Official Title: A Phase II, Open-Label Extension Study of Patients Previously Enrolled in Study GA30044 to Evaluate the Long-Term Safety and Efficacy of GDC-0853 in Patients With Moderate to Severe Active Systemic Lupus Erythematosus

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PROTOCOL

TITLE:	**A PHASE II, OPEN-LABEL EXTENSION STUDY OF PATIENTS PREVIOUSLY ENROLLED IN STUDY GA30044 TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS**
PROTOCOL NUMBER:	GA30066
VERSION NUMBER:	1
EUDRACT NUMBER:	2017-001764-37
IND NUMBER:	130011
TEST PRODUCT:	GDC-0853 (RO7010939)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	20-Jun-2017 20:24:16

TABLE OF CONTENTS

PROTOCOL ACCEPTANCE FORM 10

PROTOCOL SYNOPSIS 11

1. BACKGROUND 20
   - 1.1 Background on Systemic Lupus Erythematosus 20
   - 1.2 Background on Bruton's Tyrosine Kinase and GDC-0853 21
   - 1.2.1 Bruton's Tyrosine Kinase 21
   - 1.2.2 Nonclinical Experience with GDC-0853 21
   - 1.2.3 Clinical Experience with GDC-0853 23
   - 1.3 Study Rationale and Benefit–Risk Assessment 24
   - 1.3.1 Primary Nonclinical Toxicity Findings 25
   - 1.3.2 Potential Risks for Clinical Toxicities 26
   - 1.3.2.1 Infections 27
   - 1.3.2.2 Vaccinations 27
   - 1.3.2.3 Bleeding 27
   - 1.3.2.4 Cytopenias 27
   - 1.3.2.5 Gastrointestinal Effects 28
   - 1.3.2.6 Hepatotoxicity 28
   - 1.3.2.7 Cardiovascular Effects 28
   - 1.3.2.8 Vascular Inflammