescent assay with titer ≥ 1:80; OR
  - Positive anti-double-stranded DNA (anti-dsDNA) antibodies; OR
  - Positive anti-Smith antibody
- At both screening and Day 1, moderate to severe active SLE, defined as meeting all of the following unless indicated otherwise:
  - SLEDAI-2K score ≥ *8* (at screening only) with clinical SLEDAI-2K score ≥ 4.0 *(at both screening and Day 1)*
  - Physician's Global Assessment ≥ 1.0 (out of 3)
  - Currently receiving at least one standard oral treatment *(e.g., corticosteroids, anti-malarials, and/or immunosuppressants)* for SLE *within the dose ranges, as specified below*
    - If on an OCS, the dose must be ≤40 mg/day prednisone (or equivalent) and must have been stable for at least 2 weeks prior to screening as well as during screening
    - If on anti-malarial or *immunosuppressant* therapies, may only be receiving medications from the following list within the specified dose range; dose and route of administration must be stable for 8 weeks prior to screening as well as during screening:
      - Azathioprine: 1 to 2.5 mg/kg/day
      - Methotrexate: 7.5 to 25 mg/week
      - Mycophenolate mofetil: 500 to *3000* mg/day

- Mycophenolic sodium: 360 to *2160* mg/day
- Hydroxychloroquine: 200 to 400 mg/day
- Chloroquine: 100 to 250 mg/day
- Quinacrine: 100 to 200 mg/day
- Other: Consult with Medical Monitor

Note: Any combination of azathioprine, methotrexate, mycophenolate mofetil, or mycophenolic sodium is prohibited.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the study treatment period and for a minimum of 60 days after the last dose of study drug or longer as required by local requirements for other standard of care medications. Women using estrogen-containing hormonal contraceptives as a method of contraception must also use a barrier.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (> 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Established proper use of hormonal contraceptives that inhibit ovulation also have a failure rate of < 1% per year; however, women using estrogen-containing hormonal contraceptives as a method of contraception must also use a barrier, such as a male condom, in conjunction with the hormonal contraceptives.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm as defined below:
  - Men with female partners of childbearing potential must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 120 days (16 weeks) after the last dose of study treatment. Men must refrain from donating sperm during this same period.
  - Men with pregnant female partners must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study treatment to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- *Proteinuria > 3.5 g/24 h or equivalent using urine protein-to-creatinine ratio (uPCR) in a first morning void urine sample*
- *Active proliferative lupus nephritis (as assessed by the investigator) or histological evidence of active Class III or Class IV lupus nephritis on renal biopsy performed in the 6 months prior to screening (or during the screening period)*

- *History of having required hemodialysis or high dose corticosteroids (>100 mg/d prednisone or equivalent) for the management of lupus renal disease within 90 days of Day 1*
- Neuropsychiatric or central nervous system lupus manifestations, including but not limited to: seizure, psychosis, or acute confusional state within 52 weeks of screening
- *Serum creatinine* > *2.5 mg/dL, or* estimated glomerular-filtration rate (based on the 4-variable Modification of Diet in Renal Disease equation) < 30 mL/min or on chronic renal replacement therapy
- History of receiving a solid organ transplant
- Newly diagnosed (within the last 24 weeks) transverse myelitis
- History of anti–phospholipid antibody syndrome (APLS) with or without associated consumptive coagulopathy [catastrophic anti-phospholipid syndrome] at any time*;* presence of anti-phospholipid antibodies or a history of fetal loss, but without a history of thromboembolism or current requirement for anti-coagulation, are not exclusionary.
  - Patients on *either* aspirin *up to* 325 mg/day *or clopidogrel* are not excluded. *The permitted dose of aspirin to reduce the risk of non-fatal stroke, non-fatal myocardial infarction, and vascular death in patients at high risk of arterial thrombosis should follow local regulations and guidelines.*
- Evidence of active, latent, or inadequately treated infection with *Mycobacterium tuberculosis* (TB) as follows:
  - A positive QuantiFERON TB-Gold® (QFT) *performed at screening visit*
    - *If QFT unavailable,* a Mantoux purified protein derivative (PPD) skin test *as defined by the* Centers for Disease Control and Prevention (CDC) *guidelines*, performed at the screening visit or within the 12 weeks prior to screening *and read locally*
  - A chest radiograph taken at the screening visit or documented results within the 12 weeks prior to screening (chest radiograph must be read by a radiologist), without changes suggestive of active TB infection
  - If a patient has previously received an adequate documented course of therapy for either latent (36 weeks of isoniazid in a locale where rates of primary multi-drug resistant TB infection are < 5% or an acceptable alternative regimen, according to local guidelines) or active (acceptable multi-drug regimen, according to local guidelines) TB infection, neither a PPD test nor a QFT test need to be obtained, but a chest radiograph must still be obtained if not performed within the prior 12 weeks; this chest radiograph must be without changes suggestive of active TB infection
- *NOTE:* Patients with a history of *Bacille Calmette-Guérin (*BCG*)* vaccination should be screened using the QFT test only.

  If *the* initial QFT *test* is indeterminate, a confirmatory test with either a QFT or T-SPOT® *TB test* (*performed locally* if available). The PI may consult with the Medical Monitor to discuss selection of confirmatory test based on the patient's disease status and baseline immunosuppression.
  - An indeterminate QFT test followed by a negative QFT or negative T-SPOT® test should be considered a negative diagnostic TB test.
  - An indeterminate QFT test followed by an indeterminate QFT test or indeterminate T-SPOT® test should be considered a positive diagnostic TB test
- Women who are pregnant or nursing (breastfeeding; within the last 12 weeks), or women intending to become pregnant, donate eggs or breast milk, or participate in in vitro fertilization during the study
  - For women of childbearing potential: Positive serum pregnancy test result at screening or on Day 1 (a serum pregnancy test is needed on Day 1 ONLY if the urine pregnancy test is positive)

- Significant and uncontrolled medical disease within the 12 weeks prior to screening in any organ system (e.g., cardiac, neurologic, pulmonary, renal, hepatic, endocrine [including uncontrolled diabetes mellitus], metabolic, GI, or psychiatric [including suicidality]) not related to SLE, which, in the investigator's or Sponsor's opinion, would preclude patient participation
- Concomitant chronic conditions, in addition to SLE, (e.g., asthma, Crohn's disease) that required oral, IV, or intramuscular (IM) steroids or immunosuppressive use in the 24 weeks prior to screening or are likely to require these during the course of the study
- History of non–gallstone-related pancreatitis or chronic pancreatitis that is judged to be clinically significant, in the opinion of the investigator (e.g., accompanied by upper abdominal pain or malabsorptive diarrhea)
- Evidence of autoimmune myositis
- History of cancer, including hematological malignancy and solid tumors, within 10 years of screening; basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix adequately treated by curative therapy more than 1 year prior to screening are not exclusionary
- History of alcohol, drug, or chemical abuse within the 1 year prior to screening as determined by the investigator
- Major surgery requiring hospitalization within 4 weeks of screening
- History of cerebrovascular accident (CVA) within 10 years or any history of hemorrhagic CVA, any history of spontaneous intracranial hemorrhage or a history of traumatic intracranial hemorrhage within 10 years
- History of clinically uncontrolled cardiac arrhythmias
- Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including
  - QT interval corrected using Fridericia's formula (QTcF) $>$ 450 msec for female patients and $>$ 430 msec for male patients demonstrated by at least two ECGs $>$ 30 minutes apart
- History of clinically significant ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as long QT syndrome or other genetic risk factors (e.g., Brugada syndrome), structural heart disease (e.g., severe left ventricular systolic dysfunction, severe left ventricular hypertrophy), coronary heart disease (symptomatic, or with ischemia demonstrated by diagnostic testing, prior coronary artery bypass grafting, or coronary lesions $>$ 70% diameter stenosis that have not been or cannot be re-vascularized), or family history of sudden unexplained death or cardiac ion channel mutations
- Current treatment with medications that are well known to prolong the QT interval (except for anti-malarials) at doses that have a clinically meaningful effect on QT, as determined by the investigator. The investigator may contact the Sponsor for confirmation if needed. The investigator may reference the website: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf
- Any condition possibly affecting oral drug absorption (e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass); procedures, such as gastric banding, that simply divide the stomach into separate chambers are not exclusionary
- Need for systemic anticoagulation with warfarin, *or* other oral or injectable anticoagulants *(*other than NSAIDs, aspirin ($\leq$ 325 mg/day), or other salicylates*)*
- Known bleeding diathesis
- Any history of hospitalization or transfusion for a GI bleed
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection or IgG $<$ 500 mg/dL

- Any known active infection during screening up to and including at the time of enrollment (with the exception of fungal nail infections or oral herpes)
- History of treated recurrent bacterial, viral, mycobacterial, or fungal infections, defined as $>$ 2 similar episodes requiring anti-microbial treatment within the past 52 weeks, with the exception of the following:
  - Oral or genital herpes (herpes simplex virus 1 [HSV1]/ herpes simplex virus 2 [HSV2])
  - Uncomplicated cystitis or asymptomatic bacteriuria
  - Uncomplicated viral, bacterial or culture-negative bronchitis without pneumonia
  - Bacterial or viral sinusitis
  - Bacterial or fungal (yeast) vaginal infections
- Any history of opportunistic infections that, in the Investigator's or Sponsor's judgment, would raise safety concerns regarding the patient's participation in the study
- Any major episode of infection requiring hospitalization or treatment with IV or IM antimicrobials within 4 weeks prior to or during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening (with the exception of prophylaxis for *Pneumocystis jiroveci* pneumonia)
- History of severe and/or disseminated viral infections, particularly herpes viruses, such as HSV1, HSV2, varicella zoster virus (VZV), cytomegalovirus (e.g., herpes encephalitis, ophthalmic herpes, disseminated zoster, cytomegalovirus colitis); uncomplicated influenza during a flu season*, herpes labialis, and genital herpes are* not exclusionary
- Evidence of chronic and/or active hepatitis B or C
  - Positive hepatitis B surface antigen (HBsAg) or hepatitis C serology (regardless of treatment status)
  - Positive hepatitis B core antibody (HBcAb)
- Received any of the following medications *and/or treatments* within the indicated period of time:
  - Plasmapheresis or IV Ig in the last 12 weeks *prior to screening*
  - B cell–depleting therapy (e.g., anti-CD20 or anti-CD19) within 24 weeks prior to screening
  - Belimumab, blisibimod, tabalumab (or other anti-B-cell activating factor [BAFF] agents), atacicept (or other anti-transmembrane activator and calcium-modulator and cyclophilin ligand [CAML] interactor [TACI] agents), epratuzumab (or other anti-CD22 agents), or denosumab within *5 half-lives or 12 weeks (whichever is longer)* prior to screening
  - Cyclophosphamide or other alkylating agents within 12 weeks prior to screening
  - Oral cyclosporine, tacrolimus, topical calcineurin inhibitors, anakinra (inhibitor IL-1), sirolimus (inhibitor IL-2), or other calcineurin inhibitors within 4 weeks prior to screening
  - Thalidomide or thalidomide derivatives within 24 weeks prior to screening
  - Tumor necrosis factor (TNF)-antagonists, tocilizumab, or other biologics not previously mentioned above within *12 weeks* prior to screening
  - Any investigational drug within 4 weeks or 5 half-lives, whichever is longer, of screening
  - Any parenteral (IV), IM, or intra-articular steroid administration within *4 weeks* prior to screening
  - Any other immunosuppressive medication for SLE not listed in the inclusion criteria, within 12 weeks or 5 half-lives prior to screening, whichever is longer, unless approved by the Medical Monitor
  - Live vaccines within 6 weeks prior to randomization; seasonal influenza and H1N1 vaccination are permitted if the inactivated vaccine formulation is administered

- Use of any of the medications, herbal supplements, or foods in the categories below should be avoided within 1 week or 5 half-lives, whichever is longer, prior to randomization, on the basis of possible drug interactions with GDC-0853 unless otherwise advised by the Medical Monitor (or delegate) as part of the adjudication process (see Section 4.4 for additional information; the screening period may be extended to meet these criteria if approved by the Medical Monitor):
  - *S*trong CYP3A inhibitors (refer to Appendix 19 for examples)
  - *Moderate or strong* CYP3A inducers (refer to Appendix 19 for examples)
- Any uncontrolled, clinically significant, laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study
- Any of the following laboratory results, for which testing may be repeated once if the initial results are out of range during screening:
  - AST or ALT $>$ 1.5 $\times$ ULN
  - Total bilirubin $>$ 1.2 ULN
  - Amylase or lipase $>$ 2 $\times$ ULN
  - Hemoglobin $<$ 7 g/dL
  - Absolute neutrophil count (ANC) $<$ 1.5 $\times$ 10^9/L
  - Absolute lymphocyte count (ALC) $<$ 0.5 $\times$ 10^9/L
  - Platelet count $<$ 50,000/μL
  - *Note: Other abnormal labs may be repeated at the discretion of the investigator. Final determination of whether the lab result is exclusionary will be made by the adjudication committee and Medical Monitor.*

End of Study

The end of study is defined as the last patient, last safety follow-up visit in this protocol, last patient to discontinue from the study, or the last patient enrolled into an OLE, if initiated, whichever occurs latest.

Length of Study

The maximum length of time on study for a patient is *61* weeks, including screening for up to 35 days, treatment for 48 weeks, and a safety follow-up period for 8 weeks *(unless enrolled* into an OLE study*)*.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is GDC-0853 50-mg tablets.

Comparator

The comparator will comprise corresponding matching placebo tablets, which will be indistinguishable in appearance.

Non-Investigational Medicinal Products

All patients who enter the study on oral immunosuppressant therapy (not including corticosteroids) *or anti-malarial medications* will be instructed to maintain their medications and doses from screening throughout the rest of the study treatment period. After entering the study, patients may not begin taking a new oral immunosuppressant except in the case of increased clinical activity requiring escape therapy.

Corticosteroids

For all patients who enter the study on oral prednisone (or permitted equivalent OCS), there will be two, 12-week, OCS taper windows (Weeks *0* to 12, and Weeks 24 to 36) where their dose, if $\geq$ 10 mg/day, will be tapered to $<$ 10 mg/day. During a taper window, patients will continue to receive their designated dose of study treatment.

The OCS rules are as follows: the OCS dose level achieved at the end of each OCS taper window will be maintained during the 12-week, OCS stability windows (Weeks 12 to 24 and Weeks 36 to 48), whether or not the target OCS dose was achieved. Patients will be instructed not to deviate from this dose level achieved at the end of the OCS taper window, unless considered clinically appropriate by the investigator.

Patients should follow the appropriate tapering schedule as determined by the investigator, taking into account the taper window timing and the target OCS dose ($<$ 10 mg/day and $\leq$ Day 1 dose). The investigator may modify a tapering schedule based on the patient's response to the reduction in corticosteroid dose. A suggested prednisone tapering schedule is provided; in addition, the investigator may consult the Medical Monitor. Once $<$ 10 mg/day is achieved, tapering completely off corticosteroids is allowed if this is deemed clinically appropriate by the investigator (i.e., if there is minimal risk of inducing flare).

It is recommended that all patients receiving corticosteroids should receive appropriate supportive therapy to help prevent steroid-induced osteoporosis (e.g., calcium, vitamin D supplements, bisphosphonates) as per local guidelines and physician preference. *Pneumocystis jiroveci* pneumonia prophylaxis is also recommended to be used as per local SOC.

Intra-articular injections and intra-lesional cutaneous injections of corticosteroids must be avoided during the *study* if possible, as these interventions will confound the efficacy assessments.

If a patient entered the study on low potency topical steroids *(e.g., Class VI and Class VII)*, the steroid can be continued during the course of the study at a stable dose

Burst Treatment

In the case of increased disease activity, the patient will have the opportunity to receive burst treatment, in addition to the study treatment, during the defined burst treatment window. The patient should return to the clinic, either at a scheduled study visit or unscheduled flare visit, to be evaluated and to receive an increase or new dose of oral prednisone as follows:

- Burst Window 1 (Weeks 0 to 10): An increase or new dose of oral prednisone up to 40 mg/day (or equivalent)
- Burst Window 2 (Weeks 24 to 34): An increase or new dose in oral prednisone up to 20 mg/day (or equivalent)

When using corticosteroids as a burst treatment, the investigator will temporarily increase the dose of corticosteroids and then taper the patient back down to their previous corticosteroid dose *used prior to the initiation of the burst*, all over the course of 2 weeks. Patients will continue to receive their designated dose of study treatment during the burst treatment. The previous corticosteroid dose is defined as the dose of corticosteroids taken for the 2 weeks prior to the burst (if the dose changed during the 2 weeks, the investigator may choose which dose to use). If the patient was not previously on corticosteroids, the investigator will taper the patient back off corticosteroids completely. If the patient was on a corticosteroid-tapering schedule at the time of the burst treatment, the investigator will revise the tapering schedule as necessary to meet the target OCS dose ($<$ 10 mg/day and $\leq$ Day 1 dose) by the end of the taper window, *if clinically appropriate.*

Patients may receive corticosteroids for emergent illness other than SLE (e.g., trauma, asthma) or if clinically warranted to prevent adrenal crisis (e.g., prior to surgery). If possible, treatment in these cases should last no more than 7 days.

Escape Therapy

If an increase in immunosuppressive therapy (referred to as "escape therapy") is deemed medically necessary due to increased SLE disease activity, the patient will be given escape therapy, which will be recorded on the Steroid and Immunosuppressant eCRF. Patients receiving the following escape therapies, *may* be allowed to remain on study drug *after discussion with the Medical Monitor* but will be considered a protocol-defined "non-responder" in the primary analysis:

- IV *or IM* steroids *(at doses greater than 40 mg prednisone PO or equivalent)*

- OCS doses exceeding the limits described elsewhere in the protocol *(e.g., prednisone (or equivalent) doses of > 40 mg/day during the first 24 weeks of the study, or > 20 mg/day between Weeks 24 and 48)*
- New or increased doses of an immunosuppressant *or anti-malarial* medication up to the maximum allowed in the study

NOTE: Combinations of immunosuppressant medications that are not allowed in the inclusion and exclusion criteria are prohibited during the study.

Statistical Methods

Primary Analysis

The primary efficacy *endpoint* for this study is SRI-4 response at Week 48.

The primary *endpoint will be compared between each of the two GDC-0853 arms and the placebo arm by using the Cochran-Mantel-Haenszel test statistic, stratified by the factors used at randomization. The absolute difference in remission rates and 95% CI for the point estimate will be provided.*

Determination of Sample Size

The purpose of this study is estimation and hypothesis generation regarding the effect of GDC-0853 on Week 48 SRI-4 response rate relative to placebo in moderate to severe active SLE patients and a biomarker-defined subgroup of patients. A total of 240 patients will be randomly allocated in a 1:1:1 ratio to receive one of two doses of GDC-0853 (200 mg BID GDC-0853 [Arm A] or 150 mg QD GDC-0853 [Arm B]) or placebo (Arm C). This sample size will provide approximately 88% power at a 2-sided 0.05 significance *level* to detect a 25% absolute improvement in the response rate for a GDC-0853 containing arm relative to the placebo arm assuming a placebo response-rate of 50%. Patients without post-baseline response assessments will be treated as non-responders. For an evaluation of efficacy in a subgroup defined by a predictive biomarker with 50% prevalence, the total sample-size of 80 patients per arm provides approximately 80% power to detect a 25% improvement with *2-sided* 0.20 *significance level*, using the Fisher's Exact Test. No adjustment for multiple comparisons will be made.

Interim Analyses

An interim analysis will be performed after 50–80 patients in each of treatment arm have completed their 24-week SRI-4 response evaluation. The purpose of the interim analysis is to conduct a preliminary benefit-risk assessment of GDC-0853 treated arms compared with the placebo-treated arm and enable potential stopping for futility and/or safety concerns or to potentially inform the clinical development plan for GDC-0853. The interim analysis will be performed and interpreted by the IMC in conjunction with a Scientific Oversight Committee who will be unblinded at the treatment group level. Additional personnel, such as Clinical Pharmacology *and biomarker* scientists, may be unblinded in order to prepare additional data displays relevant for IMC and Scientific Oversight Committee review.

The study will continue to enroll while the interim analysis is being performed. If the interim analysis indicates that one of the two dose levels of GDC-0853 does not have an appropriate safety profile or meets futility criteria as defined in the interim analysis plan in the DAP which will be written prior to conducting the interim analysis, the Sponsor may discontinue enrollment into that dose arm and switch patients to the other dose arm for the remainder of the study. The Sponsor may also elect to amend the protocol to change the dose level of GDC-0853.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct an additional efficacy interim efficacy analysis in order to further guide internal decision making around issues such as the adequacy of dose ranging, the adequacy of sample sizes for safety and/or efficacy analyses, or to inform the clinical development plan for GDC-0853. The study will not be stopped for any other reason other than futility or safety concerns at the time of the interim analysis. The interim analysis will be performed and interpreted by the IMC in conjunction with a Scientific Oversight Committee who will be unblinded at the treatment group level. Additional personnel, such as Clinical Pharmacology *and biomarker* scientists, may be unblinded in order to prepare additional data displays relevant for IMC and Scientific Oversight Committee review. The decision to conduct an additional interim analysis and the timing of the

analysis will be documented in the Sponsor's trial master file and updated DAP prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
AESI	adverse event of special interest
ALP	alkaline phosphatase,
ALT	alanine aminotransferase
ANA	antinuclear antibody
ALC	absolute lymphocyte count
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the concentration time–curve
AUC_{0-24}	area under the concentration time–curve from time 0 to Hour 24
BAFF	anti-B-cell activating factor
BCG	Bacillus Calmette-Guérin
BCR	B-cell receptor
BCRP	*breast cancer resistance protein*
BICLA	BILAG-based Composite Lupus Assessment
BID	twice daily
BILAG	British Isles Lupus Activity Group
BTK	Bruton's tyrosine kinase
C_{max}	maximum concentration observed
$C_{ss,ave}$	mean plasma concentration
C_{trough}	steady-state concentration at the end of a dosing interval
CAML	calcium-modulator and cyclophilin ligand
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CIA	collagen-induced arthritis
CK	creatinine kinase
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLL	chronic lymphocytic leukemia
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
CyTOF	mass cytometry
DAP	data analysis plan

Abbreviation	Definition
DLAE	dose-limiting adverse event
DMARD	disease-modifying antirheumatic drug
dsDNA	double stranded DNA
E.U.	European Union
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EDTA	European Dialysis and Transplant Association
ERA	European Renal Association
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GTCI	Glucocorticoid Toxicity Change Index
H2RA	H2 receptor antagonists
$HbA1_c$	hemoglobin $A1_c$
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HN	home nurse
HPF	high-power field
HSV1	herpes simplex virus 1
HSV2	herpes simplex virus 2
[redacted]	[redacted]
[redacted]	[redacted]
ICH	International Conference on Harmonisation
IFN	interferon
IFN-α	interferon-alpha
Ig	immunoglobulin
IL	interleukin
IM	intramuscular

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
K_i	inhibitory constant
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LPLV	last patient, last visit
MAD	multiple-ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDD	minimal detectible difference
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NZB	New Zealand Black
NZW	New Zealand White
OCS	oral corticosteroids
OLE	open-label extension
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative
PPI	proton pump inhibitors
PRO	patient-reported outcome
PT	prothrombin time
QTcF	QT interval corrected using Fridericia's formula
QFT	QuantiFERON TB-Gold®
QD	daily
RA	rheumatoid arthritis
RBC	red blood cell
RBR	Research Biosample Repository
RDW	red cell distribution width
SAD	single-ascending dose
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment

Abbreviation	Definition
SFI	SELENA- SLEDAI Flare Index
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SOC	standard of care
SRI	Systemic Lupus Erythematosus Responder Index
SUSAR	serious, unexpected suspected adverse reaction
$t_{1/2}$	half-life
t_{max}	time to maximum concentration
TACI	transmembrane activator and CAML interactor
TB	tuberculosis
TBNK	*T, B, and natural killer cells*
TDAR	T-dependent antigen response test
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
TWEAK	TNF-like weak inducer of apoptosis
U.S.	United States
ULN	upper limit of normal
VAS	visual analogue scale
VZV	varicella zoster virus
WBC	white blood cell
WGS	whole-genome sequencing
XLA	X-linked agammaglobulinemia

1. BACKGROUND

1.1 BACKGROUND

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease that occurs primarily in women of childbearing age. It is characterized by multisystem involvement and immunological abnormalities, and much of the tissue damage is thought to occur through autoantibody formation and immune complex deposition. The disease is heterogeneous in its clinical presentation, course, and prognosis. However, most patients present with joint involvement, skin rashes, mouth ulcers, Raynaud's phenomenon, and/or severe fatigue. Inflammation of pericardial and pleural tissues may also be present. The most serious manifestations include central nervous system and renal involvement, which correlate with poor outcomes that include temporary or permanent disability or death. Typically, the disease follows a relapsing-remitting course with intermittent periods of disease activity (flare) interspersed with periods of relative quiescence.

The incidence and prevalence of SLE varies with sex, race, and ethnicity. The estimated prevalence of SLE ranges between 65 and 155 per 100,000 (Walsh et al. 2001; Ward 2004; Naleway et al. 2005; Chakravarty et al. 2007; Molina et al. 2007; Sacks et al. 2010; Feldman et al. 2013; Furst et al. 2013; Lim et al. 2014). In adulthood, approximately nine times as many women as men are affected. The disease has a higher incidence and worse outcome among African-Americans, Afro-Caribbeans, Hispanics, and Asians compared with Caucasians.

Medications for the successful treatment of SLE as measured by long-term remission are limited, and only one new medication for SLE treatment has been approved in more than 50 years (Burness and McCormack 2011). Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) provide partial symptomatic relief. Anti-malarial drugs are generally well tolerated by patients with SLE and appear to have a beneficial effect on the prevention of lupus flares, increasing long-term survival, and possibly ameliorating certain types of organ damage (Ruiz-Irastorza et al. 2009). However, these agents are generally regarded as having insufficient efficacy for moderate to severe manifestations of SLE.

The mainstays of therapy for more significant manifestations of SLE are corticosteroids and off-label use of immunosuppressive drugs (e.g., methotrexate, mycophenolic acid [as either mycophenolate mofetil or Myfortic® (mycophenolic acid as sodium salt)], azathioprine, and cyclophosphamide), which have profound and diverse effects on the immune system in patients with lupus (Tunnicliffe et al. 2015). However, the use of these immunosuppressant agents is limited by their safety profiles. Corticosteroids, for example, are effective for many of the manifestations of SLE but have significant short- and long-term adverse effects, including infections, osteoporosis, hyperglycemia, hypertension, osteonecrosis, cataracts, and hyperlipidemia.

As a measure of unmet need, the risk of mortality remains elevated for patients with lupus. In the modern era, on the basis of a multisite international cohort of 9500 patients with lupus, the standardized mortality ratio was 2.4, with particularly high mortality seen with renal disease (Fors Nieves and Izmirly 2016). The development of new treatments for SLE patients with increased efficacy and decreased toxicity remains an important and a necessary area of investigation.

1.2 BACKGROUND ON BRUTON'S TYROSINE KINASE AND GDC-0853

1.2.1 Bruton's Tyrosine Kinase

Discovery of the genetic basis for primary immunodeficiencies has been the source of new therapeutic targets in immunomodulatory therapies (Puri et al. 2013; Bugatti et al. 2014; Whang and Chang 2014). In humans, inactivating mutations in the gene for Bruton's Tyrosine Kinase (BTK), which is located on the X chromosome, can result in the development of an immunodeficiency state characterized by a significant absence of circulating B cells (Bruton 1952; Tsukada et al. 1993; Vetrie et al. 1993; Conley et al. 2005) and very low immunoglobulin (Ig) levels due to a defect in B-cell differentiation at the pro- to pre-B cell stage that precludes assembly of the B-cell receptor (BCR) complex and Ig gene expression (Reth and Nielsen 2014). Affected male patients have a primary immune deficiency called X-linked agammaglobulinemia (XLA) and are susceptible to recurrent infections starting shortly after birth. XLA patients can live relatively normal lives on a standard therapy of intravenous (IV) Ig (Kaveri et al. 2011), suggesting that BTK can be safely inhibited especially in people with established immune systems.

BTK is a tyrosine kinase essential for signaling events required for the differentiation and activity of B cells during immune system ontology and normal adaptive immune responses. In addition, BTK is required for signaling associated with FcγR, expressed on a variety of myeloid cells. BTK is activated by phosphatidylinositol 3-kinase–dependent plasma membrane recruitment and phosphorylation on tyrosine Y551 by the Src-family kinase Lyn. Autophosphorylation and activation also occurs on tyrosine Y223 in a BTK-specific manner. Once activated, BTK induces PLCγ2- and $Ca2^{+}$-dependent signaling, which leads to the activation of NF-κB– and NFAT-dependent pathways leading to cellular activation and differentiation (Niiro and Clark 2002).

The therapeutic potential of BTK inhibitors as anti-cancer agents has been established in clinical trials with agents, including ibrutinib, a covalent inhibitor of BTK, which has been approved in the United States and Europe for use in patients with mantle-cell lymphoma, chronic lymphocytic leukemia (CLL), and Waldenstrom's macroglobulinemia.

1.2.2 Nonclinical Experience with GDC-0853

GDC-0853 is a highly selective, orally administered, reversible inhibitor of BTK that is being developed by Genentech, Inc. as a potential therapeutic for autoimmune diseases,

including rheumatoid arthritis (RA) and SLE. GDC-0853 has undergone extensive investigation in nonclinical in vitro and in vivo studies to characterize its pharmacological, metabolic, and toxicological properties (see the GDC-0853 Investigator's Brochure).

In vitro cell-based experiments suggest that antagonism of BTK leads to inhibition of BCR-dependent cell proliferation and a reduction of inflammatory cytokine production from myeloid cells (including tumor necrosis factor alpha [TNF-α], interleukin [IL]-1, and IL-6) by preventing signaling through the FcγRIII receptor (di Paolo et al. 2011; Liu et al. 2011). GDC-0853 effectively blocks BCR- and CD40-mediated activation and proliferation of B cells. BTK in B cells also plays a role in TLR4-mediated B-cell proliferation and class switching. In monocytes, GDC-0853 inhibits TLR4- and immune complex-mediated inflammatory cytokine production, including TNF-α, which contributes to disease pathogenesis in SLE (Mina-Osorio et al. 2013; Bender et al. 2016). In dendritic cells, BTK contributes to TLR8-mediated cytokine production (TNF-α and IL-6) (Sochorová et al. 2007). In basophils, BTK-dependent activation of the FcεR leads to activation and up-regulation of CD63. In addition, GDC-0853 has been shown to inhibit the differentiation of human plasmablasts into plasma cells in vitro (see the GDC-0853 Investigator's Brochure). Patients with lupus have multiple abnormalities in the blood, including increased levels of plasmablasts (Anolik et al. 2004). Together, these data suggest that lupus patients with elevated levels of plasmablasts might demonstrate a more robust clinical response to GDC-0853. Therefore, an RNA signature biomarker encompassing genes preferentially expressed in plasmablasts was developed to detect the presence of elevated plasmablasts in the peripheral blood. In addition, efficacy in patients with high or low levels of the plasmablast signature will be compared for potential increased or decreased efficacy, respectively (see Table 1).

The efficacy of GDC-0853 has been investigated in inflammatory models of arthritis as well as immune-complex mediated renal-injury models similar to the manifestations of human SLE. Arthritis was investigated in female Lewis rats with developing Type II collagen-induced arthritis (CIA). GDC-0853 treatment was well tolerated and resulted in significant and dose-dependent reduction in ankle swelling. GDC-0853 was effective at significantly reducing anti-rat collagen II IgG antibodies in the serum (obtained on Day 16) with daily (QD) doses $\geq$0.25 mg/kg/day. However, there was no effect of GDC-0853 treatment on total anti-rat IgG antibodies in the serum. Findings from the histopathology evaluation were consistent with the clinical findings. Immune-complex mediated inflammation (induced by autoantibodies) and tissue injury is central to the pathogenesis and the majority of clinical manifestations of SLE. GDC-0853 in nonclinical studies is a potent inhibitor of these processes. Studies in interferon-alpha (IFN-α)–accelerated, New Zealand Black (NZB)/New Zealand White (NZW), lupus-prone mice have shown that BTK-inhibition resulted in dose-dependent improvement in survival (see the GDC-0853 Investigator's Brochure). In addition, BTK inhibition reduces the development and levels of splenic plasmablasts, a pool of activated

antibody-producing B-cells, and systemic inflammation as evidenced by a decrease in the Type-1 interferon (IFN) signature in peripheral blood mononuclear cells (PBMCs).

The GDC-0853 safety profile has been assessed in repeat-dose, general toxicology studies (daily oral dosing) ranging from 1 week to 9 months in rats and dogs; in vitro and in vivo genetic toxicology studies; in vitro phototoxicity evaluation; in vitro and in vivo safety pharmacology studies of the central nervous, respiratory, and cardiovascular system; and embryo-fetal development (Seg II) studies in rats and rabbits. Overall, GDC-0853 was well tolerated for 6 months in rats (up to 104 $\mu M \cdot hr$) and 9 months in dogs (up to 36 $\mu M \cdot hr$). Notable findings identified in nonclinical toxicology studies include vascular inflammation in dogs ($\geq$ 56 $\mu M \cdot hr$), hepatotoxicity in dogs (180 $\mu M \cdot hr$), and a minimal increase in corrected QT interval in dogs (QTc; 7 msec or 3%; extrapolated unbound maximum observed concentration [C_{max}] of 3.17 μM). Fetal malformations in rats (at 627 $\mu M \cdot hr$) and rabbits ($\geq$ 10.6 $\mu M \cdot hr$) warrant the continued use of contraception in clinical trials. On the basis of the nonclinical and clinical safety data to date, GDC-0853 is expected to be well tolerated at the doses and duration administered in the current study, GA30044.

1.2.3 Clinical Experience with GDC-0853

As of January 2016, GDC-0853 has been administered to 179 subjects (i.e., 155 healthy subjects, and 24 patients with hematological malignancies, at doses ranging from 0.5 to 600 mg, and has been well tolerated with no safety signals. In the single-ascending dose (SAD; GP29318), multiple-ascending dose (MAD; GA29347), ongoing relative bioavailability (GP29832), and oncology (GO29089) studies, GDC-0853 was generally well tolerated with adverse events being mostly non-serious, mild, and self-limited and with no dose-limiting adverse events (DLAEs) or dose-limiting toxicities.

In healthy volunteer studies, there were no DLAEs, serious adverse events, study drug discontinuations for adverse events, or concerning patterns of adverse events that would preclude further development of GDC-0853. Adverse events in healthy volunteers were all mild and included skin reactions (rash, contact dermatitis, and skin irritation from electrocardiogram [ECG] leads; 1 subject each), nausea (2 subjects), headache, toothache, contusion, and asymptomatic bacteriuria (1 subject each).

In patients with hematological malignancies, the majority of adverse events were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 1 or Grade 2 and included fatigue, nausea, diarrhea, headache, abdominal pain, dizziness, cough, and thrombocytopenia. There were nine serious adverse events reported in 5 patients: abdominal pain, lung infiltration, lung infection and pneumonia, febrile neutropenia, gastrointestinal (GI) hemorrhage and upper GI hemorrhage, and H1N1 influenza and influenza pneumonia. There were two deaths during the study due to complications of confirmed influenza (H1N1 influenza and influenza pneumonia). As of March 2016, 7 patients remain on GDC-0853 (400 mg QD)

in Study GO29089 with daily dosing lasting up to 23 months (range 18–23, average 21 months).

Refer to the GDC-0853 Investigator's Brochure for additional details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The results from the Phase I studies, nonclinical toxicology studies, and studies in a nonclinical model of SLE support further evaluation of GDC-0853 as a potential treatment for SLE. The goal of this Phase II study (GA30044) is to evaluate the safety and efficacy of GDC-0853 in combination with standard of care (SOC; see Section 2) in patients with moderate to severe SLE. The study will test two dose levels of GDC-0853 in comparison to placebo when added to background SOC. The study is powered to detect a meaningful clinical benefit, in a composite measure of disease activity across multiple organ systems (see Section 3.3.6.2), and includes multiple safety assessments and monitoring by an unblinded Internal Monitoring Committee (IMC) and a Scientific Oversight Committee.

Inhibition of BTK offers a promising mechanism for the treatment of autoimmune diseases, such as RA and SLE (Section 1.2.1); however, data from clinical studies are lacking. Humans with a mutation in the XLA gene and who, therefore, lack functional BTK from birth, can live relatively normal lives on a standard therapy of IV Ig (Kaveri et al. 2011), suggesting that BTK can be safely inhibited, especially in people with established immune systems. GDC-0853 did not deplete IgG substantially during short term treatment of healthy subjects in Phase I studies (see GDC-0853 Investigator's Brochure), but it is not known whether longer term treatment of patients will induce depletion, therefore IgG levels will be monitored in this study. Clinical data to date suggest that IgG levels in patients with an established immune system may not be significantly depleted, perhaps because BTK inhibitors target only the kinase domain and other BTK activities remain intact (Byrd et al. 2013).

Overall, GDC-0853 has been well tolerated in Phase I healthy subjects and oncology studies. Based on the compelling mechanism for BTK inhibition in SLE and the promising results in NZB/NZW lupus-prone mice, the risk-benefit ratio for this study is considered appropriate (see the GDC-0853 Investigator's Brochure). The safety profile of GDC-0853 will be further characterized in this Phase II study, and a robust safety-monitoring plan that describes the potential risks for GDC-0853 and the risk-mitigation strategies to minimize risks for the patients in this trial is provided in Section 5.1.

Clinical experience with GDC-0853 to date has not generated safety concerns that would preclude further evaluation in patients with autoimmune diseases (see the GDC-0853 Investigator's Brochure).

1.3.1 Primary Nonclinical Toxicity Findings

The no observed adverse effect levels (NOAELs) determined in the repeat-dose, 6-month Wistar Han rat (20 mg/kg; 104 μM • hr) and 9-month dog (10 mg/kg; 36 μM • hr) studies support multiple-dose exposures in SLE patients at the proposed clinical doses, [redacted] The primary toxicities identified in animals include the following (see Section 1.2.2 and the GDC-0853 Investigator's Brochure for details):

- Vascular inflammation in dogs, characterized by endothelial necrosis, proliferation and hypertrophy, vascular/perivascular lymphocyte and macrophage infiltrates, and occasional necrosis of the medial smooth-muscle cells were observed in a 4-week toxicity study at ≥56 μM • hr, and these changes were not completely reversed by the end of the 4-week recovery period. However, in the 9-month toxicity study in dogs, no GDC-0853-related vascular inflammation was observed up to the highest dose of 10 mg/kg/day (36 μM • hr). [redacted]
- Effects on lymphocytes and immunoglobulins in rats and dogs were reversible and considered to be related to pharmacological activity involving BTK inhibition. In rats, after 4 weeks of dosing, elevated circulating total lymphocyte counts were observed at ≥20 mg/kg/day (≥104 μM • hr). In dogs, after 4 months dosing, decreased circulating total lymphocytes was observed at ≥10 mg/kg/day (≥36 μM • hr). Peripheral blood immunophenotyping showed decreased circulating B-cell counts in male rats at 20 mg/kg/day and in dogs at ≥1 mg/kg/day (≥2.1 μM • hr); there were no GDC-0853−related effects on total T, helper T, or cytotoxic T cells. Ig isotyping in high-dose dogs (36 μM • hr) and rats (104 μM • hr) showed decreased IgG concentration; mid- and high-dose rats (≥17 μM • hr) also had decreased IgM. Histopathology in rats and dogs showed a decrease in the number of lymphocytes in follicular germinal centers in the spleen, mesenteric and mandibular lymph nodes, and/or Peyer's patches.
- Minimal to marked, dose-dependent increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or bilirubin have been observed in rats administered ≥6 mg/kg/day (≥17 μM • hr). Hepatotoxicity in dogs, consisting of increases in ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and/or total bilirubin levels correlated with microscopic findings of minimal hepatocyte degeneration/disorganization, Kupffer cell hypertrophy/hyperplasia and pigment, and perivascular mixed cell infiltrates. Serum chemistry and histopathology findings were observed in the 4-week toxicity study at ≥56 μM • hr and 180 μM • hr, respectively, and were considered monitorable with liver function tests (see Section 1.3.2.6). The hepatotoxicity findings in dogs were associated with moribundity in two high-dose animals. The NOAEL for these findings was considered to be 10 mg/kg (36 μM • hr) in dogs, the most sensitive species, given the absence of GDC-0853–related hepatotoxicity at this dose when administered for 9 months. These findings were fully reversible and considered

monitorable by changes in plasma transaminases and bilirubin that occurred at doses lower than those producing histopathology findings. No adverse liver findings were observed in the chronic toxicity studies in rats (≤104 μM•hr) and dogs (≤36 μM•hr). See Section 4 of the GDC-0853 Investigator's Brochure for further details.

- Fetal malformations were observed in rats (i.e., cleft palate observed at 627 μM•hr) and rabbits (i.e., domed-shaped heads with enlarged lateral/third ventricles at ≥10.6 μM•hr). Thus, highly effective contraception will be mandatory for trial participation, and pregnancy monitoring will be performed at least monthly in Study GA30044.
- Pancreatic findings observed in rats administered GDC-0853, and other BTK inhibitors, were considered to be an on-target, species-specific effect, supported by a number of investigative studies (see the GDC-0853 Investigator's Brochure for details).

1.3.2 Potential Risks for Clinical Toxicities

GDC-0853 is in early clinical development and there is limited safety experience, so the actual risks in patients with SLE are unknown. However, there are several potential risks on the basis of the expected mechanism of action of GDC-0853, published literature for similar molecules, nonclinical and clinical studies. Several measures will be taken to ensure the safety of patients participating in this study based on these potential risks (see Section 5.1 for details). In addition, guidelines for the management of study treatment in patients who experience specific adverse events have been established (see Section 5.1.2 and Table 4). Eligibility criteria in this study have been designed to exclude patients at higher risk for potential toxicities (see Section 4.1).

1.3.2.1 Infections

GDC-0853 is a targeted immunomodulator and the degree to which GDC-0853 antagonism of BTK signaling may suppress immune activity is unknown. Patients participating in this study may be at risk for infections, including opportunistic infections. Therefore, the eligibility criteria are intended to protect patient safety and exclude patients that may be at a particularly increased risk of infection including those with marked baseline lymphopenia. Total Ig concentrations will also be measured regularly throughout the study. During the study, any serious infection, any infection requiring IV antimicrobials, or any opportunistic infection is considered an adverse event of special interest (AESI) with expedited reporting requirements to the Sponsor.

1.3.2.2 Vaccinations

The effect of GDC-0853 upon the efficacy of vaccinations is unknown. It is recommended that appropriate vaccinations per European League Against Rheumatism (EULAR) recommendations (van Assen et al. 2010) or local guidelines be up to date before study participation. However, as a safety measure, patients will be excluded from study participation and will not be dosed with GDC-0853 if they have been vaccinated with live, attenuated vaccines (e.g., the intranasal live attenuated influenza vaccines,

Bacillus Calmette-Guérin virus [BCG], and varicella) within 6 weeks before planned dosing.

1.3.2.3 Bleeding

BTK is expressed in platelets and is involved in platelet function via GPVI/Collagen receptor signaling and GP1b receptor signaling. Platelets from patients with XLA demonstrate decreased activation in response to submaximal collagen stimulation but normal response to thrombin. However, clinically, there is no reported bleeding propensity in XLA patients (Howard et al. 2006). In the GDC-0853 clinical study involving patients with cancer, two patients experienced Grade $\geq$3 GI bleeding. These events were not dose related and occurred in patients on NSAIDs/acetylsalicylic acid with a history of gastroesophageal or peptic ulcer disease.

It is unknown if GDC-0853 will increase the risk of bleeding in SLE patients receiving antiplatelet or anticoagulant therapies. Therefore, the eligibility criteria will exclude patients at highest risk for GI bleeding. Patients at high risk for NSAID-related GI injury are advised to follow local or recognized guidelines, including concomitant use of proton pump inhibitors (PPIs), if indicated. Any bleeding event of Grade 2 or above is considered an AESI with expedited reporting requirements to the Sponsor (see Section 5.4.2).

1.3.2.4 Cytopenias

Neutropenia, anemia, and thrombocytopenia have been observed in patients with hematologic malignancies who received GDC-0853. Events have been monitorable and clinically manageable without dose discontinuations. As patients with SLE may have cytopenias as a result of their intrinsic SLE disease activity, study eligibility criteria are designed to exclude those patients with more marked baseline cytopenias that may affect patient safety, and complete blood counts (CBCs) will be monitored regularly throughout the study.

1.3.2.5 Gastrointestinal Effects

Healthy subjects in the multiple ascending-dose study, GA29347, reported events of mild self-limited nausea. In addition, Grade 1 diarrhea, nausea, and abdominal pain have been reported in patients with hematological malignancies treated with GDC-0853; however, the events resolved and have not led to study drug discontinuation. Throughout the study, patients will be monitored for GI side effects.

1.3.2.6 Hepatotoxicity

Evidence of hepatobiliary injury was observed in animals administered relatively high doses of GDC-0853 in repeat-dose toxicity studies. In clinical studies to date, including single dose and multiple dosing for 14 days in healthy subjects and daily dosing for over 1 year in patients with hematological malignancies, there have been no adverse events of liver enzyme elevations or trends towards elevations in laboratory evaluations. For inclusion in this study, AST and ALT levels should be no more than 1.5 times the upper

limit of normal (ULN), and total bilirubin levels should be normal at screening. Baseline and routine evaluations of AST/ALT and total bilirubin levels will be performed throughout the study. Elevated AST or ALT levels of Grade ≥ 3 ($> 5 \times$ ULN) or cases of potential drug-induced liver injury that include an elevated ALT or AST level in combination with either an elevated bilirubin level or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6), are AESIs with expedited reporting requirements to the Sponsor (see Section 5.4.2).

1.3.2.7 Cardiovascular Effects

GDC-0853 is considered to have a low potential to cause QT interval prolongation or to directly affect other cardiovascular parameters at therapeutic exposures. A minimal increase in corrected QT (QTc; 7 msec or 3%) interval was noted at 45 mg/kg in the single-dose cardiovascular safety pharmacology study in telemetry-instrumented dogs that was not considered to be clinically significant/meaningful. Analysis of ECG data from the SAD and MAD studies in healthy subjects did not demonstrate any significant increase in either QRS interval or QTcF intervals. Cardiac safety will be evaluated in all patients at baseline and throughout the study with routine monitoring of vital signs, including heart rate and blood pressure, collection of ECGs, and reporting of cardiac adverse events. Patients with high cardiovascular risk will be excluded from study participation.

1.3.2.8 Vascular Inflammation

The risk to human safety based on toxicological findings of vascular inflammation in animal studies is uncertain. As a safety risk-mitigation measure, CBC results, creatinine levels, and urinalysis findings will be monitored in all patients during the study. Any patient that develops treatment-emergent vasculitis should be discussed with the Medical Monitor.

1.3.2.9 Malignancy

The impact of BTK inhibition on the development of malignancies is not known; however, malignancies are considered a potential concern for all immunomodulatory agents. Patients with a history of cancer within 10 years of screening will be excluded from study participation, except for basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy more than 1 year prior to screening. All malignancies are AESIs with expedited reporting requirements to the Sponsor.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of GDC-0853 compared with placebo in patients with moderately to severely active SLE. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the clinical efficacy of GDC-0853 in combination with SOC	• SRI-4 response at Week 48
Secondary Efficacy Objectives:	
• To evaluate the clinical efficacy of GDC-0853 over time using the SRI-4 as a standardized disease activity measure	• SRI-4 response at Week 48 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 36 through Week 48 • SRI-4 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24 • SRI-4 response at Week 24
• To evaluate if patients with high plasmablast signature levels have an enhanced clinical response to GDC-0853 relative to patients with low levels	• *SRI-4 response at Week 48* • *SRI-4 response at Week 48 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 36 through Week 48*
• *To evaluate the clinical efficacy of GDC-0853 over time using BICLA and SRI-6 as standardized disease activity measures*	• *SRI-6 response at Weeks 24 and 48* • *BICLA response at Weeks 24 and 48*
Exploratory Efficacy Objectives:	
• To evaluate the clinical efficacy of GDC-0853 over time with multiple standardized disease activity measures	• SRI-5*, 7, and* 8 response at Week 48 • SRI-5-8 response at Week 48 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 36 through Week 48 • SRI-5*, 7, and* 8 response at Week 24 • SRI-5-8 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24
• To evaluate the ability of GDC-0853 to prolong the time to first SLE flare	• Time to first SLE Flare as defined by the SFI • Time to first SLE Flare as defined by the BILAG
• To evaluate the ability of GDC-0853 to decrease the number of total SLE flares	• Total number of SLE flares as defined by the SFI • Total number of SLE flares as defined by the BILAG
• *To evaluate the clinical efficacy of GDC-0853 over time based on the individual components of the SRI*	• *Reduction of ≥ 4 points from baseline in the SLEDAI-2K at Weeks 24 and 48*
• *To evaluate if patients with high plasmablast signature levels have an enhanced clinical response to GDC-0853 relative to patients with low levels*	• *SRI-4 response at Week 24* • *SRI-4 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24*
• To evaluate the ability of GDC-0853 to improve cutaneous manifestations of SLE	• Change in CLASI Total Activity Score at Week 24 and Week 48 relative to baseline (i.e., Day 1) • ≥ 50% improvement in CLASI score in patients with at least moderate skin involvement (baseline CLASI ≥ 10)

Table 1 Objectives and Corresponding Endpoints (cont'd)

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives (cont'd):	
• To evaluate the ability of GDC-0853 to *prevent* systemic damage	• Change in SLICC/*ACR Damage Index* at Week 24 and Week 48 relative to baseline
• To evaluate the ability of GDC-0853 to improve arthritis	• Change in joint involvement at Week 24 and Week 48 relative to baseline using the 28-Joint Count assessment • ≥ 50% improvement in the 28 Joint Count assessment for patients with ≥ 8 swollen or tender joints at baseline
• To evaluate the ability of GDC-0853 to improve fatigue	• Change in FACIT-Fatigue score at Week 24 and Week 48 relative to baseline
• To evaluate the ability of GDC-0853 to improve Patient's Global Assessment	• Change in Patient's Global Assessment of disease activity at Week 24 and Week 48 relative to baseline
• To evaluate if GDC-0853 is steroid sparing	• Change in cumulative steroid dose at Week 24 and Week 48 relative to baseline • Glucocorticoid toxicity at Weeks 12, 24, 36, and 48 relative to baseline using the GTCI • Achieving a corticosteroid dose of < 10 mg/day among patients at ≥ 10 mg/day at baseline
Safety Objective:	
• To evaluate the safety of GDC-0853 in combination with SOC therapy in patients with moderate to severe active SLE	• The nature, frequency, severity, and timing of adverse events using the NCI CTCAE scale to grade adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results following GDC-0853 administration
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of GDC-0853 in patients	• *Plasma concentrations of GDC-0853 at specified timepoints*
Exploratory Pharmacokinetic Objectives:	
• To evaluate the relationship between measures of drug exposure and pharmacodynamic effect, efficacy, and safety of GDC-0853	• Exploratory biomarker measures in Table 3 • SRI-4 response and other measures of efficacy or clinical activity • The nature, frequency, severity, and timing of adverse events • Changes in vital signs, ECGs, and clinical laboratory results following GDC-0853 administration

Table 1 Objectives and Corresponding Endpoints (cont'd)

Objectives	Corresponding Endpoints
Exploratory Pharmacokinetic Objectives (cont'd):	
• To evaluate the impact of selected covariates on measures of GDC-0853 exposure and/or response	• Gender, age, body weight, and other patient demographics • *GDC-0853 PK* • SRI-4 and other measures of efficacy or clinical activity
• To evaluate the impact of genetic polymorphisms on measures of GDC-0853 exposure	• Presence of genetic polymorphisms and/or genotype(s) • *GDC-0853 PK*
Exploratory Biomarker Objectives:	
• To evaluate the relationship of GDC-0853–induced changes in biomarkers (see Table 3) and efficacy	• Primary and secondary endpoints at mentioned above • Biomarker endpoints (see Table 3)
• To evaluate whether biomarkers (e.g., but not limited to plasmablasts, autoantibodies and other inflammatory biomarkers) measured at baseline may identify patients with enhanced clinical response to GDC-0853	• Primary and secondary efficacy endpoints as noted above • Time to first SLE Flare as defined by the SFI • Time to first SLE Flare as defined by the BILAG • Total number of SLE flares as defined by the SFI and BILAG
• To evaluate whether the levels of the aforementioned biomarkers associate with disease progression	• Primary and secondary efficacy endpoints as noted above

BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Activity Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FACIT = Functional Assessment of Chronic Illness Therapy; GTCI = Glucocorticoid Toxicity Change Index; NCI = National Cancer Institute; OCS = oral corticosteroids; PK = pharmacokinetic; QOL = quality of life; SLEDAI -2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SFI = SELENA-SLEDAI Flare Index; SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus; SOC = standard of care; SRI = Systemic Lupus Erythematosus Responder Index.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Study Design

This is a multicenter, Phase II, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the safety and efficacy of GDC-0853 in combination with SOC therapy in patients with moderate to severe active SLE. Moderate to severe SLE will be defined at screening and baseline (i.e., Day 1) as having serologic evidence of SLE *with* clinical disease activity and active oral treatment for SLE (see Section 4.1.1 for details).

The study will consist of a screening period (up to 35 days) and a 48-week treatment period, followed by either an 8-week safety follow-up visit at Week 56 or possible enrollment into an open-label extension (OLE) study. Approximately 240 patients, meeting all eligibility criteria, will be randomized in a 1:1:1 ratio to receive GDC-0853 at one of two doses (200 mg BID [Arm A] or 150 mg QD [Arm B]) or placebo (Arm C), in combination with background SOC therapy. Randomization will be stratified by disease activity at screening, entry dose of oral corticosteroids (OCS), and geographic region. All patients will receive blinded study drug twice daily (GDC-0853, placebo, or both to maintain the blind) from baseline to Week 48 and will be assessed at site visits every 4 weeks (including a site-initiated phone call at Week 1) during the treatment period (see Figure 1).

Pre-enrollment adjudication by the Medical Monitor and his/her designees will occur for all patients who complete screening prior to their randomization into the study (see Appendix 3). The Medical Monitor or assigned designee will make the final decision whether or not a patient is eligible for randomization.

Background SOC therapy may consist of an OCS (which must be stable for 2 weeks prior to screening, dose not to exceed 40 mg/day of prednisone or equivalent) and/or certain oral immunosuppression regimens (which must be stable for 2 months prior to screening; see Section 4.1.1). All immunosuppressive and anti-malarial medication will be kept stable throughout the trial unless dose reductions are necessary due to toxicity. All patients receiving immunosuppressive treatments are also encouraged to be on supportive therapy (e.g., folic acid, calcium, vitamin D). For patients who are on angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) at study entry, doses of ACE inhibitors or ARBs should be kept stable for at least 10 days prior to randomization and throughout the trial whenever possible. *It is strongly recommended that* ACE inhibitors or ARBs *not* be initiated during the OCS stability windows.

For patients on an OCS at baseline, there will be two, 12-week, OCS taper windows available to achieve the pre-specified OCS taper of <10 mg/day prednisone or equivalent (see Appendix 4 and Figure 1). The dose at the end of each OCS-stability window (i.e., the 12-week period immediately following the 12-week OCS taper window) will then be kept stable for an additional 12 weeks. See Section 4.3.2.3 for more details.

In the case of increased SLE disease activity, there can be two temporary increases in the corticosteroid dose, called “bursts,” that may be administered if needed (Figure 1). A burst may only be administered during a burst window (defined as the first 10 weeks of each OCS taper window) and only once per window (see Section 4.3.2.3.3). A burst is defined as a temporary increase in corticosteroid dose (up to 40 mg/d prednisone or equivalent for Burst Window 1, and up to 20 mg/d prednisone or equivalent for Burst Window 2) with a taper back down to the dose immediately preceding the burst, all within a 2-week period.

If additional treatment is needed beyond the permitted burst therapy because of active SLE, as identified by the investigator, the patient may receive escape therapy; however, such patients will be considered trial-defined non-responders for the purposes of the primary analysis (see Section 4.3.2.3.4).

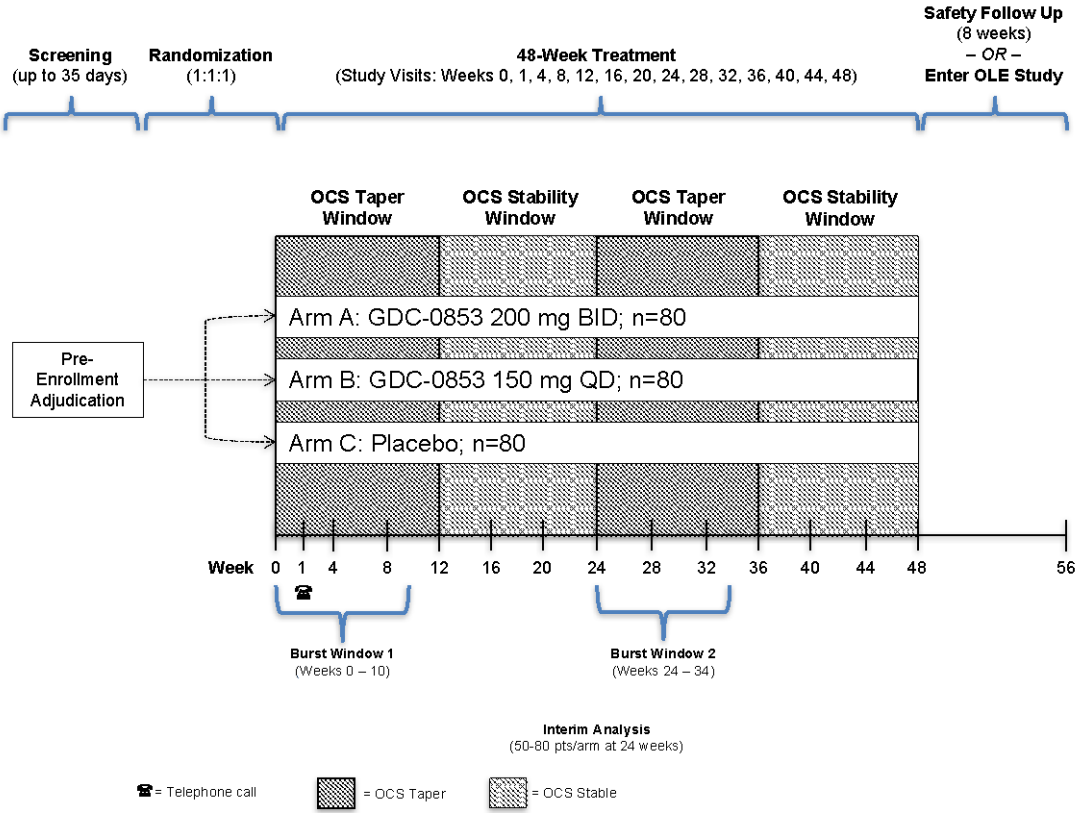
During taper, burst, and permitted escape therapies, patients will continue to receive their designated dose of study treatment (see Section 4.3.2).

Starting at the screening period, all patients must record their actual OCS use weekly, as instructed by study staff (see Section 4.3.2.4).

An unblinded IMC and Scientific Oversight Committee will be used to monitor multiple safety assessments (see Section 3.1.2). In addition, an interim analysis will be conducted after 50–80 patients in each treatment arm have completed 24 weeks of treatment and have been evaluated for SLE Responder Index (SRI)-4 response, in order to conduct a preliminary assessment of the benefit-risk profile of GDC-0853 and potentially enable early stopping for futility and/or safety issues (see Figure 1 and Section 6.8 for details).

The study schema is displayed in Figure 1, and a schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



BID = twice daily; OCS = oral corticosteroid; OLE = open label extension; QD = daily.

3.1.2 Internal Monitoring Committee and Scientific Oversight Committee

Regular safety reviews and the interim analysis will be performed by the Sponsor's IMC. This committee will be unblinded to treatment assignments and will include a clinical scientist, in conjunction with a safety scientist, biostatistician, and statistical programmer from the Sponsor who are not members of the study management team. The IMC members will not have direct contact with investigational staff or site monitors. The IMC may request that additional Sponsor scientists (e.g., clinical pharmacology, biomarker) participate in data analysis. The IMC members will also be part of a companion Scientific Oversight Committee. This committee will review safety, pharmacokinetic (PK), and pharmacodynamic (PD) data and make recommendations to the Sponsor regarding continuation of the study and/or study drug dose modifications. For further information, please see the Internal Monitoring Committee Charter.

The Scientific Oversight Committee will be unblinded to treatment assignments and will include the IMC members and at least two external SLE experts who are not investigators in this study. The Scientific Oversight Committee will meet periodically to review the study data.

After each meeting, either the IMC or Scientific Oversight Committee will recommend that the Sponsor proceed with one of the four following actions: 1) continue the study unchanged, 2) discontinue the study for safety reasons, 3) discontinue the study for futility (at the interim analysis), or 4) amend the study protocol. For further information, please see the IMC and Scientific Oversight Committee Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

3.2.1 Length of Study

The maximum length of time on study for a patient is *61* weeks, including screening for up to 35 days, treatment for 48 weeks, and a safety follow-up period for 8 weeks *(unless enrolled* into an OLE study*)*.

3.2.2 End of Study

The end of study is defined as the last patient, last safety follow-up visit in this protocol, last patient to discontinue from the study, or the last patient enrolled into an OLE, whichever occurs latest.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for GDC-0853 Dose and Schedule

The proposed GDC-0853 doses of 150 mg QD and 200 mg BID for 48 weeks are expected to be well tolerated and to demonstrate BTK inhibition on the basis of the available safety, PK, and PD results from Phase I studies, nonclinical toxicology studies, and studies in nonclinical inflammatory models.

These doses are expected to achieve exposures (i.e., area under the concentration–time curve [AUC] and C_{max}) below those achieved at the highest doses evaluated in the Phase I SAD and MAD studies (GP29318 and GA29347, respectively) and 5-fold below the exposures at the NOAEL of the nonclinical chronic toxicity studies (see the GDC-0853 Investigator's Brochure). In healthy subjects, doses up to 600 mg in Study GP29318 and 250 mg BID and 500 mg QD in Study GA29347 were well tolerated; all adverse events were Grade 1 (mild) and transient, there were no DLAEs, and no maximum tolerated dose (MTD) was identified.

Dose-dependent BTK inhibition was demonstrated in the Phase I SAD and MAD studies (GP29318 and GA29347, respectively) through use of PD biomarker assays (e.g., CD63 expression in basophils, phosphorylated-BTK inhibition). PK and PD data from these studies were used to model the relationship between GDC-0853 systemic exposures and BTK-dependent biomarker inhibition. [redacted]

- [redacted]

- [redacted]

The efficacy of GDC-0853, as well as GDC-0834 *(Liu et al. 2011)* and G-744 (related small-molecule BTK inhibitors used to demonstrate the effect of BTK inhibition in nonclinical studies), was evaluated in nonclinical inflammatory models of arthritis and immune complex–mediated renal injury (see *Liu et al. 2011 for GDC-0834, and* the GDC-0853 Investigator's Brochure *for GDC-0853 and G-744*), in which disease manifestations are similar to those of human SLE. In female Lewis rats with developing Type II CIA, GDC‑0853 treatment was well tolerated and resulted in significant and beneficial dose-dependent effects on ankle swelling. Doses ≥0.25 mg/kg/day of GDC-0853 significantly reduced serum levels of anti‑rat collagen II IgG, whereas total anti-rat IgG antibody serum levels did not change. The histopathology findings were consistent with the clinical findings. Studies in NZB/NZW lupus-prone mice with G-744 have shown that BTK inhibition resulted in dose-dependent improvement in survival (see GDC-0853 Investigator's Brochure).

These nonclinical studies suggest that 70% BTK inhibition, as measured by phosphorylated-BTK inhibition, is required for half-maximal activity in disease models (see the GDC-0853 Investigator's Brochure; Liu et al. 2011). [redacted] however, whether BTK inhibition in the rat CIA or the mouse SLE model accurately predicts efficacy in human SLE is currently unknown.

The Sponsor believes that the existing clinical and nonclinical data support the proposed GDC-0853 doses of 150 mg QD and 200 mg BID for 48 weeks. In addition, the Sponsor believes that these doses will enable robust characterization of exposure-response relationships across a wide range of exposures because of inter-individual PK variability.

[redacted]

3.3.2 Rationale for Patient Population

A substantial number of SLE patients fail to achieve an adequate response on the current SOC therapy and often the patients experience flares despite their current

treatment and medical compliance. Furthermore, the mainstay of therapy for SLE is systemic corticosteroids, which can lead to significant morbidities. Given the limitations with the current therapeutic options for SLE, there remains a need for therapies that provide a higher degree of both safety and efficacy.

BTK inhibition should target several pathways and cell types central to SLE pathogenesis. B-cell activation and differentiation into plasma cells is central to the development of pathogenic autoantibodies (see the GDC-0853 Investigator's Brochure for details). BTK activity is central to B-cell activation and autoantibody production. In addition, autoantigen-containing immune complexes are bound to Fc receptors on myeloid cells and their activation can lead to both inflammatory cytokine production as well as the presentation of additional autoantigens. These processes can lead to a cycle of tissue injury, inflammation, and new autoantibody production. BTK inhibition of both B cells and myeloid cells may contribute to efficacy (Chang et al. 2011; di Paolo et al. 2011). In addition, the reversible inhibition of BTK by GDC-0853 may allow for more rapid removal of suppression if infection occurs.

This Phase II study will evaluate patients with unmet need due to active SLE despite being treated with SOC, including corticosteroids and/or concomitant immunosuppression. Eligibility criteria for this study are similar to other Phase II proof-of-concept SLE studies and have been customized in some cases for patient safety (see Section 4.1).

3.3.3 Rationale for Control Group

All patients in this study will receive SOC therapy for SLE. Arm C is treated with placebo in combination with SOC in order to maintain the blind. It is not known whether GDC-0853 will be better or worse than placebo in combination with SOC.

The placebo-treated control group in Arm C is required for this study to achieve the safety and efficacy objectives. Historical control groups are not sufficiently comparable given changes in SLE populations and treatment patterns over time and around the world. Furthermore, refinements in study conduct, inherent variability in the subjective assessments and regional differences in the management of SLE patients require a placebo-treated control group to accurately determine the safety and efficacy of GDC-0853 relative to current SOCs. The study treatment period, including the placebo-treatment period, will be 48 weeks, which has been the time necessary to establish the peak-level efficacy of SLE therapeutics, based on prior SLE studies. Multiple recent Phase II and Phase III studies incorporate 48-week placebo-comparator groups (*Furie et al. 2017*; Khamashta et al. 2016; Navarra et al. 2011). If placebo patients have increased SLE disease activity, burst therapy, escape therapy, or both will be available (see Section 4.3.2.3.3 and Section 4.3.2.3.4 for details).

3.3.4 Rationale for Biomarker Assessments

*Diagnostic b*iomarker assessments aim to identify a biomarker that predicts response to GDC0853, which would be valuable to patients and treating physicians as an aid in identifying patients with increased likelihood to achieve clinical benefit, thus guiding treatment decisions. *In addition, a*t various timepoints after treatment, *pharmacodynamic* biomarker samples will be collected and used to advance the understanding of the mechanism of action of GDC-0853 and define PK/PD relationships in SLE patients aiding in dose evaluation in this study as well as dose-regimen selection for future studies (see Appendix 2).

3.3.5 Rationale for PK Sample Collection Schedule

PK results will be used to perform robust exposure-response and exposure-safety analyses, which will help to characterize how safety and efficacy are impacted by drug exposure and, thus, inform appropriate doses and regimens for future studies of GDC-0853. The PK sampling schedule is designed to capture data at several points during the study in order to *enable the estimation of systemic GDC-0853 exposures and subsequent* exposure-response evaluations and dose-regimen selection for future studies (see Appendix 2)*, which may be reported separately*.

3.3.6 Rationale for Other Study Design Elements

3.3.6.1 Pre-Enrollment Adjudication

Enrollment into this trial is subject to adjudication by the Sponsor's Medical Monitor or medically qualified designee. The objective of the adjudication process is to ensure that eligibility is based on objectively ascertained, well-documented, and clinically important disease activity. The scope and detailed procedures for the adjudication process are described in Appendix 3.

3.3.6.2 Efficacy Measurements

The primary efficacy endpoint in this study is a composite of the Systemic Lupus Erythematosus Responder Index (SRI)-4 at Week 48 (see Table 1). The SRI-4 response criterion is commonly used in SLE studies, is accepted by health authorities to measure reduction in SLE disease activity, and it is a composite measure that includes the SLE Disease Activity Index (SLEDAI-2K), British Isles Lupus Activity Group (BILAG) 2004, and Physician Global Assessment. SRI responses have been detected at timepoints as early as 12 weeks in prior clinical trials; however, therapeutic benefit is often measured at 24 weeks with maximal benefit seen as late as 48-52 weeks post-treatment intervention (Burgess and McCormack 2011; *Furie et al. 2017*; Khamashta et al. 2016; Navarra et al. 2011). SRI-4 alone is the primary efficacy endpoint. Achievement of a low, stable, corticosteroid dose has been added to the SRI-4 in the secondary endpoint in order to minimize the confounding effect of corticosteroids, including inflation of the response rates in the comparator arm that can obscure detection of an efficacy signal. *The BILAG-based Composite Lupus Assessment (BICLA) and the SRI-6 are also secondary endpoints as they provide a meaningful metric of SLE disease activity.*

In addition to the primary and secondary SRI endpoints, SRI 5*, 7, and* 8 are exploratory efficacy endpoints. Furthermore, several other clinically meaningful and exploratory aspects of SLE disease activity will be evaluated, using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), *SLICC/ACR Damage Index,* Physician Global Assessment, SELENA-SLEDAI Flare Index (SFI), 28-joint count, and patient-reported outcome (PRO) measures (i.e., Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue and Patient Global Assessment). Each of these measures has been well established and validated in previous studies.

3.3.6.3 Corticosteroid Taper

There is a substantial unmet need for effective corticosteroid-sparing treatments for SLE and this study will assess the corticosteroid sparing potential of GDC-0853. Chronic corticosteroid use has many adverse short- and long-term consequences, so reducing corticosteroid doses in patients with SLE will decrease the incidence of short- and long-term co-morbidities and potential adverse events, including in patients in this trial. The Glucocorticoid Toxicity Change Index (GTCI) will be used to determine the potential of GDC-0853 to reduce steroid-induced systemic side effects (see Appendix 12). In addition, the unrestricted use of corticosteroids in SLE clinical trials can confound safety and efficacy measurements and decrease the ability to detect the biologic activity/efficacy of the experimental drug (Reddy et al. 2013). Thus, to best determine the safety and efficacy of GDC-0853, corticosteroids should be tapered according to a suggested taper schedule, as tolerated (see Appendix 4). Furthermore, if a patient requires a corticosteroid burst during the Burst Windows, corticosteroids should be tapered back down to baseline (either the Day 1 dose or lowest stable dose the patient achieves) using the suggested taper schedule. Study patients with disease activity that precludes tapering corticosteroid to the target level will be considered trial defined non-responders for the analysis of secondary and exploratory endpoints that incorporate the requirement for OCS tapering.

3.3.6.4 Clinical Outcomes Assessments

PRO and clinician-reported outcome data will be collected to more fully characterize the clinical profile of GDC-0853. To minimize the confounding of PRO assessments that evaluate pain, any potentially painful procedures (e.g., blood draws) should be performed after the pain assessment.

3.3.6.5 Stratification

Randomization will be stratified by disease activity based on the SLEDAI-2K score, entry dose of OCS, and geographic region obtained at screening.

Levels of baseline disease activity (SLEDAI-2K score) and corticosteroid use as well as geographic region independently impact a patient's ability to achieve response on the primary efficacy endpoint. Specifically, a reduction of ≥ 4 points in the SLEDAI-2K must be achieved to be classified as a responder. In addition, use of corticosteroids in SLE clinical trials can confound efficacy measurements and decrease the ability to detect the

biologic activity/efficacy of the experimental drug. For this reason, it is important to prevent treatment imbalances in these factors at baseline and thus randomization will be stratified by both SLEDAI-2K score (≥10 or <10) and baseline corticosteroid use. Geographic region was chosen as the third strata, because regional variations in the management of SLE can manifest as variability in response rates, including differences in placebo rates (Kalunian et al. 2016; Khamashta et al. 2016). The stratification is intended to balance the proportion of patients from different regions across the study arms in order to limit any confounding of the study results.

3.3.6.6 Concomitant Medication Rationale

Patients in this study will continue on their background SOC therapy in order to ensure that all patients receive effective therapy for SLE. GDC-0853 or placebo will be added to determine if GDC-0853 improves clinical response and/or reduces the need for systemic steroids in combination with SOC. The eligibility criteria exclude patients on certain SLE therapies in order to reduce the risk of participation in this study. Concomitant SLE therapies other than OCS will not be changed during the study (except in the event of toxicity), in order to reduce confounding effects on the safety and efficacy results of the study. OCS doses may be changed during certain time windows to minimize toxicity or for short-term treatment of increased SLE disease activity (see Section 4.3.2.3.3).

For guidance on concomitant medications that are unrelated to background SOC therapy, please refer to Section 4.4.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 240 patients with moderate to severe active SLE will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years, inclusive
- Able to comply with the study protocol
- Fulfillment of SLE classification criteria according to either the current American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria at any time prior to or at screening (see Appendix 5 and Appendix 6, respectively)
- At least one serologic marker of SLE at screening as follows:
  - Positive antinuclear antibody (ANA) test by immunofluorescent assay with titer ≥1:80; OR
  - Positive anti-double-stranded DNA (anti-dsDNA) antibodies; OR

  - Positive anti-Smith antibody

- At both screening and Day 1, moderate to severe active SLE, defined as meeting all of the following unless indicated otherwise:
  - SLEDAI-2K score ≥ *8* (at screening only) with clinical SLEDAI-2K score ≥ 4.0 *(at both screening and Day 1)* (see Appendix 10)
  - Physician's Global Assessment ≥ 1.0 (out of 3) (see Appendix 15)
  - Currently receiving at least one standard oral treatment *(e.g., corticosteroids, anti-malarials, and/or immunosuppressants)* for SLE *within the dose ranges, as specified below* (see Appendix 18):
    - If on an OCS, the dose must be ≤40 mg/day prednisone (or equivalent, see Appendix 18) and must have been stable for at least 2 weeks prior to screening as well as during screening
    - If on anti-malarial or *immunosuppressant* therapies, may only be receiving medications from the following list within the specified dose range; dose and route of administration must be stable for 8 weeks prior to screening as well as during screening:
      - Azathioprine: 1 to 2.5 mg/kg/day
      - Methotrexate: 7.5 to 25 mg/week
      - Mycophenolate mofetil: 500 to *3000* mg/day
      - Mycophenolic sodium: 360 to *2160* mg/day
      - Hydroxychloroquine: 200 to 400 mg/day
      - Chloroquine: 100 to 250 mg/day
      - Quinacrine: 100 to 200 mg/day
      - Other: Consult with Medical Monitor

  Note: Any combination of azathioprine, methotrexate, mycophenolate mofetil, or mycophenolic sodium is prohibited.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods listed in Appendix 8 that result in a failure rate of <1% per year during the study treatment period and for a minimum of 60 days after the last dose of study drug or longer as required by local requirements for other standard of care medications. Women using estrogen-containing hormonal contraceptives as a method of contraception must also use a barrier.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (>12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormone-releasing intrauterine

devices, and copper intrauterine devices. Established proper use of hormonal contraceptives that inhibit ovulation also have a failure rate of < 1% per year; however, women using estrogen-containing hormonal contraceptives as a method of contraception must also use a barrier, such as a male condom, in conjunction with the hormonal contraceptives.

  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm as defined below. Please also see Appendix 8 for details:
  - Men with female partners of childbearing potential must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 120 days (16 weeks) after the last dose of study treatment. Men must refrain from donating sperm during this same period.
  - Men with pregnant female partners must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study treatment to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- *Proteinuria > 3.5 g/24 h or equivalent using urine protein-to-creatinine ratio (uPCR) in a first morning void urine sample*
- *Active proliferative lupus nephritis (as assessed by the investigator) or histological evidence of active Class III or Class IV lupus nephritis on renal biopsy performed in the 6 months prior to screening (or during the screening period)*
- *History of having required hemodialysis or high dose corticosteroids (>100 mg/d prednisone or equivalent) for the management of lupus renal disease within 90 days of Day 1*
- Neuropsychiatric or central nervous system lupus manifestations, including but not limited to: seizure, psychosis, or acute confusional state within 52 weeks of screening
- *Serum creatinine > 2.5 mg/dL, or* estimated glomerular-filtration rate (based on the 4-variable Modification of Diet in Renal Disease equation) < 30 mL/min, or on chronic renal replacement therapy
- History of receiving a solid organ transplant

- Newly diagnosed (within the last 24 weeks) transverse myelitis
- History of anti–phospholipid antibody syndrome (APLS) with or without associated consumptive coagulopathy [catastrophic anti-phospholipid syndrome] at any time; presence of anti-phospholipid antibodies or a history of fetal loss, but without a history of thromboembolism or current requirement for anti-coagulation, are not exclusionary.
  - Patients on *either* aspirin *up to* 325 mg/day *or clopidogrel* are not excluded. *The permitted dose of aspirin to reduce the risk of non-fatal stroke, non-fatal myocardial infarction, and vascular death in patients at high risk of arterial thrombosis should follow local regulations and guidelines.*
- Evidence of active, latent, or inadequately treated infection with *Mycobacterium tuberculosis* (TB) as follows:
  - A positive QuantiFERON TB-Gold® (QFT) *performed at screening visit*
    - *If QFT unavailable,* a Mantoux purified protein derivative (PPD) skin test *as defined by the* Centers for Disease Control and Prevention (CDC) *guidelines*, performed at the screening visit or within the 12 weeks prior to screening *and read locally*
  - A chest radiograph taken at the screening visit or documented results within the 12 weeks prior to screening (chest radiograph must be read by a radiologist), without changes suggestive of active TB infection
  - If a patient has previously received an adequate documented course of therapy for either latent (36 weeks of isoniazid in a locale where rates of primary multi-drug resistant TB infection are < 5% or an acceptable alternative regimen, according to local guidelines) or active (acceptable multi-drug regimen, according to local guidelines) TB infection, neither a PPD test nor a QFT test need to be obtained, but a chest radiograph must still be obtained if not performed within the prior 12 weeks; this chest radiograph must be without changes suggestive of active TB infection
- *NOTE:* Patients with a history of *Bacille Calmette-Guérin (*BCG*)* vaccination should be screened using the QFT test only.

  If *the* initial QFT *test* is indeterminate, a confirmatory test with either a QFT or T-SPOT® *TB test* (*performed locally* if available). The PI may consult with the Medical Monitor to discuss selection of confirmatory test based on the patient's disease status and baseline immunosuppression.
  - An indeterminate QFT test followed by a negative QFT or negative T-SPOT® test should be considered a negative diagnostic TB test.
  - An indeterminate QFT test followed by an indeterminate QFT test or indeterminate T-SPOT® test should be considered a positive diagnostic TB test
- Women who are pregnant or nursing (breastfeeding; within the last 12 weeks), or women intending to become pregnant, donate eggs or breast milk, or participate in in vitro fertilization during the study

- For women of childbearing potential: Positive serum pregnancy test result at screening or on Day 1 (a serum pregnancy test is needed on Day 1 ONLY if the urine pregnancy test is positive)

- Significant and uncontrolled medical disease within the 12 weeks prior to screening in any organ system (e.g., cardiac, neurologic, pulmonary, renal, hepatic, endocrine [including uncontrolled diabetes mellitus], metabolic, GI, or psychiatric [including suicidality]) not related to SLE, which, in the investigator's or Sponsor's opinion, would preclude patient participation
- Concomitant chronic conditions, in addition to SLE, (e.g., asthma, Crohn's disease) that required oral, IV, or intramuscular (IM) steroids or immunosuppressive use in the 24 weeks prior to screening or are likely to require these during the course of the study
- History of non–gallstone-related pancreatitis or chronic pancreatitis that is judged to be clinically significant, in the opinion of the investigator (e.g., accompanied by upper abdominal pain or malabsorptive diarrhea)
- Evidence of autoimmune myositis
- History of cancer, including hematological malignancy and solid tumors, within 10 years of screening; basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix adequately treated by curative therapy more than 1 year prior to screening are not exclusionary
- History of alcohol, drug, or chemical abuse within the 1 year prior to screening as determined by the investigator
- Major surgery requiring hospitalization within 4 weeks of screening
- History of cerebrovascular accident (CVA) within 10 years or any history of hemorrhagic CVA, any history of spontaneous intracranial hemorrhage or a history of traumatic intracranial hemorrhage within 10 years
- History of clinically uncontrolled cardiac arrhythmias
- Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including
  - QT interval corrected using Fridericia's formula (QTcF) $>$ 450 msec for female patients and $>$ 430 msec for male patients demonstrated by at least two ECGs $>$ 30 minutes apart
- History of clinically significant ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as long QT syndrome or other genetic risk factors (e.g., Brugada syndrome), structural heart disease (e.g., severe left ventricular systolic dysfunction, severe left ventricular hypertrophy), coronary heart disease (symptomatic, or with ischemia demonstrated by diagnostic testing, prior coronary artery bypass grafting, or coronary lesions $>$ 70% diameter stenosis that have not been or cannot be re-vascularized), or family history of sudden unexplained death or cardiac ion channel mutations
- Current treatment with medications that are well known to prolong the QT interval (except for anti-malarials) at doses that have a clinically meaningful effect on QT, as

determined by the investigator. The investigator may contact the Sponsor for confirmation if needed. The investigator may reference the website: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf

- Any condition possibly affecting oral drug absorption (e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass); procedures, such as gastric banding, that simply divide the stomach into separate chambers are not exclusionary
- Need for systemic anticoagulation with warfarin, *or* other oral or injectable anticoagulants *(*other than NSAIDs, aspirin (≤325 mg/day), or other salicylates*)*
- Known bleeding diathesis
- Any history of hospitalization or transfusion for a GI bleed
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection or IgG <500 mg/dL
- Any known active infection during screening up to and including at the time of enrollment (with the exception of fungal nail infections or oral herpes)
- History of treated recurrent bacterial, viral, mycobacterial, or fungal infections, defined as >2 similar episodes requiring anti-microbial treatment within the past 52 weeks, with the exception of the following:
  - Oral or genital herpes (herpes simplex virus 1 [HSV1]/ herpes simplex virus 2 [HSV2])
  - Uncomplicated cystitis or asymptomatic bacteriuria
  - Uncomplicated viral, bacterial or culture-negative bronchitis without pneumonia
  - Bacterial or viral sinusitis
  - Bacterial or fungal (yeast) vaginal infections
- Any history of opportunistic infections that, in the Investigator's or Sponsor's judgment, would raise safety concerns regarding the patient's participation in the study
- Any major episode of infection requiring hospitalization or treatment with IV or IM antimicrobials within 4 weeks prior to or during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening (with the exception of prophylaxis for *Pneumocystis jiroveci* pneumonia)
- History of severe and/or disseminated viral infections, particularly herpes viruses, such as HSV1, HSV2, varicella zoster virus (VZV), cytomegalovirus (e.g., herpes encephalitis, ophthalmic herpes, disseminated zoster, cytomegalovirus colitis); uncomplicated influenza during a flu season*, herpes labialis, and genital herpes are* not exclusionary
- Evidence of chronic and/or active hepatitis B or C
  - Positive hepatitis B surface antigen (HBsAg) or hepatitis C serology (regardless of treatment status)

  - Positive hepatitis B core antibody (HBcAb)
- Received any of the following medications and/or treatments within the indicated period of time:
  - Plasmapheresis or IV Ig in the last 12 weeks prior to screening
  - B cell–depleting therapy (e.g., anti-CD20 or anti-CD19) within 24 weeks prior to screening
  - Belimumab, blisibimod, tabalumab (or other anti-B-cell activating factor [BAFF] agents), atacicept (or other anti-transmembrane activator and calcium-modulator and cyclophilin ligand [CAML] interactor [TACI] agents), epratuzumab (or other anti-CD22 agents), or denosumab within *5 half-lives or 12 weeks (whichever is longer)* prior to screening
  - Cyclophosphamide or other alkylating agents within 12 weeks prior to screening
  - Oral cyclosporine, tacrolimus, topical calcineurin inhibitors, anakinra (inhibitor IL-1), sirolimus (inhibitor IL-2), or other calcineurin inhibitors within 4 weeks prior to screening
  - Thalidomide or thalidomide derivatives within 24 weeks prior to screening
  - Tumor necrosis factor (TNF)-antagonists, tocilizumab, or other biologics not previously mentioned above within *12 weeks* prior to screening
  - Any investigational drug within 4 weeks or 5 half-lives, whichever is longer, of screening
  - Any parenteral (IV), IM, or intra-articular steroid administration within *4 weeks* prior to screening
  - Any other immunosuppressive medication for SLE not listed in the inclusion criteria, within 12 weeks or 5 half-lives prior to screening, whichever is longer, unless approved by the Medical Monitor
  - Live vaccines within 6 weeks prior to randomization; seasonal influenza and H1N1 vaccination are permitted if the inactivated vaccine formulation is administered
- Use of any of the medications, herbal supplements, or foods in the categories below should be avoided within 1 week or 5 half-lives, whichever is longer, prior to randomization, on the basis of possible drug interactions with GDC-0853 unless otherwise advised by the Medical Monitor (or delegate) as part of the adjudication process (see Section 4.4 for additional information; the screening period may be extended to meet these criteria if approved by the Medical Monitor):
  - *S*trong CYP3A inhibitors (refer to Appendix 19 for examples)
  - *Moderate or strong* CYP3A inducers (refer to Appendix 19 for examples)
- Any uncontrolled, clinically significant, laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study
- Any of the following laboratory results, for which testing may be repeated once if the initial results are out of range during screening:

- AST or ALT $> 1.5 \times$ ULN
- Total bilirubin > 1.2 ULN
- Amylase or lipase $> 2 \times$ ULN
- Hemoglobin < 7 g/dL
- Absolute neutrophil count (ANC) $< 1.5 \times 10^9$/L
- Absolute lymphocyte count (ALC) $< 0.5 \times 10^9$/L
- Platelet count $< 50{,}000/\mu L$
- *Note: Other abnormal labs may be repeated at the discretion of the investigator. Final determination of whether the lab result is exclusionary will be made by the adjudication committee and Medical Monitor.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The Sponsor will define the randomization algorithm for implementation by the IxRS vendor. Randomization will be stratified by region, entry dose of OCS, and disease activity at screening.

To minimize bias in safety and efficacy assessments, this study uses a blinded, matching placebo for GDC-0853.

To maintain the blind, after screening, sites will not receive data related to selected laboratory parameters, including but not limited immunophenotyping.

PK samples will be collected from patients assigned to all arms in order to maintain the blinding of the treatment assignments. Since PK assay results for patients in the placebo arm are generally not needed for the safe conduct or proper interpretation of this trial, samples from patients assigned to the placebo arm will not be analyzed except by request (e.g., to evaluate a possible error in dosing). Sponsor personnel responsible for performing PK assays and PK/PD assessments, which may include contracted laboratory personnel, will be unblinded to patients' treatment assignment to identify appropriate samples to be analyzed.

Additional Sponsor staff will be unblinded to patients' treatment assignments in order to support the IMC and Scientific Oversight Committee, including a clinician, statistician, statistical programming analyst, biomarker scientist, clinical pharmacologist, and others at the request of the IMC. Certain Sponsor representatives not involved with study conduct or the study team (e.g., governance committee members) may review unblinded safety data or interim efficacy data to enable decision-making.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event or unanticipated pregnancy for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in

emergency situations. If the investigator wishes to know the identity of the study drug for any other reasons, he or she should contact the medical monitor directly to discuss the rationale for unblinding and further management plan for the patient (e.g., discontinuing drug treatment), prior to contacting the IxRS for unblinding. The Medical Monitor is not allowed to break the blinding on the investigator's behalf. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding and unblinding due to a serious adverse event), without disclosing the treatment assignment in the documentation.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (SUSARs, see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is GDC-0853 50-mg tablets.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 GDC-0853 50-mg Tablet and Placebo Tablet

GDC-0853 will be provided by the Sponsor as 50-mg dose strength tablets with corresponding matching placebo tablets, which will be indistinguishable in appearance. Tablets will be supplied in blister wallets for the treatment arm to which the patient is randomized. GDC-0853 and placebo tablets should be stored at 2°C – 8°C.

For information on the formulation and handling of GDC-0853, see the GDC-0853 Investigator's Brochure.

4.3.1.2 Background Standard of Care Therapy

For information on the formulation, packaging, and handling of background SOC therapy (i.e., immunosuppressive therapy and corticosteroids) see the local prescribing information.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 GDC-0853 and Placebo Dose and Administration

The GDC-0853 dose levels are 150 mg QD and 200 mg BID with matching placebo (see Table 2). Patients will receive GDC-0853/placebo BID approximately every 12 hours starting on Day 1 and ending on the evening (p.m. dose) prior to the Week 48 visit. Patients should be directed to take one dose (a total of 4 tablets) BID (total of 8 tablets each day). On clinic visit days when PK assessments are performed (Day 1, Week 4, and Week 24), patients should be instructed that study drug will be administered in the clinic.

In general, a dosing window of ±2 hours is acceptable. If a dose is taken more than 2 hours late or is missed altogether, the patient should resume normal dosing with the

next scheduled dose. Patients should record the dose that was missed on the blister wallet. Doses that are vomited will be considered missed doses.

GDC-0853 or placebo will be orally administered and may be taken with or without food, except the dose of oral study drug taken at the clinic visit on Day 1 and Week 24 (see Section 4.4.4 and Appendix 1 and Appendix 2), which will be administered at the clinic visit while fasting. The dates and times of the most recent prior meal, last dose of oral study drug (prior to clinic visit), and timing of oral study drug administration in clinic should be recorded at clinic visits with PK and/or fasting lipid assessments. In addition, any use of PPIs, H2 receptor antagonists (H2RAs), and/or short-acting antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) should be recorded as concomitant medications, including date and time of last administration prior to the PK clinic visits. Administration of study drug should be staggered with short-acting antacid use (i.e., oral study drug should be taken 2 hours before or 2 hours after the short-acting antacid). Staggering is not required for PPIs or H2RAs; however, PPI and H2RA medications *are recommended to* be maintained at a constant dose and regimen throughout the study if possible.

Table 2 Study Drug Dosing Regimen by Treatment Arm

Arm	GDC-0853 Dose (mg)	Number of GDC-0853 Tablets (a.m./p.m.)	Number of placebo (a.m./p.m.)
A	200 BID	4/4	0/0
B	150 QD	3/0	1/4
C	0	0/0	4/4

a.m. = in the morning; BID = twice daily; p.m. = in the afternoon; QD = daily.

Note: All patients will take 4 tablets BID (i.e., 8 tablets daily) regardless of assigned GDC-0853 dose regimen in order to maintain the blind.

At study visits, sufficient study medication will be dispensed to complete dosing until the next scheduled visit. When study medication is administered at the site, it will be administered under supervision of study personnel, and the amount of study medication dispensed must be recorded.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 GDC-0853 and Placebo Compliance

The following measures will be taken to assess patient compliance with study drug: Sites will be responsible for prepopulating the dates on the blister wallets for when patients are scheduled to take study drug. Under the corresponding dates listed, the patients will record the times (a.m. or p.m.) that they take each dose directly on the blister wallet. Patients should only remove tablets from the wallet at the time they take

the tablets (e.g., patients should not transfer the tablets to another container with their other medications for future use). Patients will be instructed *by the site staff on how to properly take the study drug, including recording the IP intake time on the blister wallet and a reminder to* bring all blister wallets (used and unused) to each study visit for assessment of compliance (based on the tablets remaining in the wallets as well as the recorded dates and times) and for medication disposal.

Compliance will be documented on the source record. If compliance is ≤80% (correct dosage at the correct time), the investigator or designee is to counsel the patient and ensure steps are taken to improve compliance.

In order to maintain the proper source documentation of subjects' IP compliance, the investigator should follow one of the two processes listed below:

1. *The site will keep the blister wallets on-site, together with all other subject source documents (e.g. signed ICFs, medical notes, completed PROs, etc.). Blister wallets may not be destroyed until all trial related documents are approved to be discarded if this process is followed.*
2. *Site staff will generate certified copies of the blister wallets, showing IP intake times recorded by the subjects on the wallets. After PI accountability is performed, blister packs are checked by the site monitor, and sponsor approval is obtained, the blister packs may be destroyed at the site or returned for destruction. If the investigator chooses to follow this process, all copies of blister wallets must be signed and dated by the person making the copy and noted with a statement such as "I certify that this is the true and correct copy of the original." For this trial, only printed copies of blister wallets will be accepted. Electronic copies are not allowed.*

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.3 Background Standard of Care Therapy

4.3.2.3.1 Immunosuppressant Therapy

All patients who enter the study on oral immunosuppressant therapy (not including corticosteroids) *or anti-malarial medications* will be instructed to maintain their medications and doses from screening throughout the rest of the study treatment period. After entering the study, patients may not begin taking a new oral immunosuppressant except in the case of increased clinical activity requiring escape therapy, as described in Section 4.3.2.3.4.

If dose reduction of an immunosuppressant is required because of toxicity, this must be recorded as an adverse event on the Adverse Event eCRF, and the dose modification must be recorded in the Immunosuppressant Review eCRF.

Any overdose or incorrect administration of an immunosuppressant should be noted on the Immunosuppressant Review eCRF. Adverse events associated with an overdose or incorrect administration of an immunosuppressant should be recorded on the Adverse Event eCRF.

4.3.2.3.2 Corticosteroid

For all patients who enter the study on oral prednisone (or permitted equivalent OCS; see Appendix 18), there will be two, 12-week, OCS taper windows (Weeks 0 to 12 and Weeks 24 to 36) where their dose, if $\geq$10 mg/day, will be tapered to $<$10 mg/day. During taper windows, patients will continue to receive their designated dose of study treatment (see Section 4.3.2).

The OCS rules are as follows: the OCS dose level achieved at the end of each OCS taper window will be maintained during the 12-week, OCS stability windows (Weeks 12 to 24 and Weeks 36 to 48; see Figure 1), whether or not the target OCS dose was achieved. Patients will be instructed not to deviate from this dose level achieved at the end of the OCS taper window, unless considered clinically appropriate by the investigator.

Patients should follow the appropriate tapering schedule as determined by the investigator, taking into account the taper window timing and the target OCS dose ($<$10 mg/day and $\leq$Day 1 dose). The investigator may modify a tapering schedule based on the patient's response to the reduction in corticosteroid dose. A suggested prednisone tapering schedule is provided in Appendix 4; in addition, the investigator may consult the Medical Monitor. Once $<$10 mg/day is achieved, tapering completely off corticosteroids is allowed if this is deemed clinically appropriate by the investigator (i.e., if there is minimal risk of inducing flare).

Inability to comply with any of the OCS rules and any change in steroid dose must be recorded on the Corticosteroid Medication eCRF. In addition, the patient will be considered a non-responder for the analysis that requires the steroid taper criteria to be satisfied (see Section 3.3.6.3).

It is recommended that all patients receiving corticosteroids should receive appropriate supportive therapy to help prevent steroid-induced osteoporosis (e.g., calcium, vitamin D supplements, bisphosphonates) as per local guidelines and physician preference. *Pneumocystis jiroveci* pneumonia prophylaxis is also recommended to be used as per local SOC.

Intra-articular injections and intra-lesional cutaneous injections of corticosteroids must be avoided during the $study$ if possible, as these interventions will confound the efficacy assessments.

If a patient entered the study on low potency topical steroids *(e.g., Class VI and Class VII)*, the steroid can be continued during the course of the study at a stable dose.

4.3.2.3.3 Burst Treatment

In the case of increased disease activity, the patient will have the opportunity to receive burst treatment, in addition to the study treatment, during the defined burst treatment window (see Figure 1). The patient should return to the clinic, either at a scheduled study visit or unscheduled flare visit, to be evaluated and to receive an increase or new dose of oral prednisone as follows:

- Burst Window 1 (Weeks 0 to 10): An increase or new dose of oral prednisone up to 40 mg/day (or equivalent; see Appendix 18)
- Burst Window 2 (Weeks 24 to 34): An increase or new dose in oral prednisone up to 20 mg/day (or equivalent; see Appendix 18)

When using corticosteroids as a burst treatment, the investigator will temporarily increase the dose of corticosteroids and then taper the patient back down to their previous corticosteroid dose *used prior to the initiation of the burst*, all over the course of 2 weeks. Patients will continue to receive their designated dose of study treatment (see Section 4.3.2) during the burst treatment. The previous corticosteroid dose is defined as the dose of corticosteroids taken for the 2 weeks prior to the burst (if the dose changed during the 2 weeks, the investigator may choose which dose to use). If the patient was not previously on corticosteroids, the investigator will taper the patient back off corticosteroids completely. If the patient was on a corticosteroid-tapering schedule at the time of the burst treatment, the investigator will revise the tapering schedule as necessary to meet the target OCS dose ($<$10 mg/day and $\leq$Day 1 dose) by the end of the taper window*, if clinically appropriate*.

Patients may receive corticosteroids for emergent illness other than SLE (e.g., trauma, asthma) or if clinically warranted to prevent adrenal crisis (e.g., prior to surgery). If possible, treatment in these cases should last no more than 7 days.

Any dose of steroid higher than the maximum burst levels above, any failure to taper the burst down to the previous level over the course of 2 weeks, or any necessity for additional burst treatments for increased SLE-related activity (either a second treatment within the burst window or a burst treatment outside the burst window), as determined by the investigator, will be recorded in the Steroid and immunosuppressant eCRF.

Use of burst therapy to treat worsening of lupus will be captured on the Adverse Event eCRF (see Section 5.3.5.9). If any patient needs additional corticosteroids for any reason *that falls outside the permitted OCS rules stated above (Sections 4.3.2.3.2 and 4.3.2.3.3)*, the Medical Monitor needs to be informed and the reason recorded on the Corticosteroid Medication eCRF.

4.3.2.3.4 Escape Therapy

If an increase in immunosuppressive therapy (referred to as "escape therapy") is deemed medically necessary due to increased SLE disease activity, the patient will be given escape therapy, which will be recorded on the Steroid and Immunosuppressant eCRF. Patients receiving the following escape therapies *may* be allowed to remain on study drug *after discussion with the Medical Monitor* but will be considered a protocol-defined "non-responder" in the primary analysis:

- IV *or IM* steroids *(at doses greater than 40 mg prednisone PO or equivalent)*
- OCS doses exceeding the limits described elsewhere in the protocol *(e.g., prednisone (or equivalent) doses of > 40 mg/day during the first 24 weeks of the study, or > 20 mg/day between Weeks 24 and 48)*
- New or increased doses of an immunosuppressant *or anti-malarial* medication up to the maximum allowed in the study (see Section 4.3.2.3)

NOTE: Combinations of immunosuppressant medications that are not allowed in the inclusion and exclusion criteria (see Section 4.1) are prohibited during the study (see Section 4.6.2).

Whenever possible, a patient being evaluated for escape therapy will undergo assessment at either an unscheduled or flare visit prior to the increase in immunosuppression in order to quantify and record the increased disease activity, unless this occurs at a scheduled study visit (see Appendix 1).

If the patient requires any further treatment for SLE activity beyond the escape therapy described above (e.g., prohibited medications as defined in Section 4.4.2 or any accepted immunosuppressive that exceeds the maximum dose as defined by the protocol, or any increase in therapy not approved by the Medical Monitor), the patient should stay in the study but will be discontinued from study treatment (see Section 4.6.2).

Use of escape therapy to treat worsening of lupus will be captured on the Adverse Event eCRF (see Section 5.3.5.9). If any patient needs additional corticosteroids for *this* or any other reason, the Medical Monitor needs to be informed and the reason recorded on the Corticosteroid Medication eCRF.

4.3.2.4 Background Standard of Care Therapy Compliance

Starting at the screening period, all patients must keep a weekly diary of their actual OCS use as instructed by study staff. Patients will record their actual OCS dose on a weekly basis using a paper diary and as instructed by study staff. OCS usage will be recorded in the Corticosteroid Medication eCRF.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (GDC-0853 50-mg tablet and placebo tablet) will be provided by the Sponsor where required by local health authority

regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to GDC-0853

Patients may be screened for enrollment into an OLE study. If they meet all OLE eligibility criteria, they may be enrolled if considered appropriate for participation, according to the investigator.

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide GDC-0853 or any other study treatments or interventions to patients who have completed the study and are not qualified or elect not to enter an OLE study, if available, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug through 8 weeks after the last dose of study drug or entrance into an OLE, if initiated, whichever occurs first. All concomitant medication taken during the study must be documented on the eCRF along with indication, daily dose, and start and stop dates of administration. Adverse events related to the administration of a concomitant medication or the performance of a procedure must also be documented on the appropriate adverse event page of the eCRF.

It is recommended that patients avoid changing other concomitant prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives, whichever is longer, prior to the first dose of study medication and throughout the study.

4.4.1 Permitted Therapy

Note for all concomitant immunosuppressive and anti-malarial medications: reductions to the concomitant immunosuppressive medication dose will not be allowed except in the case of intolerance or toxicity or for the safety of the patient, as determined by the investigator; any changes in the doses of concomitant immunosuppressive and anti-

malarial medications must be discussed in advance with the Medical Monitor unless medically emergent. Patients who require a new or increased dose of concomitant immunosuppressive medications will be considered protocol-defined non-responders (see Section 4.3.2.3).

Addition, discontinuation, and dose adjustment of concomitant medications for conditions other than SLE are discouraged but permitted when required for the safe and effective treatment of patients.

Any case of medication intolerance or toxicity must be recorded as an adverse event and any dose modification recorded in the eCRF.

Certain combinations of the SLE therapies below are not permitted (see Section 4.1)

4.4.1.1 Anti-malarials (E.g., Hydroxychloroquine, Chloroquine)

Patients taking anti-malarial medications at study entry should be on a stable dose for at least 8 weeks prior to screening and should maintain a constant dosage throughout the study. Patients not previously on anti-malarial medications may be enrolled in the study but should not initiate anti-malarial medications during the course of the blinded study. Replacement of one anti-malarial with another may be allowed in cases where there is limited supply of the original medication, or if there are issues with toxicity or intolerance; however, the change must be discussed with the Medical Monitor. Refer to Appendix 18 for anti-malarial list.

4.4.1.2 Mycophenolate Mofetil/Mycophenolic Acid

All patients who are taking mycophenolate mofetil (or mycophenolic acid) should be on a stable dose for 8 weeks prior to screening. When mycophenolic acid is used instead of mycophenolate mofetil, a 360-mg dose of mycophenolic acid is considered to be equivalent to a 500-mg dose of mycophenolate mofetil. Mycophenolate mofetil may have an interaction with oral contraceptives that may decrease their effectiveness; however, patients enrolling in this study and using hormonal contraceptives as a method of contraception are required to also use a barrier, such as a male condom.

4.4.1.3 Azathioprine

It is strongly recommended that prior to starting azathioprine*,* patients should have been evaluated for thiopurine methyltransferase variant alleles that have been associated with decreased activity in vitro and lead to the accumulation of the drug and/or its metabolites. A stable dose *used* for at least 8 weeks duration prior to screening of up to 2.5 mg/kg/day is allowed.

4.4.1.4 Methotrexate

Treatment must have been stable for at least the 8 weeks before screening. Patients taking methotrexate (oral or parenteral) must stay on the same dose delivered by the same route for the duration of their participation in this study. To prevent methotrexate-

associated adverse events, all patients on methotrexate are required to take folic acid *(e.g., 1 mg/day)* or equivalent at a stable dose of at least 5 mg/week or equivalent *as per local standard of care*.

4.4.1.5 Non-Steroidal Anti-inflammatory Drugs

As needed use of NSAIDs should be avoided within 24 hours before a visit where clinical efficacy assessments are scheduled to be performed and recorded.

Aspirin can be taken to reduce cardiovascular risk, but the dose is not to exceed 325 mg/day.

In order to prevent NSAID-related GI complications in high-risk patients, concomitant acid reducing agents (e.g., PPIs) should be used according to local guidelines (see Section 5.1.1.3).

Note that patients on anti-platelet agents may not be taking aspirin at the same time.

4.4.1.6 ACE Inhibitors and ARBs

For patients who are on ACE inhibitors or ARBs at study entry, *it is strongly recommended that* doses of ACE inhibitors or ARBs be kept stable for at least 10 days prior to randomization and throughout the trial whenever possible. *It is strongly recommended that* ACE inhibitors or ARBs *not* be initiated during the OCS stability windows.

4.4.1.7 Dietary Supplements

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties. Vitamins, minerals, and purified food substances are allowed in amounts not known to be associated with adverse events (e.g., hypervitaminosis). Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no CYP3A inhibition or induction (refer to Appendix 19).

for a list of prohibited concomitant medications, including herbal products). Otherwise, herbals with pharmaceutical properties must be discontinued for at least 4 weeks prior to the first dose of study medication, unless there is sufficient data available regarding the duration of an herbal medication's PK and PD effects to allow a shorter washout to be specified (e.g., 5 half-lives). Please direct any questions to the Medical Monitor.

4.4.1.8 Acid Reducing Agents

Patients who use short-acting antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids® for symptomatic relief of heartburn) should take GDC-0853 or matching placebo 2 hours before or 2 hours after short-acting antacid administration because gastric acid improves GDC-0853 absorption. Patients may be treated with PPIs or H2RAs at up to the maximum recommended dose according to local labeling. The dose should remain stable for at least the 2 weeks before randomization and throughout the study. At visits

with scheduled PK assessments (see Appendix 1 and Appendix 2), *the date and time of last administration of* any PPIs, H2RA, and/or short-acting antacids *taken* should be recorded *on the* concomitant medication *eCRF*.

4.4.2 Prohibited Therapy

A listing of concomitant medications and foods that are prohibited or should be used with caution due to potential PK drug-drug interactions is provided in Appendix 19. Biologic response modifiers and disease-modifying antirheumatic drugs (DMARDs) other than those mentioned above are not allowed during this study and any use will require discontinuation of study treatment.

Specifically, the use of the following therapies is prohibited in conjunction with study drug treatment:

- All biosimilar and biological agents (e.g., TNF inhibitors, IL-17, IL-12/23, abatacept, denosumab) as well as biosimilars (investigational or approved)
- Anti-CD20 monoclonal antibody
- Belimumab (Benlysta)
- Chlorambucil
- Cyclophosphamide
- Heparin, low molecular weight heparin, and other injectable systemic anticoagulants
- Immunosorbent column
- Investigational therapy other than study drug
- IV Ig
- Oral anticoagulants, including but not limited to warfarin, dabigatran, rivaroxaban, and apixaban
- Sirolimus
- Systemic calcineurin inhibitors (e.g., tacrolimus, cyclosporine)
- Tocilizumab and other anti-IL6R or anti-IL6 agents
- Tofacitinib and other JAK inhibitors
- *IV or IM steroids at doses greater than 40 mg prednisone PO or equivalent with the exception of use as escape therapy*

Please see Appendix 19 for additional prohibited therapies during this study.

4.4.2.1 Live or Attenuated Vaccinations

Immunization with a live or attenuated vaccine is prohibited within 6 weeks prior to randomization and for the duration of study participation, including the 8-week follow-up period after the administration of the last dose. See Section 5.1.1.2 for further details and precautions around vaccinations.

4.4.2.2 CYP3A *and BCRP-Mediated Drug Interactions*

Preliminary data from a clinical drug-drug interaction study (Study GP39616) suggest that GDC-0853 may be classified as a mild inhibitor of CYP3A at clinically relevant doses. It is possible that GDC-0853 inhibition of CYP3A may alter the metabolism of CYP3A substrates and result in increased plasma concentrations of CYP3A substrates.

Therefore, *medications in the following categories (listed in detail in Appendix 19)* should be used with caution in consultation with the Medical Monitor (or delegate) as necessary unless otherwise specified in Section 4.4.2:

- Sensitive CYP3A substrates
- CYP3A substrates with a narrow therapeutic index

The use of hormone-replacement therapy or hormonal contraceptives containing the CYP3A substrate ethinylestradiol (with the concomitant use of a barrier method) is permitted; however, patients should be counseled regarding the potential risks and benefit of these medications per the local prescribing information. Any increase in ethinylestradiol plasma concentrations is anticipated to be modest at most due to the relatively minor contribution of CYP-mediated oxidation in the clearance of orally administered ethinylestradiol (Zhang et al. 2007); however, increased ethinylestradiol plasma concentrations may lead to an increase in common side effects (e.g. nausea, breast tenderness, and headaches) and a theoretical increase in rare dose-related events (e.g. thromboembolism; Inman et al. 1970).

Preliminary data from Study GP39616 also suggest that GDC-0853 may be classified as a moderately sensitive substrate of CYP3A at clinically relevant doses. *There is a moderate* potential for a drug-drug interaction with any medication that strongly inhibits or induces this enzyme. Therefore, medications in the following categories (listed in detail in Appendix 19) should be avoided for 7 days or 5 half-lives, whichever is longer, prior to the first dose of study drug until the last dose of study drug, unless otherwise advised by the Medical Monitor (or delegate). If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with study drug.

- *S*trong CYP3A inhibitors
- Moderate or strong CYP3A inducers

Lastly, preliminary data from Study GP39616 suggest that GDC-0853 is a moderate inhibitor of the breast cancer resistance protein (BCRP) (also known as ABCG2) transporter protein at clinically relevant doses. There is a potential for increased plasma concentrations of drugs known to be substrates of the BCRP transporter. Plasma concentrations of the medications in the following category (listed in detail in Appendix 19) may increase; therefore, they should be used with caution in consultation

with the Medical Monitor (or delegate) as necessary unless otherwise specified in Section 4.4.2:

- *BCRP substrates with a narrow therapeutic index*

The medications listed in Appendix 19 are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for concomitant medications as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP3A *or is a sensitive substrate of BCRP*. The investigator should contact the Medical Monitor if questions arise regarding medications that may interact with CYP3A *or BCRP*.

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (Tables 3-1, 3-2, 3-3, and 5-1)

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

4.4.3 Prohibited Food

Use of the following foods is prohibited during the study and for at least 7 days prior to initiation of study treatment due to their effects on the cytochrome P450 3A4 enzyme, which is involved in GDC-0853 metabolism: furanocoumarin derivatives as found in grapefruit, Seville orange, pomegranate, or star fruit juice or products. Please refer to Appendix 19 for additional information.

4.4.4 Additional Restrictions

Patients should be fasting for ≥ 4 hours prior to pre-dose PK draws at Day 1 and Week 24, and also when fasting lipids are drawn (Day 1, Week 12, Week 24, Week 36, and Week 48). At Week 24, patients should also remain fasting for the 2-hour PK timepoint (see Appendix 1 and Appendix 2). The morning dose of oral study drug will be administered at the strongly recommended morning clinic visit while fasting.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 and Appendix 2 for the schedule of activities to be performed during the study.

The screening visit can occur up to 35 days prior to the first dose of study drug. The screening period may be extended upon the approval of the Medical Monitor. The Day 1 (baseline and randomization) visit occurs on the first day of study drug administration.

At applicable sites (United States only), if the patient is unable to return to the clinic at the Week 24 visit for the PK blood draw at the 8- to 10-hour timepoint, then this sample may be collected by a home nurse (HN) professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for

providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a patient and the patient gives written informed consent to participate in HN visits, the HN network will communicate with the patient and the patient's site. HN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the HN professional. The schedule of activities will specify the assessments that may be performed by an HN professional (see Appendix 1 and Appendix 2).

4.5.1 Informed Consent Forms and Screening Log

Patients will be screened within a period of up to 35 days prior to administration of study medication to confirm that they meet the entrance criteria for the study. The study investigator or sub-investigator will discuss with each patient the nature of the study, its requirements, and its restrictions and potential risks.

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Pre-enrollment adjudication by the Medical Monitor and his/her designees will occur for all patients who complete screening prior to their randomization into the study (see Appendix 3). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Eligibility Assessment at Screening

At screening, patients who fail to meet any laboratory inclusion/exclusion criteria or other eligibility criteria may be retested or rescreened per the instructions in Section 4.5.2.1 and Section 4.5.2.2, respectively.

4.5.2.1 Re-Testing: Laboratory Inclusion/Exclusion

If a patient fails certain laboratory inclusion/exclusion criteria at screening, the investigator may repeat the test once within the screening period; see Section 4.1.2 for a list of laboratory tests and levels that can be retested. If the patient passes the laboratory eligibility criteria on the second assessment, he/she will be adjudicated and may enter the study. It will not be considered a re-testing if blood samples have to be redrawn due to sample handling problems, breakage, sample integrity, or laboratory error.

4.5.2.2 Re-Screening

Re-screening refers to repeating the whole screening process. Re-screening is required if a patient has not met all of the eligibility criteria within the original screening period (Note: patients who have failed two laboratory testing attempts as described in Section 4.5.2.1 cannot be re-screened). Patients are only allowed to be re-screened once. Each patient must be re-consented before re-screening occurs. It will not be considered a re-screening if blood samples have to be redrawn due to sample handling problems, breakage, sample integrity, or laboratory error.

4.5.3 Medical History and Demographic Data

A complete medical history will be taken at the screening visit and should include details of past and current manifestations of SLE, past and current concomitant medical conditions, previous surgical procedures, and previous treatment regimens for SLE including any history of adverse drug reactions. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patients within 7 days prior to screening will be recorded.

Particular emphasis should be placed on manifestations of active SLE as well as the clinical and laboratory findings that identified the patient as having SLE (ACR or SLICC criteria) and on identifying any medical conditions (e.g., active or latent infection) that might place the patient at increased risk or which might confound the interpretation of safety or efficacy signals. At subsequent visits, the investigator will focus on changes in the patient's symptoms since the previous visit, including but not limited to features indicating current SLE activity, changes in disease activity since the previous visit, and potential adverse events.

The medical history must also include clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, family history of autoimmunity, vaccine history, smoking history, use of alcohol, and drugs of abuse.

A detailed history of medication used for SLE is required. All prior immunosuppressant drugs used to treat lupus 12 months prior to screening (including drug name, maximum dose used, and start and stop dates, as applicable) will be recorded. The year of onset as well as the symptoms that lead to the diagnosis of SLE in the patient as defined by either the ACR or SLICC inclusion criteria should be captured.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.4 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Particular attention should be given to evaluation of potential manifestations of active SLE and of infections or other medical conditions, which could place the patient at increased risk.

At subsequent visits (or as clinically indicated), limited, efficacy assessment–directed or symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures while the patient is in a seated position for at least 5 minutes.

4.5.6 Chest Radiograph

Chest radiographs of appropriate quality (to adhere to local standards for the exclusion of active TB) and with formal readings by a radiologist will be obtained at screening. If chest radiographs have been taken and read by a radiologist within 12 weeks prior to screening and documented results (as read by a radiologist) show no clinically significant abnormality as determined by the investigator, the chest radiograph does not need to be repeated.

4.5.7 Tuberculin Purified Protein Derivative Skin Test

The QuantiFERON TB-Gold® (QFT) should be used as the initial screening test for tuberculosis and, if indeterminate, this QFT test should be followed by a repeat QFT or a T-SPOT® test. If QFT is not available, a Mantoux PPD skin test will be performed at the screening visit or within the 12 weeks prior to screening and read locally. The PPD skin test will be performed per the CDC guidelines using 5 tuberculin units per 0.1 mL [5TU]. An intradermal injection into flexor or dorsal surface of forearm will be performed.

4.5.8 SLE Disease Activity Assessments

The following applicable SLE disease activity assessments will be used in this study: BILAG-2004, SLEDAI-2K, SELENA-SLEDAI Flare Index (SFI), Glucocorticoid Toxicity Change Index [GTCI], SLICC/*ACR Damage Index (SDI)*, 28-Joint Count, CLASI, Physician's Global Assessment, and Patient's Global Assessment. In addition, the SRI and BICLA composite endpoints will be evaluated. Throughout the study, each assessment ideally should be conducted by the same assessor, if possible (e.g., the same assessor should conduct the 28-joint count at each visit for a particular patient, if possible). Detailed instructions and training on the use of clinical instruments performed by the investigators in this study will be provided by the Sponsor or Sponsor designee. Investigators must demonstrate the ability to perform disease activity assessments

and/or they must provide valid training certificates obtained within 2 years of the start of the study for versions used in this study.

4.5.8.1 BILAG 2004 Index

The BILAG 2004 index (BILAG) will be used as a method to assess disease activity in this study.

The BILAG assesses 97 clinical signs, symptoms, and laboratory parameters across nine organ or system domains: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, GI, ophthalmic, renal, and hematological. The 97 symptoms are rated with respect to severity over the previous month (4 weeks) and with respect to any change from the previous examination (new, improving, stable, worsening, absent). For each of the nine domains, a single, alphabetic score (i.e., A through E) is then derived from the examination results in each organ category.

Detailed instructions and training on the use of the BILAG will be provided as described in Appendix 9.

4.5.8.2 Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and SELENA-SLEDAI Flare Index (SFI)

The SLEDAI-2K will be used to approximate disease activity for entry into the study and at every subsequent study visit (see Appendix 10).

SLEDAI-2K measures disease activity at the visit or within the preceding 28 days. Detailed instructions and training on the use of the SLEDAI-2K will be provided during training sessions at each investigator meeting, and through online resources. It is critical that investigators have a thorough understanding of both *the BILAG and SLEDAI-2K* instruments and the differences between them.

The SFI categorizes SLE flare as “mild or moderate” or “severe” based on 6 variables (Buyon et al, 2005; Petri et al. 1999; Petri et al. 2005):

- Change in SELENA-SLEDAI (or SLEDAI-2K) score from the most recent assessment to current
- Change in signs or symptoms of disease activity
- Change in prednisone dosage
- Use of new medications for disease activity or hospitalization
- Change in PGA score
- Hospitalization for activity (severe flare only)

The *SFI* will be modified such that severe flares *defined* only by *the occurrence of* an increase in SLEDAI-2K score to > 12 will be excluded. One or more other items defining severe flare in the SFI needed to be present for a severe flare to be recorded. This modification was made because patients entering the trial with high disease activity

(e.g., ≥ 11) could too easily trigger a severe flare by minor increases in the SLEDAI-2K score.

4.5.8.3 Glucocorticoid Toxicity Change Index

The GTCI is an exploratory standardized measure of damage related to use of glucocorticoids (see Appendix 12). The GTCI will be incorporated into this study to better quantify the accrual of damage linked to corticosteroid use in patients with lupus and may allow for an improved understanding of standard of care and patient phenotype.

4.5.8.4 Systemic Lupus International Collaborating Clinics (SLICC)/ *ACR* Damage Index for Systemic Lupus Erythematosus

The SLICC/*ACR* Damage Index *(SDI)* for SLE will be utilized to assess organ damage as opposed to the collection of disease activity (see Appendix 7). Damage is defined as non-reversible change not related to active inflammation.

4.5.8.5 28-Joint Count

For all patients, 28-joint counts should be performed at the intervals specified in the Schedule of Activities (see Appendix 1). The joint counts must be performed by an assessor with experience in performing these assessments; this may be the Principal Investigator, subinvestigator, or another trained individual approved by the Sponsor. The joint counts on a given patient *are strongly recommended to* be performed by the same assessor, whenever possible, at each study visit.

The 28 joints included in this assessment are listed in Appendix 13.

4.5.8.6 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI is an instrument designed to capture SLE-specific mucocutaneous disease manifestations (see Appendix 14). It comprises a score for the activity of the disease and a score for the damage caused by the disease. The CLASI should be completed at intervals as indicated in the schedule of assessments for any patient who has mucocutaneous manifestations of SLE at a given study visit and at all subsequent visits. The CLASI will be used to capture mucocutaneous disease in any patient with mucocutaneous disease manifestations beginning on the visit that the mucocutaneous manifestation is first observed and periodically thereafter as outlined in the Schedule of Activities (see Appendix 1).

It is important that only SLE-specific lesions are included in this assessment. Training in the use of the CLASI will be available online and will be required for any new investigator from the beginning of Study GA30044.

4.5.8.7 Physician's Global Assessment

The Physician's Global Assessment (see Appendix 15) is a visual analog scale (VAS). Physicians are to rate the patient's disease activity over the past 28 days and place a vertical tick mark on a 100-mm analog scale from 0 to 3. The left-hand extreme of the

line is described as “None” and the right–hand extreme as “Severe.” Patient history, results of the physical examination, as well as pertinent laboratory values should be taken into account when rating the patient’s disease activity. Physicians should also refer to the value recorded at the previous visit and move the tick mark as appropriate.

4.5.8.8 Patient’s Global Assessment

The Patient’s Global Assessment is a VAS (see Appendix 16). The patient’s overall assessment of their current disease activity is measured using a vertical tick mark on a 100-mm VAS. The left-hand extreme of the line is described as “None” and the right–hand extreme as “Maximum.”

4.5.8.9 Systemic Lupus Erythematosus Responder Index

The SRI is a categorical assessment that evaluates disease activity in SLE based on the different organ systems. This index utilizes a combined evaluation of the SLEDAI-2K, BILAG, and Physician Global Assessment to measure response to treatment (see Sections 4.5.8.2, 4.5.8.1; 4.5.8.7). The SRI-4 primary endpoint defines response as meeting all of the following criteria at Week 48 compared with baseline:

- ≥4 point reduction in SLEDAI-2K score
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores
- No worsening (worsening defined as a > 0.3 point increase) in the Physician’s Global Assessment.

4.5.8.10 BICLA

The BICLA is a composite index that was originally derived by expert consensus of disease activity indices (Wallace et al. 2011). BICLA response is defined as *follows*:

- At least one gradation of improvement in baseline BILAG scores in all body systems with moderate or severe disease activity at entry (e.g., all A (severe disease) scores falling to B (moderate), C (mild), or D (no activity) and all B scores falling to C or D
- No new BILAG A or more than one new BILAG B scores
- No worsening of total SLEDAI-2K score from baseline
- No significant deterioration (≤10%) in physician’s global assessment, and
- No treatment failure (initiation of non-protocol treatment)

4.5.8.11 Optional Photography *(for United States only, as applicable)*

For patients with cutaneous manifestations of SLE, optional photographs of the affected areas may be taken to document change over time while the patient is receiving study treatment. Photography is an optional assessment for patients *(United States only, as applicable)* who sign the optional photography consent and is contingent on EC/IRB approval.

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments will be performed as indicated on the Schedule of Activities (see Appendix 1 and Appendix 2). All laboratory tests will be sent to one or more central laboratories for analysis, with the exception of serum and urine pregnancy tests, and erythrocyte sedimentation rate (ESR), which will be conducted locally.

At clinic visits at which study drug will be administered, laboratory samples should generally be drawn before the administration of study drug and after the administration of PRO assessments. An exception is on Week 24, where indicated PK samples should be collected prior to dosing and at timepoints also following study treatment administration (see Appendix 1 and Appendix 2).

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- ESR: Can be performed at local laboratory or as point of care test in clinic. The kits to perform the test will be provided by the central laboratory.
- Pregnancy test
  - All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Should a positive result be recorded at any time, the procedures detailed in Section 5.4.3 should be followed.
- Direct Coombs Test: Will be performed at a local laboratory per the SOA and should also be tested if the patient develops anemia that may be autoimmune in etiology.
- T-SPOT® Test for tuberculosis: may be performed at a local laboratory (optional)

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Anti-dsDNA
- Anti-nuclear antibody test (immunofluorescence assay)
- Autoantibody panel: anti-Smith, anti-RNP, anti-Ro, anti-La, anti-cardiolipin, and anti-B2 glycoprotein
- C3, C4, and CH50
- Chemistry panel (serum or plasma): electrolytes (Na, K, Cl, bicarbonate, phosphorus), urea, creatinine, glucose, ALT, AST, amylase, lipase, total and direct bilirubin, ALP, GGT, albumin, globulin, total protein, calcium, uric acid
- Creatinine kinase (CK), aldolase, and lactate dehydrogenase (LDH)
- Coagulation panel: international normalized ration (INR), activated partial thromboplastin time (aPTT), prothrombin time (PT)

- High sensitivity C-reactive protein
- Fasting Lipids: Triglycerides, high-protein lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin $A1_c$ ($HbA1_C$), and total cholesterol
- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, calculated indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red cell distribution width [RDW]), platelets, WBC with differential
- Immunology: total immunoglobulins, IgG, IgM, IgE, and IgA
- TBNKs: Once treatment with study medication begins, TBNK results will be blinded.
- Urinalysis: dipstick (blood, protein, glucose, nitrites, and leukocyte esterase), microscopic analysis (RBC, WBC, red cell casts, white cell casts*, epithelial cells*)
- Viral serology
  - Hepatitis B: HBsAg, total HBcAb, and Hepatitis B surface antibody (HBsAb)
  - Hepatitis C (HCV) antibody
- QuantiFERON TB-Gold® (QFT); if QFT not available, a PPD skin test will be administered (see Section 4.5.7)

The following samples will be sent to the Sponsor or a designee for analysis:

- Plasma samples for PK analysis and metabolite identification, as needed.
- Plasma, serum, whole blood, urine, and RNA from blood for exploratory non-heritable PD markers potentially related to disease, drug, or clinical response; see Table 3.
- Whole blood for DNA extraction for exploratory research on inherited biomarkers (including, but not limited to, genes that express proteins which may influence GDC-0853 pharmacokinetics)

Table 3 Proposed Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Biomarkers
Plasma	Baseline and subsequent timepoints during and after treatment	• Markers including but not limited to: CCL3, CCL4
Serum	Baseline and subsequent timepoints during and after treatment	• Markers including but not limited to: CXCL13, CCL20, and autoantibodies
Whole blood for FACS	Baseline and subsequent timepoints during and after treatment	• Cells including but not limited to basophils and plasmablasts
RNA extracted from blood	Baseline and subsequent timepoints during and after treatment	• Markers including but not limited to the plasmablast signature
Blood for peripheral blood mononuclear cells for CyTOF analysis	Baseline and subsequent timepoints during and after treatment	• Cells and surface or activation markers, including but not limited to B and T cell subsets
Blood for peripheral blood mononuclear cells lysate	Baseline and subsequent timepoints during and after treatment	• Markers including but not limited to phosphorylated and total BTK protein
Urine	Baseline and subsequent timepoints during and after treatment	• Urinary biomarkers including but not limited to CXCL13, TWEAK, BAFF and lipids

BAFF = anti-B-cell activating factor; BTK = bruton's tyrosine kinase; CyTOF = cytometry by time of flight; FACS = fluorescence-activated cell sorting; TNF = tumor necrosis factor; TWEAK = TNF-like weak inducer of apoptosis.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.13), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:

- Plasma samples collected for PK analysis will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, and urine samples collected for biomarker analyses will be destroyed no later than 15 years after the final clinical study report (CSR) has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

4.5.10 Electrocardiograms

All ECG recordings must be performed using a standard, high-quality, high-fidelity, digital ECG machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible.

4.5.10.1 Timing of Electrocardiograms

Triplicate or single ECG recordings will be obtained at specified timepoints, as outlined in the Schedule of Activities (see Appendix 1). Triplicate ECG recordings will be obtained within approximately 2-5 minutes of each other.

When triplicate ECGs are required, three interpretable ECG recordings (e.g., without artifacts) must be obtained. Triplicate ECGs will be captured as follows:

- Day 1: Triplicate ECG (pre-dose)
- Week 24: Triplicate ECG (2 hours $\pm$ 30 minutes, post-dose)

The ECG intervals (e.g., PR, QRS, QT, QTcF, and RR) and heart rate from these three ECGs will be entered into the eCRF: in addition, these triplicate readings will be stored for future analysis, if needed.

Single ECG recordings may be obtained at unscheduled and other timepoints as indicated.

4.5.10.2 Patient Preparation for Electrocardiogram

ECG recordings *are recommended to* not be obtained within 3 hours after any meal, whenever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs *are strongly recommended to* be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws), whenever possible*, except for PROs which should generally be collected first at a visit*. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

4.5.10.3 Monitoring and Reporting of Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at a central laboratory. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular post-dose timepoint, the mean QTcF is $>$500 msec and/or 60 msec longer than the baseline value, another triplicate ECG must be recorded, ideally within

the next 5 minutes, and triplicate ECG monitoring should continue at least hourly until the QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. SOC treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.11 Patient-Reported Outcomes

PRO data will be collected via questionnaires to more fully characterize the clinical profile of GDC-0853. The questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Patients and clinicians will use paper based questionnaires to capture PRO data. The instructions for completing the questionnaires will be provided by the investigator staff.

4.5.11.1 Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT Fatigue)

The FACIT-Fatigue scale will be used to assess patients' fatigue (Cella et al. 2005). The 13-item questionnaire has been validated for use with SLE patients and has a 7-day recall period. Items are assessed on a 5-point Likert scale with responses ranging from 0 "not at all" to 4 "very much" and possible total scores range from 0 to 52. A higher score indicates less fatigue, and the minimal important different has been identified at a change of ≥ 3 points (Lai et al. 2011). See Appendix 17 for a list of questions in the FACIT-Fatigue.

4.5.12 Mandatory Samples for Whole Genome Sequencing

At participating sites, a blood sample will be collected for DNA extraction to enable whole genome sequencing (WGS). This sample may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research and the WGS portion of the ICF by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (i.e., Section 4.5.12) will not be applicable at that site.

Genomics are increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and,

along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in the identification of important pathways, thus guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

Patient medical information associated with WGS specimens is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from WGS specimens will, generally, not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.13 Optional Samples for Research Biosample Repository

4.5.13.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.13.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (see Section 4.5.13) will not be applicable at that site.

4.5.13.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to GDC-0853 and lupus:

- Serum and blood for RNA samples collected at screening; Day 1 (pre-dose); Weeks 12, 24, and 48; and flare visit.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.13.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.13.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.13.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GA30044 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GA30044.

4.5.13.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, as per Principal Investigator's discretion

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

If possible, the investigator will clarify the following:

- If the patient withdrew consent for the remaining study procedures *only* OR
- If the patient withdrew consent for the remaining study procedures as well as the use of all banked samples OR
- If the patient withdrew consent for the remaining study procedures as well as all use of study acquired clinical and laboratory data

If a patient discontinues the study prior to the Week 48 treatment completion visit, an early termination visit should be conducted. These patients should return for the 8-week safety follow-up visit in this study (see Appendix 1). If the patient is unable to return for a follow-up visit, the trial site may contact the patient by telephone to determine their clinical status.

Patients who discontinue the study during the safety follow-up period but prior to completion of the 8-week safety follow up will be asked to return to the clinic within 30 days (±7 days) after the last dose of study drug or last scheduled visit for an early termination visit.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment (and will continue in the study) if they experience any of the following:

- Requirement of any prohibited medication as defined in Section 4.4.2
- Treated with accepted immunosuppressive that exceeds the maximum dose as defined by the protocol (see Section 4.4.1)
- Combination immunosuppressive medications not allowed in the inclusion and exclusion criteria (see Section 4.1)

- Grade >2 AST or ALT elevation: (AST or ALT $>3\times$ ULN) in combination with total bilirubin $>2\times$ ULN or clinical jaundice as defined by Hy's law
- Grade ≥ 3 AST or ALT elevation: (AST or ALT $>5\times$ ULN)
- Grade 4 Neutropenia: ANC $<500/mm^3$
- Grade 4 Lymphopenia: absolute lymphocyte count (ALC) $<200/mm^3$
- Grade 4 Thrombocytopenia: platelet count $<25{,}000/mm^3$
- Pregnancy
- Malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin)
- An episode of torsade de pointes

Patients must discontinue study treatment if they receive any new or increased dose of SLE treatment that is not specifically permitted in this protocol (see Section 4.4.1) and approved by the Medical Monitor.

Investigators may discontinue study treatment for:

- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- The best interest of the patient
- Patient non-compliance

If study treatment is discontinued prematurely, patients will be asked to stay in the study and continue with all scheduled visits for the remainder of the 48-week treatment period.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

In some cases, study treatment may be resumed if approved by both the investigator and the Medical Monitor.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

To protect patient safety, an unblinded IMC in collaboration with a Scientific Oversight Committee will monitor safety throughout the study (see Section 3.1.2).

The safety risk management plan for patients in this study is based on nonclinical and clinical experience with GDC-0853 in completed and ongoing studies as well as published literature on other BTK inhibitors and takes into account the population under study. The important potential safety risks for GDC-0853 are outlined below. Please refer to the GDC-0853 Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for potential toxicities. Patients will undergo safety monitoring during the study, including monitoring of vital signs, physical examination, ECGs, and routine laboratory safety assessments (hematology, chemistry, and urinalysis) and assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing potential adverse events, including criteria for treatment interruption or discontinuation, and enhanced safety reporting are provided below and in Table 5.

5.1.1 Safety Plan for Potential Risks Associated with GDC-0853

5.1.1.1 Infections

On the basis of the well described phenotype of patients with XLA, a primary immunodeficiency of B cells and immunoglobulin production, it is anticipated that inhibitors of BTK may raise the risk for certain bacterial infections (Lederman and Winkelstein 1985; Broides et al. 2006), enteroviral infections (Misbah et al. 1992; Ziegner et al. 2002), intestinal infections with Giardia and *Campylobacter species* (Winkelstein et al. 2006; van den Bruele et al. 2010), or other opportunistic infections which are primarily cleared by B-cell adaptive immune responses. This risk is likely independent of sex for patients exogenously administered GDC-0853.

Unlike XLA, GDC-0853 is a reversible inhibitor of BTK that will be initiated after the immune system has developed, and so the degree to which GDC-0853 antagonism of BTK signaling may suppress immune activity or resemble XLA is unknown. However, data to date suggest that since BTK inhibitors target only the kinase domain, other BTK activities may remain intact and IgG levels in patients with an established immune system may not be significantly depleted (Byrd et al. 2013).

Effects on lymphocytes and immunoglobulins in rats and dogs were reversible and considered to be related to pharmacological activity involving BTK inhibition. See Section 1.3.1 for related primary nonclinical toxicity findings and Section 4 of the GDC-0853 Investigator's Brochure for further details.

To date, no immune-challenge experiments (e.g., T-dependent antigen response test [TDAR]) have been conducted in animals. It is not known if these effects on B cells and IgG concentrations in animals will translate to humans, or if such changes would have functional/deleterious impact on immune function.

Infections, including pneumonia and fatal influenza, have occurred in patients with B-cell malignancies treated with GDC-0853. In studies with healthy subjects with single doses and with dosing for 14 days, self-limited Grade 1 events of nasopharyngitis were reported but did not lead to any change in study drug dosing. One subject had asymptomatic bacteriuria, which resolved while study drug dosing continued.

Patients will be excluded from the study if they have a history of any major episode of infection requiring hospitalization or treatment with IV or IM antimicrobials within 4 weeks prior to or during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening, evidence of active or latent or inadequately treated infection with TB, known active infection (current) or history of recurrent infection, or any known immunodeficiency including IgG $<$500 mg/dL (see Section 4.1.2).

Total Ig concentrations will be measured regularly throughout the study. All patients in the study should be monitored for fever and potential infectious complications, including opportunistic infections and tuberculosis, and should be evaluated promptly. Physicians or a health care provider should give patients advice to prevent potential transmission of and exposure to endemic infections according to local or CDC guidelines. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of an infection. All infections occurring during the study that require treatment, including, but not limited to, respiratory infections, cutaneous infections, urinary tract infections and systemic viral infections and episodes of suspicious or febrile diarrhea, should be evaluated using serology or PCR *(*if available*, and as appropriate)* and cultured if feasible and any identified organisms noted in the Adverse Event eCRF. Any serious infection, any infection requiring IV antimicrobials (i.e., any Grade 3 infection), or any opportunistic infection is considered an adverse

event of special interest (AESI) and should reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for management of study treatment in the event that a patient experiences an infection are provided in Table 4.

5.1.1.2 Vaccinations

The effect of GDC-0853 upon the efficacy of vaccinations is unknown. It is recommended that appropriate vaccinations per EULAR (van Assen et al. 2011) recommendations or local guidelines be up to date before study participation. Patients will be excluded from study participation and will not be dosed with GDC-0853 if they have been vaccinated with live, attenuated vaccines (e.g., the intranasal live attenuated influenza vaccines, BCG, varicella) within 6 weeks before planned dosing. Immunization with a live or attenuated vaccine is prohibited for the duration of study participation, including the safety follow-up period after the administration of the last dose however inactivated vaccine formulations are permitted (e.g., seasonal influenza).

In addition, current routine household contact with children or others who have been vaccinated with live vaccine components may pose an unknown risk to the patient during study treatment with GDC-0853. Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted to the patient.

General guidelines for immunosuppressed patients suggest that exposure to vaccinated individuals should be avoided following vaccination with these vaccines for the stated time periods:

- Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination;
- Oral polio vaccination for 6 weeks following vaccination;
- Attenuated rotavirus vaccine for 10 days following vaccination;
- FluMist® (inhaled flu vaccine) for 1 week following vaccination.

5.1.1.3 Bleeding

No decrease in platelets, changes in coagulation parameters or bleeding events were observed in nonclinical studies with GDC-0853. Bleeding events, including non-serious CTCAE Grade 1 bruising and serious Grade $\geq$3 GI bleeding have been reported in patients with hematological malignancies treated with GDC-0853 in Study GO29089. The GI bleeding events have not been dose related, and the events occurred in patients who were taking concomitant NSAIDs/acetylsalicylic acid and who had a history of gastroesophageal or peptic ulcer disease. The impact of BTK inhibition as a potential risk factor for bleeding is unknown. BTK is expressed in platelets and is involved in platelet function via GPVI/Collagen receptor signaling and GP1b receptor signaling. Platelets from patients with XLA, a genetic deficiency of BTK, demonstrate decreased

activation in response to submaximal collagen stimulation but normal response to thrombin; clinically, there is no reported bleeding propensity of XLA patients (Howard et al. 2006).

Bruising or bleeding events related to GDC-0853 have not been reported in healthy subjects.

It is unknown if GDC-0853 will increase the risk of bleeding in patients, especially in those receiving antiplatelet or anticoagulant therapies. As a precautionary safety measure, patients will be excluded from study participation if they have a need for systemic anticoagulation with warfarin or other oral or injectable anti-coagulants or anti-platelet agents (other than NSAIDs, aspirin, and other salicylates), any history of hospitalizations or transfusion for a GI bleed, any history of a hemorrhagic CVA, any history of spontaneous intracranial hemorrhage, traumatic intracranial hemorrhage within 10 years prior to the study or a known bleeding diathesis. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of clinically significant bleeding.

Several risk factors including patient age, co-morbidities, concurrent medications, prior medical history, and *Helicobacter pylori* infection have been demonstrated in a variety of studies to increase the risk of NSAID-related GI injury (Lanza et al. 2009). It is unknown if GDC-0853 will increase the risk of bleeding in patients receiving NSAIDs. Therefore, in order to prevent NSAID-related GI complications in high-risk patients, concomitant use of PPI should be considered (Bhatt et al. 2008) and used according to local or recognized guidelines (e.g., ACCF/ACG/AHA 2008 Expert Consensus Document).

Patients at high risk for NSAID-related GI toxicity include the following:

- Patients using both aspirin and an NSAID
- Patients with a history of ulcer disease
- Patients with one or more of the following:
  - Age $\geq$60 years
  - High-dose NSAID use
  - Concurrent corticosteroid use
  - Dyspepsia or gastroesophageal reflux disease (GERD) symptoms

Any bleeding event Grade $\geq$2 is considered an adverse event of special interest and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for management of study treatment in the event that bleeding is observed in patients are provided in Table 4.

5.1.1.4 Cytopenias

Cytopenias have been observed in patients with hematological malignancies who received GDC-0853, including neutropenia, anemia, and thrombocytopenia; events have been monitorable and clinically manageable (see the GDC-0853 Investigator's Brochure for further details).

Patients should be monitored regularly with hematology laboratory evaluations as outlined in the schedule of assessments and should receive appropriate supportive care as clinically indicated. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of cytopenias (e.g., persistent fever, bruising, bleeding, pallor).

Guidelines for the management of study treatment, including dose holding, in the event of cytopenias in patients are provided in Table 4.

5.1.1.5 Gastrointestinal Effects

Body weight gain and food consumption changes have been observed in animals, including nonsignificant increases in male Wistar-Han rats administered $\geq$2 mg/kg/day (4.3 μM•hr) for 6 months, and significant reductions in rats administered 100 mg/kg/day (1438 μM•hr) and dogs administered 25 mg/kg (180 μM•hr) for 4 weeks. These effects on body weight gain and food consumption were reversible following discontinuation of GDC-0853 dosing.

Grade 1 diarrhea, nausea, and abdominal pain have been reported in patients with hematological malignancies treated with GDC-0853; however, the events resolved and have not led to study drug discontinuation. Healthy subjects in the multiple ascending-dose study, GA29347, reported events of mild self-limited nausea.

Throughout the study, patients will be monitored for GI side effects. Guidelines for management of study treatment in the event of GI side effects in patients are provided in Table 4.

5.1.1.6 Hepatotoxicity

Evidence of hepatobiliary injury was observed in animals administered relatively high doses of GDC-0853 in repeat-dose toxicity studies (see Section 1.3.1 for related primary nonclinical toxicity findings).

In clinical studies to date, including single dosing and multiple dosing for 14 days in healthy subjects and daily dosing for up to 2 years in patients with hematological malignancies, there have been no adverse events of liver enzyme elevations or trends towards elevations in laboratory evaluations.

As a safety risk–mitigation measure, to be eligible for the study, AST and/or ALT levels should be no more than 1.5 times the ULN and total bilirubin levels should be $\leq 1.2 \times$ ULN at screening. Safety monitoring for potential hepatotoxicity includes baseline and routine

evaluations of AST/ALT and total bilirubin levels throughout the study as outlined in the schedule of assessments.

Laboratory results of Grade ≥ 3 ($> 5 \times$ ULN) AST or ALT elevation, or ALT or AST elevations $> 3 \times$ ULN in combination with clinical jaundice (total bilirubin $> 2 \times$ ULN) are considered AESIs and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for the management of study treatment in the event of hepatotoxicity in patients are provided in Table 4.

5.1.1.7 Cardiovascular Effects

GDC-0853 is considered to have a low potential to cause QT interval prolongation or to directly affect other cardiovascular parameters, at therapeutic exposures. A minimal increase in corrected QT (QTc; 7 msec or 3%) interval was noted at 45 mg/kg in the single dose cardiovascular safety pharmacology study in telemetry-instrumented dogs. Based on extrapolated/interpolated toxicokinetic data, the unbound C_{max} at 45 mg/kg (considered a NOAEL) [redacted] There were no GDC-0853-related changes in ECG parameters in the repeat-dose 4-week or 9-month dog toxicity studies.

Analysis of ECG data from the SAD and MAD studies in healthy subjects did not demonstrate any significant increase in either QRS interval or QTcF intervals. However, cardiac safety will continue to be evaluated in all patients at baseline and throughout the study, with routine monitoring of vital signs (including heart rate and blood pressure), collection of routine safety ECGs, triplicate ECGs with appropriate PK-matched timepoints, and collection of adverse events (see Appendix 1).

Management of patients with sustained QTcF prolongation (QTcF that is > 500 msec and/or > 60 msec longer than the baseline value on at least two ECG measurements > 30 minutes apart) should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show stabilization of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients. The Medical Monitor should be notified as soon as possible (see Section 4.5.8.11 and Section 4.5.10)

Guidelines for management of study treatment in the event of cardiovascular effects in patients are provided in Table 4.

5.1.1.8 Vascular Inflammation

[redacted] The translatability of the nonclinical findings to

humans is unknown; however, Beagle dogs are susceptible to spontaneous development of polyarteritis syndrome (Snyder et al. 1995) and may be more sensitive to any drug-induced effects. Further, there are several examples of approved therapies for which there is no correlation between the finding of vasculitis in dogs or rats at clinically relevant exposures and adverse outcomes in patients (FDA 2003; FDA 2011).

As a safety risk-mitigation measure, CBC, creatinine, and urinalysis will be monitored in all patients during the study.

Guidelines for management of study treatment in the event of a new treatment emergent vasculitis in patients are provided in Table 4.

5.1.1.9 Malignancy

The impact of BTK inhibition on the development of malignancies is not known; however, malignancies have been identified as a potential concern for immunomodulatory agents. Malignancies have been reported in patients with XLA, including lymphoreticular malignancies, gastric and colorectal adenocarcinoma, and squamous cell carcinoma of the lung.

Patients with a history of cancer, including hematologic malignancy and solid tumors, within 10 years of screening will be excluded from the study. Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy more than 1 year prior to screening are not exclusionary.

All malignancies are considered adverse events of special interest for this study and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for management of study treatment in the event of malignancies in patients are provided in Table 4. Please refer to the GDC-0853 Investigator's Brochure for further details.

5.1.2 Management of Study Treatment in Patients Who Experience Specific Adverse Events

Guidelines for management of study treatment in patients who experience specific adverse events are outlined in Table 4.

Table 4 Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events

Event	Action to Be Taken [a]
Infection [b]	
Serious infection or any infection requiring treatment with an IV antimicrobial agent	Withhold study treatment. Once the infection has resolved, consult with Medical Monitor to discuss potential resumption of study treatment.
Self-limited infections that require treatment	Withhold study treatment during antimicrobial therapy.
Bleeding	Any Grade $\geq$2 bleeding event is considered an adverse event of special interest and should be reported to the Sponsor in an expedited manner. For Grade 3 or higher bleeding events or any serious bleeding event withhold study treatment and consult with the Medical Monitor. Once bleeding event has resolved, consult with Medical Monitor to discuss the potential resumption of study treatment.
Neutropenia [c]	
Grade 2: ANC $>$1000 and $<$1500/mm³	Maintain study treatment dosing.
Grade 3: ANC $>$500 and $<$1000/mm³	For the first event, hold study treatment and recheck CBC in 7 days. If neutrophil count has recovered to Grade 1 ($>$1500/mm^3) or has returned to baseline, study treatment can be resumed unless there is a concurrent serious or Grade 3 infection. If Grade 3 neutropenia persists, or for recurrent Grade 3 neutropenia, discuss with the Medical Monitor.
Grade 4: ANC $<$500 /mm³	Discontinue study treatment.
Lymphopenia	
Treatment emergent Grade 2 lymphopenia: lymphocyte count 500–800/mm³	Maintain study treatment dosing unless concurrent active infection or other clinical concern.
Treatment emergent Grade 3 lymphopenia: lymphocyte count 200–500/mm³	For the first event, hold study treatment and recheck CBC in 7 days. If lymphocyte count has recovered, study treatment can be resumed unless there is a concurrent serious or Grade 3 infection. If Grade 3 lymphopenia persists, or for recurrent Grade 3 lymphopenia, discuss with the Medical Monitor.
Grade 4 Lymphopenia**:** lymphocyte count $<$200/mm³	Discontinue study treatment.

Table 4 Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken [a]
Thrombocytopenia [d]	
Treatment-emergent Grade 1: PLT $>$ 75,000/mm³	In the absence of bleeding event(s), maintain study treatment dosing.
Treatment-emergent Grade 2: PLT 50,000–75,000/mm³	For the first treatment emergent drop in platelet count to 50,000–75,000/mm³ that cannot be attributed to an SLE flare, hold study treatment and recheck CBC in 7 days. If platelet count has recovered to >75,000/mm^3 or to baseline and there have been no bleeding events, study treatment can be resumed. For recurrent or persistent Grade 2 treatment-emergent thrombocytopenia that cannot be attributed to an SLE flare, or for thrombocytopenia associated with bleeding events, discuss with the Medical Monitor (and consider discontinuing study treatment).
Treatment-emergent Grade $\geq$ 3: PLT $<$ 50,000/mm³	For the first treatment emergent drop in platelet count to < 50,000/mm³ that cannot be attributed to an SLE flare, hold study treatment and recheck CBC in 7 days. If the platelet count has recovered to baseline or >75,000/mm^3, study treatment can be resumed. 1) If the platelet count fails to return to baseline or >75,000/mm^3, 2) if there is recurrence of Grade 3 treatment-emergent thrombocytopenia that cannot be attributed to an SLE flare, or 3) if the thrombocytopenia is associated with bleeding events, discuss with the Medical Monitor (and consider discontinuing study treatment).
Grade 4: PLT < 25,000/mm³	Discontinue study treatment
Gastrointestinal Effects	
Nausea, vomiting, and/or diarrhea	Manage according to site institutional guidelines. Consider administration of GDC-0853 with food as a possible mitigation strategy. Consult with Medical Monitor.
Malignancy	
Any malignancy	Discontinue study treatment with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin. Report event as an adverse event of special interest to the Sponsor in an expedited manner.

Table 4 Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken [a]
Hepatotoxicity	
Grade 2 AST or ALT elevation: (AST or ALT $> 3.0 - 5.0 \times$ ULN)	Withhold study treatment and consult with the Medical Monitor
Grade > 2 AST or ALT elevation; (AST or ALT $> 3 \times$ ULN) in combination with total bilirubin $> 2 \times$ ULN or clinical jaundice as defined by Hy's law	Discontinue study treatment and consult with the Medical Monitor. Recheck liver laboratory tests, to include AST/ALT, ALP, and total bilirubin, and CBC with differential (to determine eosinophil count), within 1 week (preferably within 72 hours). Assess patient for signs/symptoms of hepatic failure and assess for other causes of liver dysfunction (e.g. viral hepatitis, concomitant medications, etc.) Continue to monitor liver function tests until abnormalities resolve. Report Hy's Law cases as as adverse events of special interest to the Sponsor in an expedited manner.
Grade ≥ 3 AST or ALT elevation: (AST or ALT $> 5 \times$ ULN)	Discontinue study treatment and consult with the Medical Monitor. Recheck liver laboratory tests, to include AST/ALT, ALP, and total bilirubin, and CBC with differential (to determine eosinophil count) within 1 week (preferably within 72 hours). Assess patient for signs/symptoms of hepatic failure and assess for other causes of liver dysfunction (e.g. viral hepatitis, concomitant medications, etc.) Continue to monitor liver function tests until abnormalities resolve. Elevation of AST or ALT of Grade > 3 (i.e., AST or ALT $> 5 \times$ ULN) should be reported as an adverse event of special interest to the Sponsor in an expedited manner.
Cardiovascular Effects	
Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 msec and/or > 60 msec longer than the baseline value	Discontinue study treatment unless there is a clear alternative cause other than study drug.[e]
Sustained absolute QT that is > 515 msec or a new ECG finding of clinical concern	Discontinue study treatment and discuss with the Medical Monitor unless there is a clear cause other than study drug. [e]
An episode of torsades de pointes	Discontinue study treatment.

Table 4 Guidelines for Management of Study Treatment in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken [a]
Vascular Inflammation	
Treatment emergent vasculitis	Initiate appropriate evaluation and consult with the Medical Monitor.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CBC = complete blood count; ECG = electrocardiogram; IV = intravenous; OLE = open label extension; PLT = platelet count; SLE = systemic lupus erythematosus; ULN = upper limit of normal.

Note: "Study treatment" includes study drug (GDC-0853 or placebo)

[a] Patients who discontinue study drug treatment due to an adverse event should remain in the blinded study if feasible however they will not be eligible for an OLE, if initiated. If they discontinue the study, the patient should enter safety follow up.

[b] Appropriate laboratory investigations, including but not limited to cultures, should be performed to establish the etiology of any serious infection.

[c] Patients withdrawn from the study due to a reduced neutrophil count must be followed closely for signs of infection, with treatment and repeated laboratory analysis as deemed appropriate by the investigator including discontinuation of other treatments if indicated.

[d] Patients withdrawn from the study due to a reduced platelet count should have additional management and treatment as deemed appropriate by the investigator including discontinuation of other treatments if indicated.

[e] In rare circumstances, it may be acceptable to resume study drug, provided that any ECG abnormalities have resolved and that the patient is appropriately monitored. Prior to re-administering drug, consult with the Medical Monitor. Clinical judgment should be applied.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

Adverse Events of Special Interest for GDC-0853

- Any serious infection, any infections requiring IV antimicrobials and any opportunistic infections
- Any bleeding event Grade 2 or above
- All malignancies
- A laboratory result of Grade ≥ 3 (i.e., $> 5 \times$ ULN) AST or ALT elevation

Adverse Events of Special Interest for General Drug Development

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 – Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive

procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug the patients receives, either in this study or in an OLE, if initiated.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 ×ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of lupus.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of lupus, "*systemic* lupus *erythematosus* progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Lupus

Medical occurrences or symptoms of deterioration that are anticipated as part of lupus should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of lupus on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated *systemic* lupus *erythematosus*").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). No safety data related to overdosing of GDC-0853 are available.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D., MPH

Telephone Nos.: [redacted] ([redacted], [redacted], U.S.)

[redacted] Medical Monitor contact information:

Medical Monitors: [redacted], M.D.

Telephone No.: [redacted] ([redacted] Argentina)

24-hour Telephone No.: [redacted] *or* [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 8 weeks after the last dose of study drug the patients receives, either in this study or an OLE, if initiated. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within or within 8 weeks after the last dose of study drug, either in this study or an OLE, if initiated. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email

address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 120 days (4 months) after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. *When permitted by the site*, the pregnant partner *would* need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. *If* the authorization has been signed, the investigator *should* submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 8 weeks after the last dose of study drug the patients receives, either in this study or an OLE, if initiated), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the GDC-0853 Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An unblinded IMC and Scientific Oversight Committee will monitor the incidence of adverse events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Details of all statistical methods (including scoring of disease-activity or PRO instruments and missing data handling) will be provided in the Data Analysis Plan (DAP).

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation and hypothesis generation regarding the effect of GDC-0853 on Week 48 SRI-4 response rate relative to placebo in moderate to severe active SLE patients and a biomarker-defined subgroup of patients. A total of 240 patients will be randomly allocated in a 1:1:1 ratio to receive one of two doses of GDC-0853 (200 mg BID GDC-0853 [Arm A] or 150 mg QD GDC-0853 [Arm B]) or placebo (Arm C). This sample size will provide approximately 88% power at a 2-sided 0.05 significance *level* to detect a 25% absolute improvement in the response rate for a GDC-0853 containing arm relative to the placebo arm assuming a placebo response-rate of 50%. Patients without post-baseline response assessments will be treated as non-responders. For an evaluation of efficacy in a subgroup defined by a predictive biomarker with 50% prevalence, the total sample-size of 80 patients per arm provides approximately 80% power to detect a 25% improvement with *2-sided* 0.20 *significance level*, using the Fisher's Exact Test. No adjustment for multiple comparisons will be made.

6.2 SUMMARIES OF CONDUCT OF STUDY

The final analysis will be based upon patient data collected through patient discontinuation or study discontinuation, whichever occurs first. The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. All summaries will be presented according to randomized treatment assignment.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Treatment group comparability will be analyzed. Demographic and baseline characteristics such as age, sex, weight, and disease activity will be summarized by treatment group. For categorical variables, the descriptive statistics will include counts and proportions. For continuous variables, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, and maximum values.

6.4 EFFICACY ANALYSES

Efficacy analysis will be conducted for the intent-to-treat population, defined as all randomly allocated patients. Sensitivity analyses of additional study population (e.g., completers, *or* per protocol [excluding major protocol violators]) may also be performed *for the primary endpoint or key secondary endpoints* and will be detailed in the DAP. Biomarker-defined subgroup analyses will also be performed to identify subsets of patients who derive enhanced clinical benefit from GDC-0583. The focus of the subgroup efficacy analyses is on, but not limited to, subgroups defined by plasmablast signature levels.

Statistical tests will be conducted at the 0.05 significance level for the intent-to-treat (ITT) population and at the 0.20 significance level for plasmablast-signature defined subgroups. No multiplicity adjustments will be made to control the overall Type I error, and positive tests will be viewed as hypothesis generating rather than confirmatory.

6.4.1 Primary Efficacy Endpoint

The primary efficacy *endpoint* for this study is SRI-4 response at Week 48.

The primary *endpoint will be compared between each of the two GDC-0853 arms and the placebo arm by using the Cochran-Mantel-Haenszel test statistic, stratified by the factors used at randomization. The absolute difference in remission rates and 95% CI for the point estimate will be provided.*

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints *for this study are as follows:*

- *SRI-4 response at Week 48 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 36 through Week 48*
- *SRI-4 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24*
- *SRI-4 response at Week 24*
- *SRI-6 response at Weeks 24 and 48*
- *BICLA response at Weeks 24 and 48*
- *SRI-4 response at Week 48 in patients with high plasmablast signature levels relative to patients with low levels*
- *SRI-4 response at Week 48 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 36 through Week 48 in patients with high plasmablast signiature levels relative to patients with low levels*

The secondary endpoints will be analyzed in the same fashion as the primary endpoint.

Further details for the secondary efficacy analyses will be specified in the DAP.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- *SRI-5, 7, and 8 response at Weeks 24 and 48*
- *SRI-5-8 response at Week 48 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 36 through Week 48*
- *SRI-5-8 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24*
- Time to first SLE flare as defined by the SFI
- Time to first SLE flare as defined by the BILAG
- Total number of SLE flares as defined by the SFI
- Total number of SLE flares as defined by the BILAG
- *Reduction of ≥ 4 points from baseline in the SLEDAI-2K at Weeks 24 and 48*
- *SRI-4 response at Week 24 in patients with high plasmablast signature levels relative to patients with low levels*
- *SRI-4 response at Week 24 with a sustained reduction of OCS dose to < 10 mg/day and ≤ Day 1 dose during Week 12 through Week 24 in patients with high plasmablast signiature levels relative to patients with low levels*
- Change in CLASI Total Activity Score at Week 24 and Week 48 relative to baseline
- ≥50% improvement in CLASI score in patients with at least moderate skin involvement (baseline CLASI ≥10)
- Change in SLICC/*ACR Damage Index* at Week 24 and Week 48 relative to baseline
- Change in joint involvement at Week 24 and Week 48 relative to baseline
- ≥50% improvement in swollen or tender joint count (28 joints) for patients with ≥8 swollen or tender joints at baseline
- Change in FACIT-Fatigue score at Week 24 and Week 48 relative to baseline
- Change in Patient's Global Assessment of disease activity at Week 24 and Week 48 relative to baseline
- Change in cumulative steroid dose use at Week 24 and Week 48 relative to baseline
- *G*lucocorticoid toxicity at Weeks 12, 24, 36, and 48 relative to baseline using the GTCI
- *Achieving* corticosteroid dose of <10 mg/day among patients with a dose ≥10 mg/day at baseline

*E*xploratory endpoints will be evaluated for the ITT population. Time-to-event endpoints will be analyzed using the Kaplan-Meier methodology. Continuous endpoints will be analyzed using an appropriate analysis method, such as analysis of covariance, or

mixed-model repeated measures. Categorical endpoints will be analyzed using an appropriate statistical method, such as Cochran-Mantel-Haenszel or Fisher's exact test.

6.5 SAFETY ANALYSES

Safety analyses will include all patients who receive at least one dose of study drug (GDC-0853 or placebo) with patients grouped according to the treatment they received.

Safety will be assessed through summaries of adverse events, laboratory test results, ECGs, and vital signs. Verbatim descriptions of treatment-emergent adverse events will be coded, and their incidence will be summarized by treatment arm. A treatment-emergent adverse event is defined as any new adverse event reported or worsening of an existing condition on or after the first dose of study drug during AE reporting period. In addition, separate summaries will be generated for serious adverse events, AESI, deaths, pregnancies, malignancies, adverse events leading to discontinuation from the study, and adverse events leading to discontinuation of study drug.

6.6 PHARMACOKINETIC ANALYSES

The PK analyses will include *tabulation of plasma concentration data and summarization of plasma concentrations by visits,* with patients grouped according to treatment received. *Descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate.*

The extent of inter-patient variability will be evaluated, and potential sources of variability *may* be assessed. Relationships between *PK* and PD, efficacy, and safety endpoints *may* be explored.

Additional PK analyses will be conducted during and/or at the end of the study as appropriate *and may be reported separately.*

6.7 BIOMARKER ANALYSES

PD biomarkers (e.g., but not limited to CCL3, CCL4, and plasmablast signature) will *be analyzed to assess the pharmacological* activity and mechanism of action of GDC-0853 in patients with moderate to severe active SLE. Data will be summarized by absolute levels of the biomarker, as well as absolute and relative changes from baseline levels for each treatment group. Additional PD analyses *may* be conducted as appropriate.

6.8 INTERIM ANALYSIS

An interim analysis will be performed after 50–80 patients in each of treatment arm have completed their 24-week SRI-4 response evaluation. The purpose of the interim analysis is to conduct a preliminary benefit-risk assessment of GDC-0853 treated arms compared with the placebo-treated arm and enable potential stopping for futility and/or safety concerns or to potentially inform the clinical development plan for GDC-0853. The

interim analysis will be performed and interpreted by the IMC in conjunction with a Scientific Oversight Committee who will be unblinded at the treatment group level. Additional personnel, such as Clinical Pharmacology *and biomarker* scientists, may be unblinded in order to prepare additional data displays relevant for IMC and Scientific Oversight Committee review.

The study will continue to enroll while the interim analysis is being performed. If the interim analysis indicates that one of the two dose levels of GDC-0853 does not have an appropriate safety profile or meets futility criteria as defined in the interim analysis plan in the DAP which will be written prior to conducting the interim analysis, the Sponsor may discontinue enrollment into that dose arm and switch patients to the other dose arm for the remainder of the study. The Sponsor may also elect to amend the protocol to change the dose level of GDC-0853.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct an additional efficacy interim efficacy analysis in order to further guide internal decision making around issues such as the adequacy of dose ranging, the adequacy of sample sizes for safety and/or efficacy analyses, or to inform the clinical development plan for GDC-0853. The study will not be stopped for any other reason other than futility or safety concerns at the time of the interim analysis. The interim analysis will be performed and interpreted by the IMC in conjunction with a Scientific Oversight Committee who will be unblinded at the treatment group level. Additional personnel, such as Clinical Pharmacology *and biomarker* scientists, may be unblinded in order to prepare additional data displays relevant for IMC and Scientific Oversight Committee review. The decision to conduct an additional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file and updated DAP prior to the conduct of the interim analysis.

Further details about the interim analyses, including the IMC and Scientific Oversight Committee responsibilities and decision criteria, will be specified in the IMC and Scientific Oversight Committee Charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor or its designee will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor or functional service provider will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and any other electronic data will be sent directly to the Sponsor, using

the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a United States (U.S.) Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies

conducted in the European Union or European Economic Area will comply with the European Union (E.U.) Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will

be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The study will be conducted globally and include approximately 240 patients. The contract research organization [redacted] will be responsible for submission to IRB/ECs for approval of the study protocol, patient recruitment, study conduct, data collection, and reporting.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

	Screen −35 Days [a]		Treatment														SFU				
Study Week			0 [b]	1	4	8	12	16	20	24 [b]	28	32	36	40	44	48 [c]	56				
Day (Visit Window)	1st visit	2nd visit	1	8 (±1)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±5)	225 (±5)	253 (±5)	281 (±5)	309 (±5)	337 (±5)	393 (±5)	UV [d]	FV [e]	ET	
Informed consent	x																				
Phone call for AE assessment [f]				x																	
Eligibility criteria	x		x																		
ACR/SLICC diagnostic criteria for SLE [g]	x																				
Medical history and demographic data (see Section 4.5.3)	x		x																		
Concomitant medications [h]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCS Taper [i]			x							x											
Adverse events [j]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [k]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	x															x					
Complete PE [l]	x																				
Limited PE [m]			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-lead ECG [n]	x		x [o]		x					x [o]						x	x	x		x	

Appendix 1
Schedule of Activities (cont.)

	Screen −35 Days [a]		Treatment														SFU			
Study Week			0 [b]	1	4	8	12	16	20	24 [b]	28	32	36	40	44	48 [c]	56			
Day (Visit Window)	1st visit	2nd visit	1	8 (±1)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±5)	225 (±5)	253 (±5)	281 (±5)	309 (±5)	337 (±5)	393 (±5)	UV [d]	FV [e]	ET
Chest radiograph [p]	x																			
MTB screening [q]	x														x					
CK, aldolase, and LDH [r]	x															x		x	x	
Viral Serology [s]	x														x					
Direct Coombs test [t]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [u]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry panel [v]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation panel [w]	x		x							x						x		x		x
Total Ig, IgM, IgE, IgG, IgA [x]	x						x			x			x			x	x	x	x	x
CRP	x				x		x		x	x		x		x		x	x	x	x	x
Pregnancy test [y]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TBNK [z]	x		x		x		x			x			x			x	x	x	x	x
ANA	x																			
ESR (on site or at local laboratory)	x		x		x				x	x			x			x		x	x	x
Urinalysis [aa]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C3, C4, CH50 [bb]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

	Screen −35 Days [a]		Treatment														SFU				
Study Week			0 [b]	1	4	8	12	16	20	24 [b]	28	32	36	40	44	48 [c]	56				
Day (Visit Window)	1st visit	2nd visit	1	8 (±1)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±5)	225 (±5)	253 (±5)	281 (±5)	309 (±5)	337 (±5)	393 (±5)	UV [d]	FV [e]	ET	
Autoantibody panel [cc]	x		x							x						x				x	
Anti-dsDNA	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Protein creatinine ratio [cc]		x [ee]	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	
Blood for plasma PK [ff]			x		x					x [gg]						x		x	x	x	
Pharmacogenetic sample [hh]			x																		
Blood sample for PD RNA [ii]	x		x		x					x						x	x		x		
PD biomarker, serum [ff, jj]	x		x		x					x						x	x		x		
PD biomarker, plasma [ff, jj]	x		x		x					x						x	x		x		
Exploratory urinary biomarker collection (first void) [ff]			x		x					x						x	x		x		
Blood for PBMC (US. sites only) [ff, kk]	x		x		x					x						x	x		x		
Flow cytometry (B-cell subsets) (U.S. and selected sites only) [ff, ll]	x		x		x					x						x	x		x		
Flow cytometry (basophils) (U.S. sites only) [ff, mm]	x		x		x					x										x	
Blood for immunophenotyping			x							x											

Appendix 1
Schedule of Activities (cont.)

	Screen −35 Days [a]		Treatment														SFU			
Study Week			0 [b]	1	4	8	12	16	20	24 [b]	28	32	36	40	44	48 [c]	56			
Day (Visit Window)	1st visit	2nd visit	1	8 (±1)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±5)	225 (±5)	253 (±5)	281 (±5)	309 (±5)	337 (±5)	393 (±5)	UV [d]	FV [e]	ET
(U.S. sites only) [ff, nn]																				
BILAG 2004	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SLEDAI-2K and SFI	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
GTCI and fasting lipids [oo]			x				x			x			x			x				
SLICC/*ACR* damage index			x							x						x				
28-Joint Count & morning stiffness [pp]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CLASI	x		x		x		x			x			x			x	x	x	x	x
Optional photographic documentation *(U.S. sites only)* [qq]	x		x		x		x			x			x			x	x	x	x	x
Physician Global Assessment [rr]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient Global Assessment [ss]	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FACIT-Fatigue Scale [ss]			x				x			x			x			x	x		x	
Study drug administration in clinic [tt]			x		x					x										
Drug dispensing			x		x	x	x	x	x	x	x	x	x	x	x					
Blood for WGS [qq]			x																	
Blood for serum for RBR (optional)	x		x				x			x						x			x	

Appendix 1
Schedule of Activities (cont.)

	Screen −35 Days [a]		Treatment														SFU			
Study Week			0 [b]	1	4	8	12	16	20	24 [b]	28	32	36	40	44	48 [c]	56			
Day (Visit Window)	1st visit	2nd visit	1	8 (±1)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±5)	225 (±5)	253 (±5)	281 (±5)	309 (±5)	337 (±5)	393 (±5)	UV [d]	FV [e]	ET
[uu]																				
Blood for RNA for RBR (optional) [uu]	x		x				x			x						x			x	

ACR = American College of Rheumatology; AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BICLA = BILAG-based Composite Lupus Assessment; BID = twice daily; BILAG = British Isles Lupus Assessment Group; BMI = body mass index; CK = creatinine kinase; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CRP = C-reactive protein; dsDNA = double stranded DNA; ECG = electrocardiogram; eCRF = electronic case report form; ESR = erythrocyte sedimentation rate; ET = early termination; FACIT = Functional Assessment of Chronic Illness Therapy; FMV = first morning void; FV = flare visit; GGT = gamma-glutamyl transpeptidase; GTCI = Glucocorticoid Toxicity Change Index; $HbA1_c$ = hemoglobin $A1_c$; HBcAb = Hepatitis B core antibody; HBsAb = Hepatitis B surface antibody; HDL = high-density lipoprotein; HBsAG = Hepatitis B surface antigen; HCV Ab = Hepatitis C antibody; Ig = immunoglobulin; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MTB = mycobacterium tuberculosis; OCS = oral corticosteroid; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic; PE = physical exam; PG = pharmacogenetics; PK = pharmacokinetic; PPD = purified protein derivative; PPI = proton pump inhibitor; PRO = patient reported outcome; PT = prothrombin time; QFT = QuantiFERON Gold; RBC = red blood cell; RDW = red cell distribution width; RBR = Research Biosample Repository; SELENA = Safety of Estrogen in Lupus Erythematosus National Assessment; SFI = SELENA-SLEDAI Flare Index; SFU = safety follow-up; SLE = systemic lupus erythematosus; SLEDAI = SLE Disease Activity Index; SLICC = Systemic Lupus International Collaborating Clinics; TBNK = T, B, and natural killer cells; U.S. = United States; UV = unscheduled visit; WBC = white blood cell; WGS = whole genome sequencing.

[a] The screening period may be extended upon the approval of the Medical Monitor.

[b] A morning clinic visit (fasting) is strongly recommended for visits on Day 1 and Week 24. For other study visits, morning visits are recommended. When morning visits are strongly recommended, the patient should be fasting (≥4 hours) prior to the first PK blood draw.

[c] Week 48 visit is the last day of the study treatment period; however, no blinded study drug will be given at the Week 48 visit. The last dose of blinded study drug is the p.m. dose (evening) prior to the Week 48 visit. If eligible, patients may enroll into the open-label extension Study GA30066 to receive

their first open-label dose of GDC-0853 on Day 1 of Study GA30066 (after a trough PK level is drawn) or they will proceed to the SFU period and return for the SFU visit on Week 56 (8 weeks after last dose of study drug). For patients enrollng into the OLE Study GA30066, Day 1 is the same day as the Week 48 visit of Study GA30044.

[d] At an unscheduled visit (UV), adverse events and concomitant medications must be assessed. All other assessments are to be performed only if medically indicated based on the reason for the UV. If the patient returns for an unscheduled visit *or regular study visit* and has any evidence of increased SLE-activity requiring treatment, perform assessments required for a flare visit (FV).

[e] A flare visit (FV) is any unscheduled visit where the patient *may* require escalation of treatment for increased SLE activity. *Assessments are to be performed only if medically indicated based on the reason for the FV.*

[f] Patients will receive a telephone call from study staff to follow up for assessment of adverse events.

[g] Either the ACR or SLICC diagnostic criteria for SLE may be used at screening to determine study inclusion.

[h] Starting at the screening period, all patients must record their actual OCS use on a weekly basis and as instructed by study staff (see Section 4.3.2.4).

[i] The OCS taper windows occur during Weeks 0-12 and Weeks 24-36 (tapering may be initiated after the Week 24 assessments are completed). For complete instructions on OCS tapering, see Section 3.3.6 and Appendix 4.

[j] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[k] Includes respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressures while the patient is in a seated position for at least 5 minutes.

[l] Include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Particular attention should be given to evaluation of potential manifestations of active SLE (see Appendix 9 BILAG 2004 Index; Appendix 10, SLEDAI-2K; Appendix 14, CLASI; and Appendix 13, 28-Joint Counts, Appendix 11, SFI) and of infections or other medical conditions, which could place the patient at increased risk.

[m] Limited, efficacy assessment–directed or symptom-directed physical examinations should be performed *that also allow for completion of SLEDAI-2K and BILAG-2004 assessments*. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[n] For visits at which study drug is administered, the ECG will be recorded pre-dose (Day 1, Week 4 and Week 48). ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes prior to beginning the first ECG recording. All ECGs should be obtained prior to the other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Body position should be consistently

maintained for each ECG evaluation to prevent changes in hear rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs for each patient should be obtained from the same machine whenever possible.

[o] Triplicate digital ECG recordings are required pre-dose (Day 1) and 2 hours ±30 minutes post dose for Week 24 only. The ECG intervals (e.g., PR, QRS, QT, QTcF, and RR) and heart rate from these three ECGs will be entered into the eCRF, in addition, these triplicate readings will be stored for future analysis, if needed

[p] Not required if documented results are available of a chest radiograph (read by a radiologist) taken within the 12 weeks preceding the screening visit.

[q] PPD should be performed only if QFT (which is to be used as the initial TB screening test) is not available. For the Week 44 visit, follow the same method of testing and assessment that was completed during screening period.

[r] *Can be collected as needed to complete SLEDAI-2K or BILAG-2004 assessments, e.g. myositis.*

[s] Includes HBsAg, HBsAb, HBcAb, HCV Ab.

[t] The Coombs test *should* be performed at a local laboratory.

[u] Includes hemoglobin, hematocrit, RBC count, calculated indices (MCV, MCH, MCHC, RDW), platelet count, and WBC count with differential.

[v] Includes electrolytes (Na, K, Cl, bicarbonate, phosphorus), urea, creatinine, glucose, ALT, AST, amylase, lipase, total and direct bilirubin, alkaline phosphatase, GGT, albumin, globulin, total protein, calcium, uric acid

[w] Includes INR, aPTT, and PT.

[x] Includes total immunoglobulins, IgG, IgM, IgE, and IgA.

[y] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed locally at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (performed locally).

[z] Once treatment with study medication begins, TBNK results will be blinded.

[aa] Includes dipstick (blood, protein, glucose, nitrites, and leukocyte esterase), microscopic analysis (RBC, WBC, red cell casts, white cell casts).

[bb] C3, C4, and CH50 conducted monthly on the same day as the SLEDAI-2K.

[cc] Autoantibody panel includes anti-Smith, anti-RNP, anti-Ro, anti-La, anti-cardiolipin, and anti-beta 2 glycoprotein

[dd] A FMV urine sample must be collected at Weeks 0, 4, 24, and 48. FMV urine samples should be collected at all other indicated visits unless the patient forgets to collect the FMV or forgets to bring the urine to the visit (refer to laboratory manual for details on urine collection instructions), in which case a random urine sample is acceptable.

[ee] Screening urine sample needs to be a FMV (in mg/mg) and must be collected during the screening period (refer to laboratory manual for details on urine collection instructions). Patients will receive the urine collection kit at the first screening visit and will bring the FMV urine collection to the second screening visit.

Appendix 1
Schedule of Activities (cont.)

[ff] Collect prior to drug administration.

[gg] Collect PK samples at four timepoints: prior to study drug, 2 hours (± 30 minutes) post-dose (fasting), 4 – 6 hours post-dose, and 8 – 10 hours post dose (U.S. sites only). If the patient is unable to stay or return to clinic for the post-dose 8-10 hour timepoint, this sample may be collected by a home nurse visit.

[hh] Sample to be collected at baseline. However, if sample not drawn at baseline, it may be collected at any other timepoint.

[ii] Three PaxGene whole blood tubes to be collected prior to study drug administration for PD sample. Please see laboratory manual for PaxGene blood sample handling.

[jj] Collect serum and plasma tubes prior to study drug administration for PD biomarker serum and PD biomarker plasma.

[kk] *U.S. sites only:* Blood for PBMCs will be shipped overnight to a central laboratory for processing. To be performed at centers where samples can be shipped to central laboratory within 24 hours.

[ll] *U.S. and* selected *sites only:* Includes multi-color flow cytometry analysis of B cells and B cell subsets

[mm] Includes multi-color flow cytometry analysis of basophil activation. To be performed at centers in the United States where samples can be shipped to FACS laboratory within 24 hours.

[nn] *U.S. sites only:* Blood for PBMCs will be shipped overnight to a central laboratory for processing and cryopreserved. To be performed at centers where samples can be shipped to central laboratory within 24 hours.

[oo] Fasting lipid panel includes triglycerides, HDL, LDL, $HbA1_C$, and total cholesterol. The patient should be fasting (≥ 4 hours).

[pp] For patients with arthritis present at current visit prior to Week 24 or any past visit during the study.

[qq] WGS and photography are contingent upon the review and approval by each site's IRB/EC and, if applicable, an appropriate regulatory body.

[rr] The same clinician *is strongly recommended to* complete the Physician's Global Assessment throughout the study.

[ss] To ensure instrument validity and that data standards meet health authority requirements, the questionnaire will be self-administered before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. See Appendix 17 for sample questionnaires for FACIT-Fatigue.

[tt] Patients will receive GDC-0853/placebo BID starting on Day 1 and ending on the evening (p.m. dose) prior to the Week 48 visit. GDC-0853/placebo should be taken with water by mouth. The dates and times of the most recent prior meal and most recent prior dose of short-acting antacid, PPI, or H2RA, last dose of oral study drug (prior to clinic visit), and timing of study drug administration in clinic (if applicable) should be recorded at each clinic visit.

[uu] Not applicable for a site that has not been granted approval for RBR sampling.

Appendix 2
Schedule of Pharmacokinetic and Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day -35 to Day -1)	NA	Blood for PD RNA PD biomarker serum PD biomarker plasma Blood for PBMC *(U.S. Sites only)* Flow cytometry (B-cell subsets*) (U.S. and* selected *sites only)* Flow cytometry (basophils) *(U.S. sites only)* Blood for serum for RBR (optional) Blood for RNA for RBR (optional)
Day 1 [a], 29, 337 (Weeks 4 and 48)	Prior to dose (to be administered in clinic if applicable)	Blood for PK Blood for PG *(Day 1 only)* Blood for PD RNA PD biomarker (serum) PD biomarker (plasma) Exploratory urinary biomarker collection (first void) Blood for PBMC *(U.S. sites only)* Flow cytometry (B-cell subsets) *(U.S. and* selected *sites only)* Flow cytometry (basophils) *(U.S. sites only)* *(*Days *1 and 29 only)* Blood for immunophenotyping *(U.S. sites only)* *(Day 1 only)* Blood for serum for RBR (optional) *(Days 1 & 337 only)* Blood for RNA for RBR (optional) *(Days 1 & 337 only)* Blood for WGS for RBR (optional) *(Day 1 only)*
Day 85 (Week 12)	Prior to dose	Blood for serum for RBR (optional) Blood for RNA for RBR (optional)
Day 169 [a] (Week 24)	Prior to dose (must be administered in clinic if applicable)	Blood for PK Blood for PD RNA PD biomarker (serum) PD biomarker (plasma) Exploratory urinary biomarker collection (first void) Blood for PBMC *(U.S. sites only)* Flow cytometry (B-cell subsets) *(U.S. and* selected *sites only)* Flow cytometry (basophils) *(U.S. sites only)* Blood for immunophenotyping *(U.S. sites only)* Blood for serum for RBR (optional) Blood for RNA for RBR (optional)
	2 hr (±30 min) post dose, fasting	Blood for PK
	4–6 hr post dose	Blood for PK

Appendix 2
Schedule of Pharmacokinetic and Biomarker Samples (cont.)

Visit	Timepoint	Sample Type
	8–10 hr post dose (U.S. sites only) [b]	Blood for PK
Day 393 (SFU) (Week 56)	Prior to dose	Blood for PD RNA PD Biomarker (serum) PD biomarker (plasma) Exploratory urinary biomarker collection (first void) Blood for PBMC *(U.S. sites only)* Flow cytometry (B-cell subsets) *(U.S. and* selected *sites only)*
UV, FV or ET visits	NA	Blood for PK Blood for PD RNA *(FV and ET only)* PD biomarker (serum) *(FV and ET only)* PD biomarker (plasma) *(FV and ET only)* Exploratory urinary biomarker collection (first void) *(FV and ET only)* Blood for PBMC *(U.S. sites only) (FV and ET only)* Flow cytometry (B-cell subsets) *(U.S. and* selected *sites only) (FV only)* Flow cytometry (basophils) *(U.S. sites only) (ET only)* Blood for serum for RBR (optional) *(FV only)* Blood for RNA for RBR (optional) *(FV only)*

ET = early termination visit; FACS = fluorescence-activated cell sorting; FV = flare visit; H2RA = H2 receptor antagonist; hr = hours; min = minutes; NA = not applicable; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetic; PPI = proton-pump inhibitor; RBR = Research Biosample Repository; SFU = Safety Follow Up Visit; U.S. = United States; UV = unscheduled visit.

Note: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen

Morning clinic visits are preferred for all visits but are especially encouraged on Day 1 and Week 24. Prior to visits on Day 1, Week 4, and Week 24, patients should be instructed not to take their morning dose and to bring their study medication with them to their clinic visit. For all visits with PK samples, the date and time of the last dose of study drug, last dose of acid-reducing medication (PPI, H2RA, or short-acting antacid), and last meal should be recorded, along with the actual time of the PK blood draw. The procedures for collection, handling, and shipping of PK samples can be found in the study's Laboratory Manual.

[a] Morning visit is strongly recommended. Patients must be fasting (≥4 hours) prior to the pre-dose PK draw.

[b] **U.S. sites only:** If the patient is unable to stay or return to clinic for the post-dose 8–10 hour timepoint, this sample may be collected by a home nurse visit on the Week 24 visit.

Appendix 3
Pre-Enrollment Adjudication

Enrollment into this trial is subject to adjudication by the Sponsor's Medical Monitor or designated staff.

The purpose of the adjudication process is to ensure that clinical manifestations qualifying the patient for entry to the study (i) are adequately documented, (ii) are attributable to SLE, and (iii) are of sufficient severity to mandate significant immunomodulatory therapy.

The Medical Monitor will make the final decision regarding whether or not a patient is eligible for enrollment. Every effort will be made to complete the adjudication process as quickly as possible. In exceptional circumstances the screening period may, at the Medical Monitor's discretion, be extended to allow for completion of the adjudication process.

Steps in Adjudication Process

3. Investigative site identifies a potentially eligible patient.
4. Following informed consent, the Investigator reviews the patient for eligibility based on SLE diagnostic criteria, trial inclusion criteria (see Section 4.1.1), and the absence of exclusion criteria.
5. As soon as screening procedures are complete the Investigator completes the *forms required for screening and adjudication*.
6. The Investigator or Study Coordinator transmits the completed forms to the Sponsor or designated contract research organization.
7. The Sponsor's Medical Monitor or designee will perform an initial triage of the disease manifestations contributing to eligibility for entry. The triage decision will be based on the information supplied by the Investigator. This period may be extended if there is a delay in the availability of key screening laboratory results from the central laboratory.
8. The Sponsor's Medical Monitor or designee will review the patient's clinical and laboratory data, including additional data requested from the site, and reach a decision on the patient's eligibility for the study. This decision will be conveyed to the Investigator within approximately 3 working days of receipt of the requested additional data by the Sponsor.

Training in the Adjudication process will be provided to Investigators.

Appendix 4
Suggested Prednisone Taper Schedule Achieving < 10 mg/day by 12 and 36 Weeks

	Starting Prednisone Dose (mg/day)			
	10	20	30	40
Weeks 0–2	10	20	30	40
Weeks 3–4	< 10	15	25	30
Weeks 5–6	< 10	10	20	25
Weeks 7–8	< 10	< 10	15	15
Weeks 9–10	< 10	< 10	10	10
Weeks 11–12	< 10	< 10	< 10	< 10

	Starting Prednisone Dose (mg/day)	
	10	20
Weeks 24-26	10	20
Weeks 27-28	< 10	15
Weeks 29-30	< 10	10
Weeks 31-32	< 10	< 10
Weeks 33-34	< 10	< 10
Weeks 35-36	< 10	< 10

Appendix 5
American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	1. Pleuritis – convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria $>$ 0.5 grams per day or $>$ than 3+ if quantitation not performed OR 2. Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures – in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR 2. Psychosis – in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia—with reticulocytosis OR 2. Leukopenia – 4,000/mm^3 on $\geq$ 2 occasions OR 3. Lymphopenia – $<$ 1,500/ mm^3 on $\geq$ 2 occasions OR 4. Thrombocytopenia – $<$ 100,000/mm^3 in the absence of offending drugs

Appendix 5
American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus (cont.)

Criterion	Definition
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer OR 2. Anti-Smith: presence of antibody to Sm nuclear antigen OR 3. Positive finding of antiphospholipid antibodies on: an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, OR 4. A false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Source: Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.

Appendix 6
Clinical and Immunologic Criteria Used in the SLICC Classification System

The criteria do not need to be present concurrently. The proposed classification rule is as follows: *classify a patient as having SLE if he or she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least one clinical criterion and one immunologic criterion, OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.*

Clinical Criteria

1. Acute cutaneous lupus, including:
    - Lupus malar rash (do not count if malar discoid)
    - Bullous lupus
    - Toxic epidermal necrolysis variant of SLE
    - Maculopapular lupus rash
    - Photosensitive lupus rash in the absence of dermatomyositis -OR-
    - Subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus, including:
    - Classic discoid rash
    - Localized (above the neck)
    - Generalized (above and below the neck)
    - Hypertrophic (verrucous) lupus
    - Lupus panniculitis (profundus)
    - Mucosal lupus
    - Lupus erythematosus tumidus
    - Chillblains lupus
    - Discoid lupus/lichen planus overlap
3. Oral ulcers
    - Palate
    - Buccal
    - Tongue -OR-
    - Nasal ulcers in the absence of other causes, such as vasculitis, Behçet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods

Appendix 6
Clinical and Immunologic Criteria Used in the SLICC Classification System (cont.)

4. Non-scarring alopecia (diffuse thinning or hair fragility with visible broken hairs) in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia
5. Synovitis involving 2 or more joints, characterized by swelling or effusion -OR-
    - Tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6. Serositis
    - Typical pleurisy for more than 1 day
    - Pleural effusions
    - Pleural rub
    - Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
    - Pericardial effusion
    - Pericardial rub -OR-
    - Pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler's pericarditis
7. Renal
    - Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours -OR-
    - Red blood cell casts
8. Neurologic
    - Seizures
    - Psychosis
    - Mononeuritis multiplex in the absence of other known causes, such as primary vasculitis
    - Myelitis
    - Peripheral or cranial neuropathy in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus
    - Acute confusional state in the absence of other causes, including toxic/metabolic, uremia, drugs
9. Hemolytic anemia
10. Leukopenia ($<4{,}000/mm^3$ at least once) in the absence of other known causes, such as:
    - Felty's syndrome, drugs, and portal hypertension -OR-

Appendix 6
Clinical and Immunologic Criteria Used in the SLICC Classification System (cont.)

- Lymphopenia ($<1{,}000/mm^3$ at least once) in the absence of other known causes, such as corticosteroids, drugs, and infection

11. Thrombocytopenia ($<100{,}000/mm^3$) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

Immunologic Criteria

1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following:
   - Positive test result for lupus anticoagulant
   - False-positive test result for rapid plasma reagin
   - Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
   - Positive test result for anti–β2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement
   - Low C3
   - Low C4
   - Low CH50
6. Direct Coombs' test in the absence of hemolytic anemia

* Criteria are cumulative and need not be present concurrently.

ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; ELISA = enzyme-linked immunosorbent assay; SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus.

Appendix 7
Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Damage (non-reversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

OCULAR (either eye, by clinical assessment)		
Any cataract ever (documented by ophthalmoscopy)		1
Retinal change OR Optic atrophy (documented by ophthalmoscopy)		1
NEUROPSYCHIATRIC		
Cognitive impairment (eg memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) OR Major psychosis		1
Seizures requiring therapy for 6 months		1
Cerebrovascular accident or surgical resection (for non-malignant causes)	(score 2 if >1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)		1
Transverse myelitis		1
RENAL		
Estimated/Measured GFR < 50%		1
Proteinuria ⩾ 3.5g/24 hours		1
OR		
End-stage renal failure (regardless of dialysis or transplantation)		3
PULMONARY		
Pulmonary hypertension (right ventricular prominence or loud P2)		1
Pulmonary fibrosis (physical & radiograph)		1
Shrinking lung (radiograph)		1
Pleural fibrosis (radiograph)		1
Pulmonary infarction (radiograph) *or resection for malignancy*		1
CARDIOVASCULAR		
Angina OR Coronary artery bypass		1
Myocardial infarction ever	(score 2 if > 1)	1 (2)
Cardiomyopathy (ventricular dysfunction)		1
Valvular disease (diastolic, murmur, or systolic murmur > 3/6)		1
Pericarditis for 6 months OR Pericardiectomy		1
PERIPHERAL VASCULAR		
Claudication for 6 months		1
Minor tissue loss (pulp space)		1
Significant tissue loss ever (eg loss of digit or limb)	(score 2 if > 1 site)	1 (2)
Venous thrombosis with swelling, ulceration, OR Venous stasis		1
GASTROINTESTINAL		
Infarction or resection of bowel below duodenum, spleen, liver or gallbladder for any cause	(score 2 if > 1 site)	1 (2)
Mesenteric insufficiency		1
Chronic peritonitis		1
Stricture OR Upper gastrointestinal surgery ever		1
Pancreatic insufficiency requiring enzyme replacement or with pseudocyst		*1*
MUSCULOSKELETAL		
Muscle atrophy or weakness		1
Deforming or erosive arthritis (including reversible deformities, excluding avascular necrosis)		1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)		1
Avascular necrosis (imaging)	(score 2 if > 1)	1 (2)
Osteomyelitis		1
Tendon rupture		*1*
SKIN		
Scarring chronic alopecia		1
Extensive scarring or panniculum other than scalp and pulp space		1
Skin ulceration for > 6 months (excluding thrombosis)		1

CONTINUED…

Appendix 7
Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index for Systemic Lupus Erythematosus) (cont.)

(Cont.)
Damage (non-reversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

PREMATURE GONADAL FAILURE (secondary amenorrhoea before age 40)		1
DIABETES MELLITUS (regardless of treatment)		1
MALIGNANCY (exclude dysplasia)	(score 2 if > 1 site)	1 (2)

Source: Gladman 1997

GLOSSARY OF TERMS: SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS/AMERICAN COLLEGE OF RHEUMATOLOGY DAMAGE INDEX FOR SYSTEMIC LUPUS ERYTHEMATOSUS:
Source: Gladman 1996

Damage:
Non-reversible change, not related to active inflammation, occurring since diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

Cataract:
A lens opacity (cataract) in either eye, ever, whether primary or secondary to steroid therapy, documented by ophthalmoscopy.

Retinal change:
Documented by ophthalmoscopic examination, may result in field defect, legal blindness.

Optic Atrophy:
Documented by ophthalmoscopic examination.

Cognitive Impairment:
Memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level, documented on clinical examination or by formal neurocognitive testing.

Major Psychosis:
Altered ability to function in normal activity due to psychiatric reasons. Severe disturbance in the perception of reality characterized by the following features: delusions, hallucinations (auditory, visual), incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized or catatonic behavior.

Appendix 7
Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index for Systemic Lupus Erythematosus) (cont.)

Seizures:
Paroxysmal electrical discharge occurring in the brain and producing characteristic physical changes including tonic and clonic movements and certain behavioral disorders. Only seizures requiring therapy for 6 months are counted as damage.

CVA:
Cerebrovascular accident resulting in focal findings such as paresis, weakness, etc., or surgical resection for causes other than malignancy.

Neuropathy:
Damage to either a cranial or peripheral nerve, excluding optic nerve, resulting in either motor or sensory dysfunction.

Transverse Myelitis:
Lower-extremity weakness or sensory loss with loss of rectal and urinary bladder sphincter control.

Renal:
Estimated or measured glomerular filtration rate $<$50%, proteinuria $<$3.5gm/24 hours, or end-stage renal disease (regardless of dialysis or transplantation).

Pulmonary:
Pulmonary hypertension (right ventricular prominence, or loud P2), pulmonary fibrosis (physical and radiograph), shrinking lung (radiograph), pleural fibrosis (radiograph), pulmonary infarction (radiograph), resection for cause other than malignancy.

Cardiovascular:
Angina or coronary artery bypass, myocardial infarction (documented by electrocardiograph and enzyme studies) ever, cardiomyopathy (ventricular dysfunction documented clinically), valvular disease (diastolic murmur, or systolic murmur $>$3/6), pericarditis for 6 months, or pericardiectomy.

Peripheral Vascular:
Claudication, persistent for 6 months, by history, minor tissue loss, such as pulp space, ever, significant tissue loss, such as loss of digit or limb, or resection, ever, venous thrombosis with swelling, ulceration or clinical evidence of venous stasis.

Gastrointestinal:
Infarction or resection of bowel below duodenum, by history, resection of spleen, liver, or gall bladder ever, for whatever cause, mesenteric insufficiency, with diffuse abdominal pain on clinical examination, chronic peritonitis, with persistent abdominal pain and peritoneal irritations, on clinical examination, esophageal stricture, shown on endoscopy, upper gastrointestinal tract surgery, such as correction of stricture, ulcer surgery, etc., ever, by history.

Appendix 7
Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index for Systemic Lupus Erythematosus) (cont.)

Musculoskeletal:
Muscle atrophy or weakness, demonstrated on clinical examination, deforming or erosive arthritis, including reducible deformities, (excluding avascular necrosis) on clinical examination, osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) demonstrated radiographically, avascular necrosis, demonstrated by any imaging technique, osteomyelitis, documented clinically, and supported by culture evidence.

Skin:
Scarring, chronic alopecia, documented clinically, extensive scarring or panniculum other than scalp and pulp space, documented clinically, skin ulceration (excluding thrombosis) for more than 6 months.

Premature gonadal failure:
Secondary amenorrhea, prior to age 40.

Diabetes:
Diabetes requiring therapy, but regardless of treatment.

Malignancy:
Documented by pathologic examination, excluding dysplasias.

Appendix 8
Childbearing Potential, Pregnancy Testing, and Contraception

For Women

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and a urine pregnancy test on study day 1 prior to administration of study drug and at subsequent clinic visits. If a urine pregnancy test result is positive, study drug will not be administered until pregnancy is ruled out. The result must be confirmed by a serum pregnancy test (conducted by the local laboratory).

Refer to Section 5.4.3 of the protocol for management of a patient with a confirmed pregnancy.

All female patients are considered to be of childbearing potential unless they meet one of the following criteria:

- The patient has been postmenopausal (non−therapy-induced amenorrhea) for at least 12 continuous months with no other identified cause
- The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to enrollment
- The patient had a hysterectomy

Female patients of reproductive or childbearing potential who are unwilling to use a method of contraception that results in a failure rate of < 1 % per year or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 60 days after the last dose of study drug, or longer as required by local requirements for other standard of care medications, will be excluded from study participation.

Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Examples of contraceptive methods with a failure rate of < 1% per year include the following:

- Sterilization, bilateral surgical tubal ligation
- Intrauterine device
- Combined oral contraceptive pill*
- Contraceptive transdermal patch (estrogen and progestin containing)*
- Hormonal vaginal device
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Implants for contraception

Appendix 8
Childbearing Potential, Pregnancy Testing, and Contraception (cont.)

- Injections for contraception (with prolonged release)
- Sole sexual partner consisting of surgically sterilized male partner with appropriate postsurgical verification of the absence of spermatozoa in the ejaculate. Patients may provide verbal confirmation that the partner completed appropriate follow-up after vasectomy. Sites are not required to obtain partner medical records.
- Same sex partner

*** Women using estrogen containing hormonal contraceptives as a method of contraception must also use a barrier such as a male condom in conjunction with the hormonal contraceptives.**

For Men

All men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

- With female partners of childbearing potential (including those who have had a tubal ligation), men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 120 days (4 months) after the last dose of study treatment. Men must refrain from donating sperm during this same period.
- With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study treatment to avoid exposing the embryo.

For Men and Women

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix 9
BILAG-2004 Index Glossary

INSTRUCTIONS

- *only record features that are* ***attributable to SLE disease activity and not due to damage, infection, thrombosis (in absence of inflammatory process) or other conditions***

- *assessment refers to manifestations occurring in the* ***last 4 weeks compared with the previous 4 weeks***

- *activity refers to disease process which is reversible while damage refers to permanent process/scarring (irreversible)*

- *damage due to SLE should be considered as a cause of features that are fixed/persistent (SLICC/ACR damage index uses persistence ≥ 6 months to define damage)*

- ***in some manifestations, it may be difficult to differentiate SLE from other conditions as there may not be any specific test and the decision would then lies with the physician's judgement on the balance of probabilities***

- *ophthalmic manifestations usually need to be assessed by an ophthalmologist and these items would need to be recorded after receiving the response from the ophthalmologist*

- *guidance for recording:*

(4) NEW

- *manifestations are recorded as new when it is a new episode occurring in the last 4 weeks (compared to the previous 4 weeks) that has not improved and this includes new episodes (recurrence) of old manifestations*

- *new episode occurring in the last 4 weeks but also satisfying the criteria for improvement (below) would be classified as improving instead of new*

(3) WORSE

- *this refers to manifestations that have deteriorated/worsened significantly in the last 4 weeks compared to the previous 4 weeks, sufficient for consideration of increase in therapy*

(2) SAME

- *this refers to manifestations that have been present for the last 4 weeks and the previous 4 weeks without significant improvement or deterioration (from the previous 4 weeks)*

- *this also applies to manifestations that have improved over the last 4 weeks compared to the previous 4 weeks but do not meet the criteria for improvement*

Appendix 9
BILAG-2004 Index Glossary (cont.)

(1) IMPROVING

- *definition of **improvement**: (a) the amount of improvement is sufficient for **consideration of reduction in therapy** and would not justify escalation in therapy*

AND

*(b) improvement must be **present currently and for at least 2 weeks** out of the last 4 weeks*

OR

*manifestation that has **completely resolved and remained absent** over the **whole of last 1 week***

(0) NOT PRESENT

(ND) NOT DONE

- *it is important to indicate if a test has not been performed (particularly laboratory investigations) so that this will be recorded as such in the database & not as normal or absent (which is the default)*

Y/N - INDICATE IF ITEM IS DUE TO SLE ACTIVITY

- *for descriptors that are based on measurements (in renal and haematology systems), it is important to indicate if these are not due to lupus disease activity (for consideration of scoring) as they are usually recorded routinely into a database*

TRICKLE DOWN RULE

- *when item of highest level of severity is recorded, similar item of lower level of severity must be recorded as well (item of lower level of severity must not be recorded as not present)*

CHANGE IN SEVERITY CATEGORY

- *there are several items in the index which have been divided into categories of mild and severe (depending on definition). It is essential to record mild and severe items appropriately if the manifestations fulfil both criteria during the last 4 weeks*

- *if a mild item deteriorated to the extent that it fulfilled the definition of severe category (ie changed into severe category) within the last 4 weeks:*
  severe item scored as new (4)
  ***AND** mild item scored as worsening (3)*

Appendix 9
BILAG-2004 Index Glossary (cont.)

- *if a severe item improved (fulfilling the improvement criteria) to the extent that it no longer fulfilled the definition of severe category (ie changed into mild category) within the last 4 weeks:*

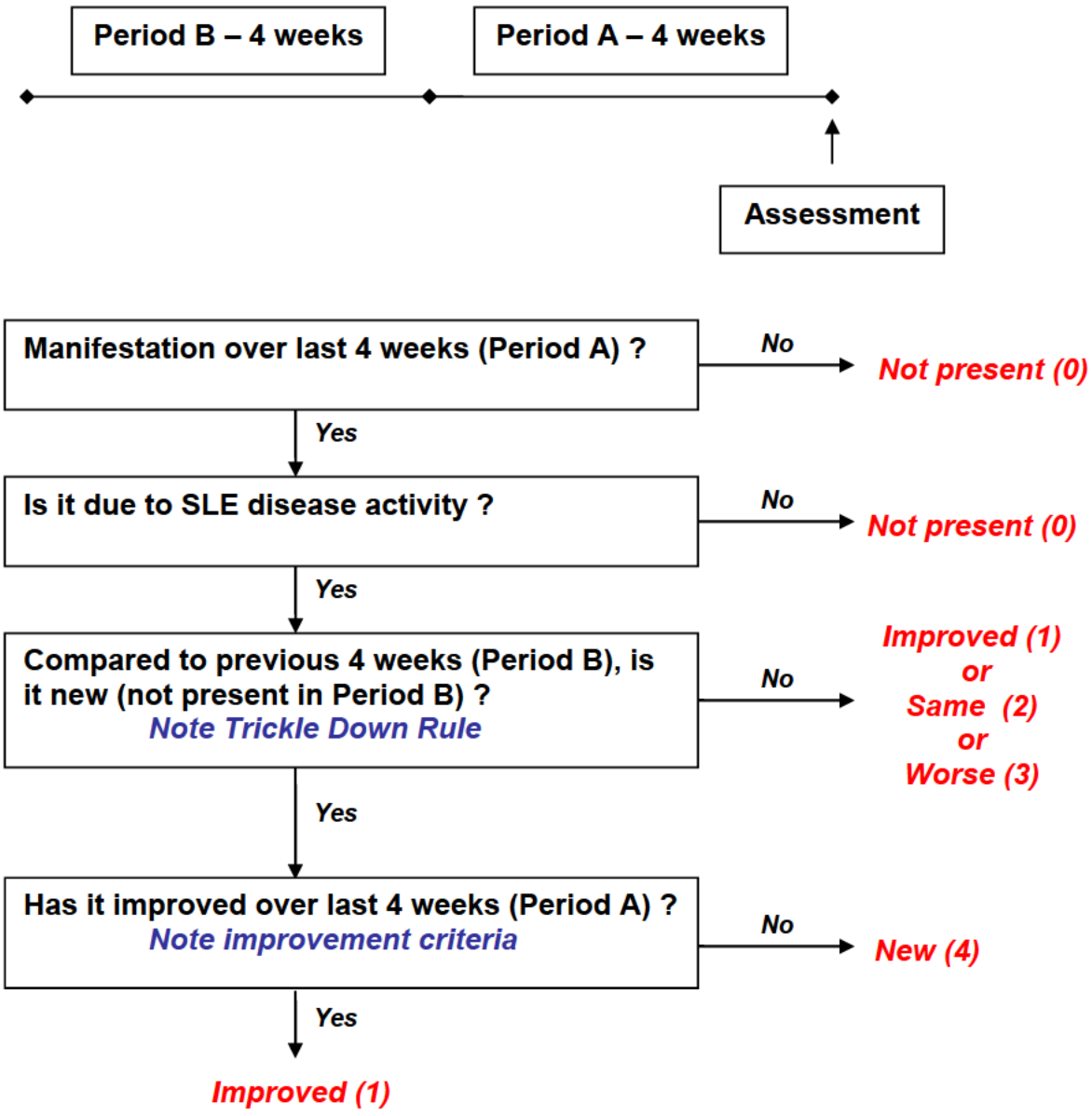
  severe item scored as not present (0) if criteria for severe category has not been met over last 4 weeks
  ***or** as improving (1) if criteria for severe category has been met at some point over last 4 weeks*

AND

mild item scored as improving (1) if it is improving over last 4 weeks
***or** as the same (2) if it has remained stable over last 4 weeks*

Appendix 9
BILAG-2004 Index Glossary (cont.)

RECORDING ALGORITHM



CONSTITUTIONAL

1. Pyrexia	*temperature > 37.5˚C documented*
2. Unintentional weight loss > 5%	
3. Lymphadenopathy	*lymph node more than 1 cm diameter*

Appendix 9
BILAG-2004 Index Glossary (cont.)

exclude infection

4. Anorexia

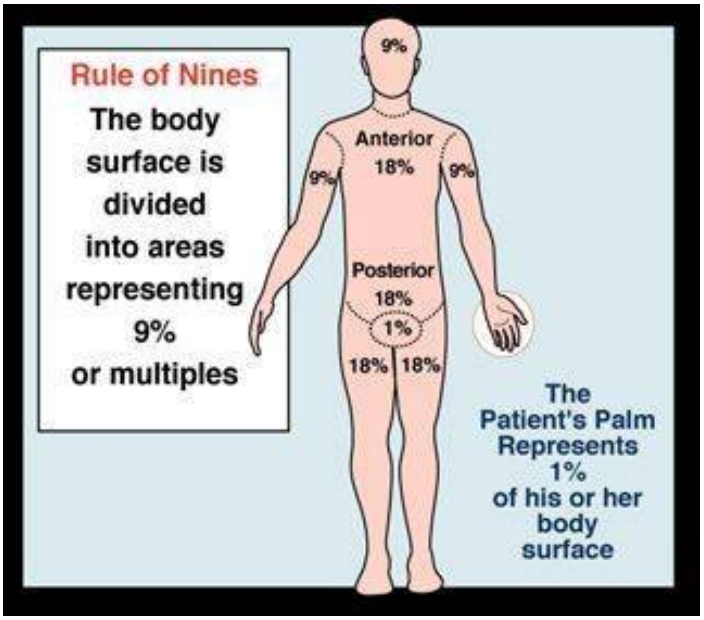
MUCOCUTANEOUS

5. Severe eruption — *> 18% body surface area*

any lupus rash except panniculitis, bullous lesion & angio-oedema

body surface area (BSA) is estimated using the rules of nines (used to assess extent of burns) as follows:

palm(excluding fingers) = 1% BSA
each lower limb = 18% BSA
each upper limb = 9% BSA
torso (front) = 18% BSA
torso (back) = 18% BSA
head = 9% BSA
genital (male) = 1% BSA



6. Mild eruption — *≤ 18% body surface area*

Appendix 9
BILAG-2004 Index Glossary (cont.)

	any lupus rash except panniculitis, bullous lesion & angio-oedema *malar rash must have been observed by a physician and has to be present continuously (persistent) for at least 1 week to be considered significant (to be recorded)*
7. Severe angio-oedema	*potentially life-threatening eg: stridor* *angio-oedema is a variant form of urticaria which affects the subcutaneous, submucosal and deep dermal tissues*
8. Mild angio-oedema	*not life threatening*
9. Severe mucosal ulceration	*disabling (significantly interfering with oral intake), extensive & deep ulceration* *must have been observed by a physician*
10. Mild mucosal ulceration	*localised &/or non-disabling ulceration*
11. Severe panniculitis or bullous lupus	*any one:* *> 9% body surface area* *facial panniculitis* *panniculitis that is beginning to ulcerate* *panniculitis that threatens integrity of subcutaneous tissue (beginning to cause surface depression) on > 9% body surface area* *panniculitis presents as a palpable and tender subcutaneous induration/nodule* *note that established surface depression and atrophy alone is likely to be due to damage*
12. Mild panniculitis or bullous lupus	*≤ 9% body surface area* *does not fulfil any criteria for severe panniculitis (for panniculitis)*
13. Major cutaneous vasculitis/thrombosis	*resulting in extensive gangrene or ulceration or skin infarction*

Appendix 9
BILAG-2004 Index Glossary (cont.)

14. Digital infarct or nodular vasculitis	*localised single or multiple infarct(s) over digit(s) or tender erythematous nodule(s)*
15. Severe alopecia	*clinically detectable (diffuse or patchy) hair loss with scalp inflammation (redness over scalp)*
16. Mild alopecia	*diffuse or patchy hair loss without scalp inflammation (clinically detectable or by history)*
17. Peri-ungual erythema or chilblains	*chilblains are localised inflammatory lesions (may ulcerate) which are precipitated by exposure to cold*
18. Splinter haemorrhages	

<u>NEUROPSYCHIATRIC</u>

19. Aseptic meningitis	*criteria (all): acute/subacute onset* *headache* *fever* *abnormal CSF (raised protein &/or lymphocyte predominance) but negative cultures* *preferably photophobia, neck stiffness and meningeal irritation should be present as well but are not essential for diagnosis* *exclude CNS/meningeal infection, intracranial haemorrhage*
20. Cerebral vasculitis	*should be present with features of vasculitis in another system* *supportive imaging &/or biopsy findings*
21. Demyelinating syndrome	*discrete white matter lesion with associated neurological deficit not recorded elsewhere* *ideally there should have been at least one previously recorded event* *supportive imaging required* *exclude multiple sclerosis*

Appendix 9
BILAG-2004 Index Glossary (cont.)

22. Myelopathy	*acute onset of rapidly evolving paraparesis or quadriparesis and/or sensory level* *exclude intramedullary and extramedullary space occupying lesion*
23. Acute confusional state	*acute disturbance of consciousness or level of arousal with reduced ability to focus, maintain or shift attention* *includes hypo- and hyperaroused states and encompasses the spectrum from delirium to coma*
24. Psychosis	*delusion or hallucinations* *does not occur exclusively during course of a delirium* *exclude drugs, substance abuse, primary psychotic disorder*
25. Acute inflammatory demyelinating polyradiculoneuropathy	*Criteria:* *progressive polyradiculoneuropathy* *loss of reflexes* *symmetrical involvement* *increased CSF protein without pleocytosis* *supportive electrophysiology study*
26. Mononeuropathy (single/multiplex)	*supportive electrophysiology study required*
27. Cranial neuropathy	*except optic neuropathy which is classified under ophthalmic system*
28. Plexopathy	*disorder of brachial or lumbosacral plexus resulting in neurological deficit not corresponding to territory of single root or nerve* *supportive electrophysiology study required*
29. Polyneuropathy	*acute symmetrical distal sensory and/or motor deficit* *supportive electrophysiology study required*

Appendix 9
BILAG-2004 Index Glossary (cont.)

30. Seizure disorder	*independent description of seizure by reliable witness*
31. Status epilepticus	*a seizure or series of seizures lasting ≥ 30 minutes without full recovery to baseline*
32. Cerebrovascular disease (not due to vasculitis)	*any one with supporting imaging:* *stroke syndrome* *transient ischaemic attack* *intracranial haemorrhage* *exclude hypoglycaemia, cerebral sinus thrombosis, vascular malformation, tumour, abscess* *cerebral sinus thrombosis not included as definite thrombosis not considered part of lupus activity*
33. Cognitive dysfunction	*significant deficits in any cognitive functions:* *simple attention (ability to register & maintain information)* *complex attention* *memory (ability to register, recall & recognise information eg learning, recall)* *visual-spatial processing (ability to analyse, synthesize & manipulate visual-spatial information)* *language (ability to comprehend, repeat & produce oral/written material eg verbal fluency, naming)* *reasoning/problem solving (ability to reason & abstract)* *psychomotor speed* *executive functions (eg planning, organising, sequencing)* *in absence of disturbance of consciousness or level of arousal* *sufficiently severe to interfere with daily activities* *neuropsychological testing should be done or*

Appendix 9
BILAG-2004 Index Glossary (cont.)

	corroborating history from third party if possible
	exclude substance abuse
34. Movement disorder	*exclude drugs*
35. Autonomic disorder	*any one:* *fall in blood pressure to standing > 30/15 mm Hg (systolic/diastolic)* *increase in heart rate to standing ≥ 30 bpm* *loss of heart rate variation with respiration (max – min < 15 bpm, expiration:inspiration ratio < 1.2, Valsalva ratio < 1.4)* *loss of sweating over body and limbs (anhidrosis) by sweat test* *exclude drugs and diabetes mellitus*
36. Cerebellar ataxia	*cerebellar ataxia in isolation of other CNS features* *usually subacute presentation*
37. Severe lupus headache (unremitting)	*disabling headache unresponsive to narcotic analgesia & lasting ≥ 3 days* *exclude intracranial space occupying lesion and CNS infection*
38. Headache from IC hypertension	*exclude cerebral sinus thrombosis*

MUSCULOSKELETAL

39. Severe myositis	*significantly elevated serum muscle enzymes with significant muscle weakness* *exclude endocrine causes and drug-induced myopathy*

Appendix 9
BILAG-2004 Index Glossary (cont.)

	electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
40. Mild myositis	*significantly elevated serum muscle enzymes with myalgia but without significant muscle weakness* *asymptomatic elevated serum muscle enzymes not included* *exclude endocrine causes and drug-induced myopathy* *electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity*
41. Severe arthritis	*observed active synovitis ≥ 2 joints with marked loss of functional range of movements and significant impairment of activities of daily living, that has been present on several days (cumulatively) over the last 4 weeks*
42. Moderate arthritis or Tendonitis or Tenosynovitis	*tendonitis/tenosynovitis or active synovitis ≥ 1 joint (observed or through history) with some loss of functional range of movements, that has been present on several days over the last 4 weeks*
43. Mild arthritis or Arthralgia or Myalgia	*inflammatory type of pain (worse in the morning with stiffness, usually improves with activity & not brought on by activity) over joints/muscle* *inflammatory arthritis which does not fulfil the above criteria for moderate or severe arthritis*

<u>CARDIORESPIRATORY</u>

44. Mild myocarditis	*inflammation of myocardium with raised cardiac enzymes &/or ECG changes and without resulting cardiac failure, arrhythmia or valvular dysfunction*

Appendix 9
BILAG-2004 Index Glossary (cont.)

45. Cardiac failure	*cardiac failure due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)* *cardiac failure due to myocarditis is defined by left ventricular ejection fraction ≤ 40% & pulmonary oedema or peripheral oedema* *cardiac failure due to acute valvular regurgitation (from endocarditis) can be associated with normal left ventricular ejection fraction* *diastolic heart failure is not included*
46. Arrhythmia	*arrhythmia (except sinus tachycardia) due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)* *confirmation by electrocardiogram required (history of palpitations alone inadequate)*
47. New valvular dysfunction	*new cardiac valvular dysfunction due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)* *supportive imaging required*
48. Pleurisy/Pericarditis	*convincing history &/or physical findings that you would consider treating* *in absence of cardiac tamponade or pleural effusion with dyspnoea* *do not score if you are unsure whether or not it is pleurisy/pericarditis*
49. Cardiac tamponade	*supportive imaging required*
50. Pleural effusion with dyspnoea	*supportive imaging required*
51. Pulmonary haemorrhage/vasculitis	*inflammation of pulmonary vasculature with haemoptysis &/or dyspnoea &/or pulmonary hypertension* *supportive imaging &/or histological diagnosis required*

Appendix 9
BILAG-2004 Index Glossary (cont.)

52. Interstitial alveolitis/pneumonitis	*radiological features of alveolar infiltration not due to infection or haemorrhage required for diagnosis* *corrected gas transfer Kco reduced to < 70% normal or fall of > 20% if previously abnormal* *on-going activity would be determined by clinical findings and lung function tests, and repeated imaging may be required in those with deterioration (clinically or lung function tests) or failure to respond to therapy*
53. Shrinking lung syndrome	*acute reduction (>20% if previous measurement available) in lung volumes (to < 70% predicted) in the presence of normal corrected gas transfer (Kco) & dysfunctional diaphragmatic movements*
54. Aortitis	*inflammation of aorta (with or without dissection) with supportive imaging abnormalities* *accompanied by > 10 mm Hg difference in BP between arms &/or claudication of extremities &/or vascular bruits* *repeated imaging would be required to determine on-going activity in those with clinical deterioration or failure to respond to therapy*
55. Coronary vasculitis	*inflammation of coronary vessels with radiographic evidence of non-atheromatous narrowing, obstruction or aneurysmal changes*
GASTROINTESTINAL	
56. Lupus peritonitis	*serositis presenting as acute abdomen with rebound/guarding*
57. Serositis	*not presenting as acute abdomen*

Appendix 9
BILAG-2004 Index Glossary (cont.)

58. Lupus enteritis or colitis	*vasculitis or inflammation of small or large bowel with supportive imaging &/or biopsy findings*
59. Malabsorption	*diarrhoea with abnormal D- xylose absorption test or increased faecal fat excretion after exclusion of coeliac's disease (poor response to gluten-free diet) and gut vasculitis*
60. Protein-losing enteropathy	*diarrhoea with hypoalbuminaemia or increased faecal excretion of iv radiolabeled albumin after exclusion of gut vasculitis and malabsorption*
61. Intestinal pseudo-obstruction	*subacute intestinal obstruction due to intestinal hypomotility*
62. Lupus hepatitis	*raised transaminases* *absence of autoantibodies specific to autoimmune hepatitis (eg: anti-smooth muscle, anti-liver cytosol 1) &/or biopsy appearance of chronic active hepatitis* *hepatitis typically lobular with no piecemeal necrosis* *exclude drug-induced and viral hepatitis*
63. Acute lupus cholecystitis	*after exclusion of gallstones and infection*
64. Acute lupus pancreatitis	*usually associated multisystem involvement*

<u>OPHTHALMIC</u>

65. Orbital inflammation	*orbital inflammation with myositis &/or extra-ocular muscle swelling &/or proptosis* *supportive imaging required*
66. Severe keratitis	*sight threatening* *includes: corneal melt* *peripheral ulcerative keratitis*
67. Mild keratitis	*not sight threatening*

Appendix 9
BILAG-2004 Index Glossary (cont.)

68. Anterior uveitis	
69. Severe posterior uveitis &/or retinal vasculitis	*sight-threatening &/or retinal vasculitis not due to vaso-occlusive disease*
70. Mild posterior uveitis &/or retinal vasculitis	*not sight-threatening* *not due to vaso-occlusive disease*
71. Episcleritis	
72. Severe scleritis	*necrotising anterior scleritis* *anterior &/or posterior scleritis requiring systemic steroids/immunosuppression &/or not responding to NSAIDs*
73. Mild scleritis	*anterior &/or posterior scleritis not requiring systemic steroids* *excludes necrotising anterior scleritis*
74. Retinal/choroidal vaso-occlusive disease	*includes: retinal arterial & venous occlusion serous retinal &/or retinal pigment epithelial detachments secondary to choroidal vasculopathy*
75. Isolated cotton-wool spots	*also known as cytoid bodies*
76. Optic neuritis	*excludes anterior ischaemic optic neuropathy*
77. Anterior ischaemic optic neuropathy	*visual loss with pale swollen optic disc due to occlusion of posterior ciliary arteries*

RENAL

78. Systolic blood pressure	
79. Diastolic blood pressure	
80. Accelerated hypertension	*blood pressure rising to > 170/110 mm Hg within 1 month with grade 3 or 4 Keith-Wagener-Barker retinal changes (flame-shaped haemorrhages or cotton-wool spots or papilloedema)*
81. Urine dipstick	
82. Urine albumin-creatinine ratio	*on freshly voided urine sample*

Appendix 9
BILAG-2004 Index Glossary (cont.)

	conversion: 1 mg/mg = 113 mg/mmol *it is important to exclude other causes (especially infection) when proteinuria is present*
83. Urine protein-creatinine ratio	*on freshly voided urine sample* *conversion: 1 mg/mg = 113 mg/mmol* *it is important to exclude other causes (especially infection) when proteinuria is present*
84. 24 hour urine protein	*it is important to exclude other causes (especially infection) when proteinuria is present*
85. Nephrotic syndrome	*criteria:* *heavy proteinuria (≥ 3.5 g/day or protein-creatinine ratio ≥ 350 mg/mmol or albumin-creatinine ratio ≥ 350 mg/mmol)* *hypoalbuminaemia* *oedema*
86. Plasma/Serum creatinine	*exclude other causes for increase in creatinine (especially drugs)*
87. GFR	*MDRD formula:* $GFR = 170 \times [\text{serum creatinine (mg/dl)}]^{-0.999} \times [\text{age}]^{-0.176} \times [\text{serum urea (mg/dl)}]^{-0.17} \times [\text{serum albumin (g/dl)}]^{0.318} \times [0.762 \text{ if female}] \times [1.180 \text{ if African ancestry}]$ *units = ml/min per 1.73 m^2* *normal: male = 130 ± 40* *female = 120 ± 40* *conversion:* *serum creatinine - mg/dl = (μmol/l)/88.5* *serum urea - mg/dl = (mmol/l) x 2.8* *serum albumin - g/dl = (g/l)/10* *creatinine clearance not recommended as it is not reliable*

Appendix 9
BILAG-2004 Index Glossary (cont.)

	exclude other causes for decrease in GFR (especially drugs)
88. Active urinary sediment	*pyuria (> 5 WCC/hpf or > 10 WCC/mm³ (μl))* *OR* *haematuria (> 5 RBC/hpf or > 10 RBC/mm³ (μl))* *OR* *red cell casts* *OR* *white cell casts* *exclude other causes (especially infection, vaginal bleed, calculi)*
89. Histology of active nephritis	*WHO Classification (1995): (any one)* *Class III – (a) or (b) subtypes* *Class IV – (a), (b) or (c) subtypes* *Class V – (a), (b), (c) or (d) subtypes* *Vasculitis* *OR* *ISN/RPS Classification (2003): (any one)* *Class III – (A) or (A/C) subtypes* *Class IV – (A) or (A/C) subtypes* *Class V* *Vasculitis* *within last 3 months* *glomerular sclerosis without inflammation not included*

HAEMATOLOGICAL

90. Haemoglobin	*exclude dietary deficiency & GI blood loss*
91. White cell count	*exclude drug-induced cause*
92. Neutrophil count	*exclude drug-induced cause*
93. Lymphocyte count	

Appendix 9
BILAG-2004 Index Glossary (cont.)

94. Platelet count	*exclude drug-induced cause*
95. TTP	*thrombotic thrombocytopaenic purpura* *clinical syndrome of micro-angiopathic haemolytic anaemia and thrombocytopenia in absence of any other identifiable cause*
96. Evidence of active haemolysis	*positive Coombs' test & evidence of haemolysis (raised bilirubin or raised reticulocyte count or reduced haptoglobulins or fragmented RBC or microspherocytes)*
97. Isolated positive Coombs' test	

ADDITIONAL ITEMS

These items are required mainly for calculation of GFR

i. Weight
ii. African ancestry
iii. Serum urea
iv. Serum albumin

References:

Rule of nines diagram. Burn Center, University of Utah Health Sciences Center (http://uuhsc.utah.edu/burncenter/emergencycare/extent.html)

Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.

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Appendix 10
Systemic Lupus Erythematosus Disease Activity Index
(SLEDAI-2K)

(Circle in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 4 weeks) (The same instrument can also be used going back only ten days)

Item no.	SLEDAI SCORE	Descriptor	Definition
1	8	Seizure	Recent onset, exclude metabolic, infectious or drug causes
2	8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganised, or catatonic behaviour. Exclude uraemia and drug causes
3	8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
4	8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes
5	8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
6	8	Lupus headache	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia THIS WOULD RARELY BE ATTRIBUTED TO SLE...ALMOST NEVER SCORED
7	8	CVA	New onset Cerebrovascular accident(s). Exclude arteriosclerosis
8	8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
9	4	Arthritis	>/= 2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion)
10	4	Myositis	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase (CK)/aldolase, or EMG changes or a biopsy showing myositis
11	4	Urinary casts	Heme-granular or RBC casts
12	4	Hematuria	> 5 RBC/high power field. Exclude stone, infection or other cause
13	4	Proteinuria	> 0.5 gram/24 hours
14	4	Pyuria	> 5 WBC/high power field. Exclude infection
15	2	Rash	Inflammatory type rash
16	2	Alopecia	Abnormal, patchy or diffuse loss of hair

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

Item no.	SLEDAI SCORE	Descriptor	Definition
17	2	Mucosal ulcers	Oral or nasal ulcerations
18	2	Pleurisy	Pleuritic chest pain or pleural rub with effusion, or pleural thickening (requires objective evidence)
19	2	Pericarditis	Classic pericardial pain and/or rub, effusion with ECG or echocardiogram confirmation (requires an objective component)
20	2	Low complement	Decrease in CH50, C3 or C4 below lower limit of normal for testing laboratory
21	2	Increased DNA binding	Increased DNA binding above normal range for testing laboratory
22	1	Fever	> 38ºC. Exclude infectious cause
23	1	Thrombocytopenia	< 100 x 10^9 platelets/L, exclude drug causes
24	1	Leukopenia	< 3 x 10^9 WBC/L, exclude drug causes

SCORE:

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

GUIDELINES FOR USE OF SLEDAI-2K MODIFIED FOR ASSESSMENT OVER 28 DAYS: TO ASSESS DISEASE ACTIVITY

General guidelines for filling out the SLEDAI-2K:

- The main principle to keep in mind is that this instrument is intended to evaluate current lupus activity and not chronic damage, severity is accounted for in part by the "weightedness" of the scale.

- Points are given exactly as defined.

- A descriptor is either scored the exact points allotted or not scored, i.e. given a zero. Descriptors are scored only if they are present at the time of the physician encounter or in the preceding 28 days. Windows acceptable in a clinical trial are acceptable in scoring the SLEDAI. However, it is never acceptable to fill in gaps which cover activity over 2-3 months or more. The reason for this is that disease activity at the visit might have changed several times in such intervals and the recording of distant activity becomes meaningless.

  Please note that in the original SLEDAI the disease activity being scored was meant to cover only a ten day period, the modification to 28 days is a more useful assessment for use in clinical trials, in order to capture disease activity between monthly visits.

- The descriptor must be documented by the notes written in the physician encounter form and generally applies to the clinical data and not to the laboratory data. The laboratory data is strictly defined as per cutoffs and documentation is provided by the reports from the commercial laboratory.

- Descriptors do not have to be new but can be. They can be ongoing, recurrent, or initial events. Each would be scored the same way. An example would be a malar rash or mucosal ulcer. In these situations a malar rash observed at the initial visit but which remains unchanged for the next six months, irrespective of any treatment, is scored 2 points each time the SLEDAI is completed. Since the nature of lupus is that manifestations are not usually fleeting it would be rare for descriptors to appear transiently during the month and not at the time of the encounter. This is discussed in more detail for each descriptor but is especially relevant for the neurologic (except for seizure or CVA), pulmonary, and cutaneous manifestations.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

- In some descriptors the exclusions written may not be exhaustive. The intent of the SLEDAI is that the descriptor be attributed to SLE. If the physician does not attribute the descriptor to SLE it should not be scored, but full documentation must be provided.

Written in italics is the definition for each descriptor precisely provided in the SLEDAI SCORE

SEIZURE

Definition: Recent onset (last 28 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.

This descriptor is scored if the patient has had a witnessed seizure or convincing description (such as tongue biting or incontinence) within 30 days of the current encounter. The patient need not have a positive EEG, CT scan, PET scan, QEEG, or MRI. The CSF may be totally normal.

A seizure is also not counted:

1. If a metabolic cause is determined.
2. In the presence of a proven infectious meningitis, brain abscess, or fungal foci.
3. If there is a history of recent head trauma.
4. In the presence of an offending drug.
5. In the presence of severe hyperthermia or hypothermia.
6. If the patient has stopped taking anticonvulsant medication.
7. If the patient has a documented sub-therapeutic anticonvulsant drug level.

PSYCHOSIS

Definition: Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.

This descriptor is scored if any of the criteria above are met.

With regard to drug causes the most problematic situation is glucocorticoids. If the treating physician attributes the psychosis to glucocorticoids this descriptor should not be counted.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

ORGANIC BRAIN SYNDROME

Definition: Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.

a. reduced capacity to focus as exemplified by new inability to perform everyday mathematical computations or disorientation to person, place, time, or purpose

OR

b. inability to carry on a conversation

OR

c. reduction in short term memory

PLUS: Documented abnormality on neuropsychiatric testing

Neuropsychiatric testing may take the form of a "mini-mental-status exam" or a formal neuropsychiatric examination. The important aspect for scoring OBS is that it be reversible. Consideration should be given to the improvement of OBS after institution of glucocorticoids.

This descriptor is not scored in the presence of a metabolic, infectious, or drug cause. If the problem is chronic this descriptor is not scored in SLEDAI but is scored on the damage index.

VISUAL DISTURBANCE

Definition: Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection or drug causes.

This is scored exactly as defined with the understanding that it must be supported by objective evidence.

CRANIAL NERVE DISORDER

Definition: New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

This is scored exactly as defined with the understanding that it must be supported by objective evidence. However, it should be noted that hydroxychloroquine can affect the eighth cranial nerve.

LUPUS HEADACHE

Definition: Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.

For this descriptor to be counted, the headache must be present for greater than 24 hours and must not be responsive to narcotic analgesia. Objective documentation need not be present although it is expected that such a complaint, given the severity, would prompt formal testing such as MRI, CT, LP, etc. Furthermore, the headache should be of sufficient severity to warrant the initiation of glucocorticoids or additional immunosuppressive agents. Scoring of this descriptor means attribution of the headache to CNS lupus.

Most headaches, including most severe and/or migrainous headaches are not attributable to lupus and this descriptor should only be scored very rarely.

CVA

Definition: New onset of cerebrovascular accident (s). Exclude arteriosclerosis or hypertensive causes.

This descriptor is scored if the patient has had a CVA within 28 days of the current encounter. A patient recovering from a CVA that was documented more than 28 days prior to the current encounter is not given points for this descriptor. A patient may have had a previous CVA but to be scored the current CVA must be new.

This descriptor is scored in the presence or absence of anti-phospholipid antibodies, i.e., the precise pathophysiologic mechanism need not be known.

The CVA is scored even in the presence of a normal CT or MRI. A TIA is also scored if the patient gives a convincing history. To exclude atherosclerosis the patient has to have a normal carotid and/or vertebral Doppler and cannot have uncontrolled hypertension.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

VASCULITIS:

Definition: Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.

To score this descriptor the above definitions must be present. For example, erythematous lesions on the hands or feet which may be characteristically considered "leukocytoclastic vasculitis" but do not fulfill at least one of the above definitions and if not biopsied, are not counted. Similarly livedo reticularis is not counted. Healed ulcers with residual scar are not to be counted, but be sure to count these in the damage index. A lesion consistent with erythema nodosum should be counted regardless of whether it is biopsied or not. Purpura in the presence of a normal platelet count should be counted regardless of whether it has been biopsied or not.

ARTHRITIS

Definition: Two or more joints with pain and signs of inflammation, i.e., tenderness, swelling, or effusion.

Arthritis is scored if it is ongoing; it need not be new or recurrent.

Arthritis is scored only if at least two joints manifest signs of inflammation. The rheumatologist must be convinced that this is active arthritis due to lupus.

Inflammation of the tendons, ligaments, bursae, and other periarticular structures are not scored. For example subacromial bursitis and trochanteric bursitis are not scored. If further evaluation reveals osteonecrosis or osteoarthritis, this descriptor is not counted.

MYOSITIS

Definition: Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.

The patient complains of muscle aching and/or weakness in the proximal muscles PLUS one of the following must be present:

1. elevated serum creatinine phosphokinase and/or aldolase
2. abnormalities on electromyogram consistent with myositis
3. biopsy-proven myositis

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

RENAL: Note that the following domains (urinary casts, hematuria, proteinuria, and pyuria) can only be evaluated on clean catch urinalysis specimens.

URINARY CASTS

Definition: Heme-granular or red blood cell casts.

This is scored if red blood cell casts are seen, even if it is only one. Pigmented casts are counted but non-pigmented granular casts, hyaline or waxy casts are not counted.

HEMATURIA

Definition: >5 red blood cells/high power field. Exclude stone, infection or other cause.

With regard to this descriptor, every attempt should be made to see patients when they are not menstruating. If this is not possible the urinalysis should be deferred until the next visit.

This descriptor is not scored if there is documented renal calculi or infection. The latter must be confirmed by a positive urinary culture. However it is acknowledged that associated conditions such as chlamydia or urethral irritation may result in mild hematuria and the physician's best judgment is warranted. **The important point is attribution: there must be other evidence of nephritis and other causes of hematuria must be excluded.**
In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely unless pathology is limited to the mesangium.

PROTEINURIA

Definition: proteinuria of more than 0.5 g/24 hours (or equivalent by spot urine protein to creatinine ratio).

Must be attributed to active lupus nephritis.

PYURIA

Definition: >5 white blood cells/high power field. Exclude infection.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

This descriptor is not scored if there is evidence of vaginal contamination (presence of any squamous epithelial cells) or a documented infection. The latter must be confirmed by a positive urinary culture. However, it is acknowledged that associated conditions such as chlamydia, trichomonas or urethral irritation may result in mild pyuria and the physician's best judgment is warranted. **The important point is attribution; there must be other evidence of nephritis, and other causes of pyuria should be excluded.** In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely unless pathology is limited to the interstitium.

RASH

Definition: Ongoing inflammatory lupus rash.

A rash is scored if it is ongoing, new or recurrent. Even if it is identical in terms of distribution and character to that observed on the last visit and the intensity is improved, it is counted. Therefore, despite improvement in a rash, if it is still ongoing it represents disease activity. The rash must be attributable to SLE. A description of the rash must appear in the physical exam and should include distribution, characteristics such as macular or papular, and size.

The following should not be scored:

1. Chronic scarred discoid plaques in any location.
2. Transient malar flush, i.e., it is not raised and is evanescent

A common problem one may encounter is the differentiation between scoring a lesion as "rash" and/or "vasculitis". If a lesion meets the descriptive criteria of the latter it should not also be counted as rash, i.e., the score would be 8 points not 10 points. If a separate rash characteristic of SLE is present only then would "rash" also be scored.

ALOPECIA:

Definition: Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.

This should be scored if any of the following conditions are present:

1. There is temporal thinning which is newly present for less than six months (if temporal alopecia is present for more than six months with no change it should not be counted)

2. Areas of scalp with total bald spots if present for less than six months (does not need to have accompanying discoid lesion or follicular plugging)
3. The presence of "lupus frizz" i.e., short of strands of unruly hair in the frontal or temporal area

If a patient complains of hair loss and there is nothing apparent on exam this descriptor is not scored.

MUCOSAL ULCERS:

Definition: Ongoing oral or nasal ulcerations due to active lupus.

An ulcer is scored if it is ongoing, it need not be new or recurrent. Ulcers can be present in either the nose or oral cavity. Erythema alone without frank ulceration is not sufficient to be scored, even if the erythema is present on the upper palate. Ulcers on the buccal mucosa and tongue are counted.

Mucosal ulcers are not counted as vasculitis.

PLEURISY

Definition: Classic and severe pleuritic chest pain or pleural rub with effusion or new pleural thickening due to lupus.

This descriptor is scored if the patient complains of pleuritic chest pain lasting greater than 12 hours. The pain should be classic, i.e., exacerbated by inspiration, to help distinguish it from musculoskeletal conditions such as costochondritis, which could be confused with pleurisy. The symptom must also be accompanied by objective findings.

PERICARDITIS:

Definition: Classic and severe pericardial pain with rub or effusion, or electrocardiogram or echocardiogram confirmation.

The symptom must be accompanied by objective findings.

LOW COMPLEMENT:

Definition: Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

Exclude a low C4 or CH50 in patients with known inherited deficiency of C4.

INCREASED DNA BINDING

Definition: >25% binding by Farr assay or above normal range for testing laboratory.

FEVER:

Definition: >38°C. Exclude infectious cause.

This would be scored if one of the following conditions are present:

1. A documented temperature elevation >100.4°F or >38°C at the time of the visit.
2. A convincing history from the patient that she/he has been febrile within the preceding 10 days prior to the visit without any signs or symptoms suggestive of infection. Febrile is defined as above and not simply that the patient felt feverish. In this case the patient need not be febrile at the time of the visit for a score of 2 to be given.

As stated in the SLEDAI, fever secondary to infection is not to be scored although it is acknowledged that concomitant lupus activity and infection can occur. Fever in the presence of infection should only be scored on the SLEDAI if other evidence of lupus activity is present.

THROMBOCYTOPENIA:

Definition: <100,000 platelets/mm^3.

LEUKOPENIA:

Definition: <3,000 white blood cells/mm^3. Exclude drug causes.

This is exactly as described, WBC <3,000/mm^3. The presence of an absolute lymphopenia does not count in the SLEDAI. A note of caution, do not confuse this WBC with that used to satisfy the ACR criteria for SLE which is WBC <3,500/mm^3.

With regard to current use of possible offending drugs, the following guidelines are to be considered:

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

1. The nadir after cyclophosphamide, i.e., low WBC at 10 days after receiving cyclophosphamide in a patient known to have a WBC ≥ 3,000 at the time of receiving cyclophosphamide should not be counted.
2. Do not score leukopenia appearing after initiation of a new medication known to be associated with leukopenia, such as azathioprine or sulfa drugs. If the patient develops a WBC <3000 while taking drugs which may cause leukopenia, score this only if the dosage of medication is unchanged since the last WBC determination.

Appendix 11
SELENA-SLEDAI FLARE INDEX (SFI)

(Can be used with any version of the SLEDAI)

Mild or Moderate Flare	Severe Flare
Increase in SLEDAI by ≥ 3 New or worse: Rash (discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus) Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE)	Increase in SLEDAI to > 12 New or worse (requiring doubling of prednisone, *prednisone* > 0.5 mg/kg/day, or hospitalization): CNS-SLE Vasculitis Nephritis Myositis Platelets $< 60{,}000/mm^3$ Hemolytic anemia: Hb < 7g/dL or decrease of Hb by > 3 g/dL
Increase in Prednisone, but not to >0.5 mg/kg/day	Prednisone > 0.5 mg/kg/day
Added NSAID or hydroxychloroquine for disease activity	New cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, or hospitalization (for SLE)
Increase in Physican's Global Assessment by ≥ 1.0, but not to more than 2.5	Increase in Physician's Global Assessment to > 2.5

Buyon JP et al. The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomized Trial. Ann Internal Med 2005;142:953-62.

Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999;8:685-91.

Petri M, Kim MY, Kalunian KC, et al. Combined Oral Contraceptives in Women with Systemic Lupus Erythematosus. N Engl J Med 2005;353:2550-8.

Appendix 12
Glucocorticoid Toxicity Change Index

COMPOSITE GLUCOCORTICOID TOXICITY CHANGE INDEX

1. Body mass index (BMI) (compared to baseline)
   a) Improvement (in either direction) by more than 2 BMI units toward normal BMI (normal range = 18.5–24.9 kg/m^2)
   b) No significant change (BMI remains within ± 2 BMI units compared with baseline) or BMI remains within the normal range
   c) Moderate increase in BMI (increase by more than 2 but less than 5 BMI units to above the upper limit of normal BMI [24.9 kg/m^2])
   d) Major increase in BMI (increase by more than 5 BMI units to above normal BMI [24.9 kg/m^2])

2. Glucose tolerance (compared to baseline)
   a) Improvement in glucose tolerance:
      - HbA1c (glycosylated hemoglobin) declined $> 10\%$ from baseline without medication increase

        OR

      - Decrease in diabetic medication without an increase in HbA1c of $> 10\%$ or HbA1c $< 5.7\%$
   b) No significant change in glucose tolerance:
      - HbA1c within 10% of baseline or HbA1c $< 5.7\%$ and no change in medication

        OR

      - HbA1c increased to $> 10\%$ of baseline due to a decrease in medication

        OR

      - Improvement in glucose tolerance $> 10\%$ due to an increase in medication
   c) Worsening of glucose tolerance or medication status:
      - HbA1c increased to $> 10\%$ and HbA1c $> 5.7\%$ without a change in medication

        OR

      - Increase in diabetic medication with $< 10\%$ increase in HbA1c
   d) Worsening of glucose tolerance despite treatment:
      - HbA1c $> 5.7\%$ and increased to $> 10\%$ of baseline and an increase in diabetic medication

Appendix 12
Glucocorticoid Toxicity Change Index (cont.)

3. Blood pressure (BP) (compared to baseline)
   a) Improvement in BP:
      - Decrease in BP of $>10\%$ of baseline without medication increase

        OR

      - Decrease in medication without an increase in BP of $>10\%$ or systolic BP ≤ 120 and diastolic BP ≤ 85

   b) No significant change in BP:
      - BP within 10% of baseline or systolic BP ≤ 120 and diastolic BP ≤ 85 and no change in medication

        OR

      - Deterioration in either systolic or diastolic BP $>10\%$ due to a decrease in medication

        OR

      - An improvement in either systolic or diastolic BP of $>10\%$ due to an increase in medication

   c) Worsening of hypertension:
      - Increase in BP of $>10\%$ such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication

        OR

      - Increase in anti-hypertensive medication without an improvement in BP $>10\%$

   d) Worsening of hypertension despite treatment:
      - Increase in BP of $>10\%$ such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg and an increase in medication

4. Hyperlipidemia (compared to baseline)
   a) Improvement in lipids:
      - Decrease in low-density lipoprotein (LDL) concentration $>10\%$ of baseline without medication increase toward the target range

        OR

      - Decrease in medication without an increase in LDL of $>10\%$ or LDL remains within target range

Appendix 12
Glucocorticoid Toxicity Change Index (cont.)

b) No significant change in LDL:

- LDL within 10% of baseline or within the target range for patient and no change in medication

OR

- Increase in LDL > 10% due to a decrease in medication

OR

- Improvement in LDL of > 10% due to an increase in medication

c) Worsening of LDL or medication status:

- Increase in LDL of > 10% to above target range without increase in medication

OR

- Increase in medication without > 10% change in LDL

d) Worsening of LDL despite treatment:

- Increase in LDL of > 10% and an increase in medication

5. Steroid myopathy

a) No steroid myopathy

b) Mild steroid myopathy (weakness without functional limitation)

c) Moderate steroid myopathy (weakness with functional limitation)

See steroid myopathy definitions below.

6. Skin

a) No skin toxicity

b) Mild

c) Moderate

See skin definitions below.

7. Neuropsychiatric

a) No neuropsychiatric symptoms

b) Mild

c) Moderate

See neuropsychiatry definitions below.

Appendix 12
Glucocorticoid Toxicity Change Index (cont.)

8. Infection (since last assessment)
   a) No significant infection
   b) Specific infections $<$ Grade 3 (oral or vaginal candidiasis, uncomplicated zoster)
   c) Grade 3

   See infection notes below.

9. Bone mineral density (BMD) (compared to baseline)
   a) Improvement – increase in BMD by $>3\%$
   b) No significant change (BMD between -3% and $+3\%$)
   c) Deterioration – decrease by $\geq 3\%$

   % refers to total BMD in gms/cm^2
   If BMD not evaluated, then option "b" should be selected.

GLUCOCORTICOID-INDUCED MYOPATHY DEFINITIONS

- Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy and not due to any other apparent cause. Muscle enzymes are typically within normal limits.
- Mild and moderate myopathy are defined by muscle strength of 4 on the standard Medical Research Council strength testing scale. A 4 means weaker than normal but greater than anti-gravity strength.
- "Mild" is Grade 4 weakness that does not functionally limit the patient.
- "Moderate" is Grade 4 weakness that does impose functional limitations on the patient, interfering with normal daily activities.
- Note that inability to rise from a chair without assistance constitutes severe glucocorticoid-induced myopathy (Specific Domain)

SEVERITY OF GLUCOCORTICOID TOXICITY IN THE SKIN

Manifestations to be considered:

- Acneiform rash
- Easy bruising
- Hirsutism
- Atrophy/striae
- Erosions/tears/ulcerations

Appendix 12
Glucocorticoid Toxicity Change Index (cont.)

Skin 6b. Mild	Skin 6c. Moderate	Severe (Specific Domain)
Acneiform rash (Grades 1–2)	Acneiform rash (Grade 3)	Acneiform rash (Grade 4)
Easy bruising (Grade 1)	Easy bruising (Grade 2)	
Hirsutism (Grade 1)	Hirsutism (Grade 2)	
Atrophy/striae (Grade 1)	Atrophy/striae (Grade 2)	Atrophy/striae (Grade 3)
Erosions/tears/ulcerations (Grade 1)	Erosions/tears/ulcerations (Grade 2)	Erosions/tears/ulcerations (Grade 3)

Acneiform rash

- Grade 1: Papules and/or pustules covering < 10% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness
- Grade 2: Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental activities of daily living (ADL)
- Grade 3: Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated
- Grade 4: Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with intravenous (IV) antibiotics indicated; life-threatening consequences

Easy bruising

- Grade 1: Localized or in a dependent area
- Grade 2: Generalized

Hirsutism: In women, increase in length, thickness, or density of hair in a male distribution

- Grade 1: Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair
- Grade 2: Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact

Atrophy/striae

- Grade 1: Covering < 10% BSA; associated with telangiectasias or changes in skin color
- Grade 2: Covering 10%–30% BSA; associated with striae or adnexal structure loss
- Grade 3: Covering > 30% BSA; associated with ulceration

Appendix 12
Glucocorticoid Toxicity Change Index (cont.)

Erosions/tears/ulcerations

- Grade 1: Combined area of ulcers <1 cm; non-blanchable erythema of intact skin associated with warmth or erythema
- Grade 2: Combined area of ulcers 1–2 cm; partial thickness skin loss involving skin or subcutaneous fat
- Grade 3: Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

SEVERITY OF NEUROPSYCHIATRIC GLUCOCORTICOID TOXICITY

Manifestations to be considered:

- Insomnia
- Mania
- Cognitive impairment
- Depression

7b. Mild—No Functional Impairment	7c. Moderate—Functional Impairment	Severe (Specific Domain)
Insomnia	Insomnia	
Mania (Grade 1)	Mania (Grade 2)	Mania (Grade 3)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)	Cognitive impairment (Grade 3)
Depression (Grade 1)	Depression (Grade 2)	Depression (Grade 3)

DEFINITIONS OF SEVERITY WITHIN THE NEUROPSYCHIATRIC DOMAIN

Insomnia: Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening

- Grade 1: Not associated with functional impairment
- Grade 2: Associated with functional impairment; recorded as moderate toxicity

Mania

- Grade 1: Slightly or occasionally elevated or irritable mood and 0–1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions
- Grade 2: Frequent or moderately elevated or irritable mood and 2–3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased

talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions

- Grade 3: Severe or constantly elevated or irritable mood and 4 or more additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions

Cognitive impairment

- Grade 1: Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids
- Grade 2: New moderate cognitive deficits that were not present before initiating steroids
- Grade 3: Frank delirium

Depression

- Grade 1: Feeling slightly down or depressed and 0–2 mild or occasional additional symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite
- Grade 2: Frequent or moderate feelings of being down or depressed and/or 3–4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite
- Grade 3: Severe constant feeling of being down or depressed and/or 5 or more symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite and/or suicidal thoughts

INFECTION NOTES

- No significant infection: No specific infections or serious infections Grade 3 or greater
- Specific infections: Oral or vaginal candidiasis or zoster infections without postherpetic neuralgia or eye involvement
- Grade 3: IV antibiotic, anti-fungal, or anti-viral intervention or hospitalization indicated or radiologic or operative intervention indicated or herpes zoster complicated by postherpetic neuralgia or eye involvement
- Grade 4 or 5: Life-threatening consequences; urgent intervention indicated or death from infection (Specific Domain)

Appendix 13
28-Joint Count

The number of tender joints and the number of swollen joints will be assessed on any patient in whom arthritis is present at the current visit or in whom arthritis has been present at any previous visit during the study.

The joint counts must be performed by an assessor with experience in performing these assessments; this may be the Principal Investigator, subinvestigator, the study coordinator, or another trained individual approved by the Sponsor. The joint counts on a given patient should be performed by the same assessor at each study visit.

The 28 joints to be assessed for tenderness and swelling are as follows:

- Shoulders (2 joints)
- Elbows (2 joints)
- Wrists (2 joints)
- Interphalangeal of each thumb (2 joints)
- Proximal interphalangeal joints on fingers 2 – 5 (8 joints)
- Metacarpophalangeal joints on digits 1 – 5 (10 joints)
- Knees (2 joints)

The choice of joints included in this assessment is based on the 28-joint count performed as part of the Disease Activity Score (DAS)-28 for assessment of disease activity in rheumatoid arthritis.

Appendix 14
Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The Cutaneous Lupus Area and Severity Index (CLASI) comprises a score for the *activity* of the disease and a score for the *damage* caused by the disease (see Scoresheet in this appendix). The CLASI should be completed at intervals as indicated in the SOA (Appendix 1) for any patient who has mucocutaneous manifestations of SLE at a given study visit and then at all subsequent visits.

With the exception of alopecia, only skin lesions that are specific to SLE are included in this assessment. The cutaneous manifestations of SLE (e.g., vasculitis) are not scored for the CLASI.

1. localized and generalized manifestations of acute cutaneous lupus erythematosus (malar rash, maculopapular rash, photosensitive rash, bullous lupus erythematosus);
2. subacute cutaneous lupus erythematosus (annular / polycyclic or papulosquamous / psoriasiform); and
3. chronic cutaneous lupus erythematosus (localized and generalized discoid lupus, verruccous/hyperkeratotic discoid lupus, mucosal discoid lupus, tumid lupus, perniotic/chilblain lupus, and lupus profundus/lupus panniculitis).

Training in the use of the CLASI will be provided to Investigators.

Activity

Lesion activity is scored for 13 specified anatomical areas in terms of erythema (absent = 0; pink or faint erythema = 1; red = 2; dark red, purple, violaceous, crusted, or hemorrhagic = 3) and scale/hypertrophy (absent = 0; scale = 1; verruccous or hypertrophic = 2). The severity score for each area is based on the worst lesion within that area.

The patient is asked about mucous membrane involvement and if this is reported the affected areas are examined (absent = 0, present = 1).

The patient is asked about hair loss in the past 30 days (patient-reported absence = 0, presence = 1). Non-scarring alopecia on examination is scored by examining the scalp in quadrants (absent = 0; diffuse, non-inflammatory = 1; focal or patchy in one quadrant = 2; focal or patchy in more than one quadrant = 3). The scores for the various anatomical areas are summed.

The maximum possible score for the Activity component of the CLASI is 70.

Appendix 14
Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) (cont.)

Damage

Skin damage is scored for 12 specified anatomical areas (as for the Activity score but excluding the scalp which is scored separately, see below). Damage in each area is scored for dyspigmentation (absent = 0; present = 1) and for scarring, atrophy and panniculitis (absent = 0; scarring = 1; severe atrophic scarring or panniculitis = 2). As for the Activity component of the index, the damage severity score for each area is based on the worst lesion within that area. The scores for the various anatomical areas are then summed.

The patient is asked whether the dyspigmented cutaneous lesions usually remain visible for more than 12 months. If so, this is taken to indicate that the lesions are permanent, and the dyspigmentation score is doubled.

The scalp is examined for scarring, again by dividing into quadrants (absent = 0; scarring in one quadrant = 3; two quadrants = 4; three quadrants = 5; whole skull scarred = 6).

The maximum possible score for the Damage component of the CLASI is 56.

Reference:

Albrecht J, Werth V. Development of the CLASI as an outcome instrument for cutaneous lupus erythematosus. *Derm Ther.* 2007:20; 93-101.

Appendix 14
Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) (cont.)

Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

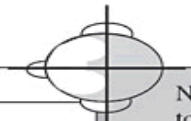
Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	



NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

Appendix 15
Physician's Global Assessment

The Investigator's global assessment of the patient's current disease activity (PGA) will be marked on a 100 mm horizontal visual analogue scale (VAS) marked from 'none' to 'severe' and graded from 0 to 3 (see example of following page). The Investigator should refer to assessments at prior visits and move the tick mark according to his or her assessment of the patient's disease activity over the preceding 28 days. The PGA should be done after the Investigator has done the clinical history and examination of the patient and has completed the BILAG-*2004* and SLEDAI-*2K* indices and (where appropriate) the CLASI and 28-joint counts.

Pertinent laboratory values should be taken into account before completing the PGA rating. If relevant laboratory results are pending, investigator may make a provisional marking on a local paper copy of the PGA case record form and finalize the assessment when all pertinent data are available.

Appendix 15
Physician's Global Assessment (cont.)

PHYSICIAN'S GLOBAL ASSESSMENT

☐ Check if assessment was not done

Date of Assessment: ___-___-___
Mo Day Year

Please answer the following questions by placing a **vertical mark through the line**

Global Assessment of Disease Activity

On the line below, where would you rate the subject's SLE over the past 28 days?

_____ mm

Rater Initials: ☐☐☐

Do not photocopy the document as this is NOT to scale

Appendix 16
Patient's Global Assessment

The patient is asked to rate her /his lupus over the previous 24 hours considering all aspects of the disease. This overall assessment of her/his current disease activity will be marked on a 100 mm horizontal visual analogue scale (VAS) marked from "None" to "Maximum." Validated translations will be provided.

The patient should complete this assessment without reference to assessments completed at previous visits, and should complete the assessment prior to receiving Investigational Product.

The Investigator or Study Coordinator will measure the distance in mm from his or her left hand end of the VAS line and record this in the box provided.

Please answer the following question by placing a vertical mark through the line.

On the line below, considering all the ways your lupus affects you, where would you rate your lupus over the last 24 hours?

None Maximum

mm

Appendix 17
Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

FOR REFERENCE ONLY

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 18
Types and Doses of Standard Oral Treatments for Systemic Lupus Erythematosus Permitted in Study

Oral corticosteroids [a]	Equivalent dose (mg)
Hydrocortisone	20
Cortisone acetate	25
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Dexamethasone	0.75
Betamethasone	0.75
Triamcinolone	4
Beclometasone	0.75
Deflazacort	6
Other [c]	—
Oral Immunosuppression and anti-malarials [b]	
Azathioprine	1 to 2.5 mg/kg/day
Methotrexate	7.5 to 25 mg/week
Mycophenolate mofetil	500 to 3000 mg/day
Mycophenolic sodium	360 to 2160 mg/day
Hydroxychloroquine	200 to 400 mg/day
Chloroquine	100 to 250 mg/day
Quinacrine	100 to 200 mg/day
Other [c]	—

[a] Cortisol (hydrocortisone) is the standard of comparison for glucocorticoid potency. Hydrocortisone is the name used for pharmaceutical preparations of cortisol.

[b] Any combination of azathioprine, methotrexate, mycophenolate mofetil, or mycophenolic sodium is prohibited.

[c] Other medications may apply based on region and should be consulted with the Medical Monitor.

Appendix 19
Concomitant Medications (Including Foods and Herbal Products)

Class	Expected Interaction	Recommendation	Examples of Drugs in this Class [a]
Antacids	Decreased GDC-0853 absorption due to increased gastric pH	Take GDC-0853 2 hours before or 2 hours after antacid	• Maalox, Pepto-Bismol, Rolaids
*S*trong CYP3A inhibitors	Increased GDC-0853 plasma concentrations due to inhibition of metabolism	Avoid for 7 days or 5 half-lives (whichever is longer) prior to first dose of study drug and during the treatment period, unless otherwise advised by the Medical Monitor or delegate[b]	• Antimicrobials (clarithromycin, erythromycin, itraconazole, ketoconazole, telithromycin, troleandamycin, voriconazole, posaconazole) • Antidepressants (nefazodone) • Other (grapefruit juice, Seville orange juice, pomegranate, star fruit)
CYP3A inducers	Decreased GDC-0853 plasma concentrations due to increased metabolism	Avoid for 7 days or 5 half-lives (whichever is longer) prior to first dose of study drug and during the treatment period, unless otherwise advised by the Medical Monitor or delegate[b]	• Antimicrobials (rifampin, rifapentine, rifabutin) • Antidepressants (St. John's wort, hyperforin) • Antiepileptics (carbamazepine, phenytoin, phenobarbital, hyperforin) • Diabetes (pioglitazone, troglitazone) • Other (modafinil, bosentan)
Sensitive and narrow therapeutic window CYP3A substrates	Potential for increased plasma concentrations of CYP3A substrates due to inhibition of metabolism by GDC-0853	Use with caution and monitor for adverse events related to CYP3A substrates as directed by product labeling; consult with the Medical Monitor as needed[b]	• Antiemetic/prokinetic (aprepitant, cisapride) • Anti-histamine (astemizole, terfenadine) • Anti-hypertensive/cardiac (dronedarone, eplerenone, felodipine, nisoldipine, quinidine, ticagrelor, vardenafil) • Benzodiazepines (alprazolam, diazepam, midazolam) • Lipid-lowering (simvastatin *[recommended maximum dose: 10 mg/day]*, lovastatin *[recommended maximum dose: 20 mg/day]*) • Migraine (eletriptan, ergotamine) • Steroids (budesonide, fluticasone) • Other (alfentanil, buspirone, conivaptan, darifenacin, dasatinib, dihydroergotamine, fentanyl, lurasidone, pimozide, quetiapine,

Appendix 19
Concomitant Medications (Including Foods and Herbal Products) (cont.)

			sildenafil, tolvaptan, triazolam)
BCRP substrates with a narrow therapeutic index	*Potential for increased plasma concentrations of BCRP substrates due to inhibition of transport by GDC-0853*	*Use with caution and monitor for adverse events related to BCRP substrates as directed by product labeling; consult with the Medical Monitor as needed*[b]	• *Anti-hypertensive (prazosin)* • *Anti-inflammatory (sulfasalazine)* • *Lipid-lowering (rosuvastatin [recommended maximum dose: 10 mg/day], atorvastatin [recommended maximum dose: 20 mg/day]* • *Muscle relaxants (dantrolene)* • *Steroids (estrone-3-sulfate)*

[a] The following list is not comprehensive. Please refer to the following websites for additional information and consult the Medical Monitor if necessary:

U.S. FDA Table of Substrates, Inhibitors, and Inducers (Tables 3-1, 3-2, 3-3*, and 5-1*) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

Indiana University Department of Medicine P450 Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/clinical-table)

[b] Potential CYP3A- *and BCRP*-mediated interactions between GDC-0853 and concomitant medications will be reviewed by the Medical Monitor or delegate during the pre-enrolment adjudication process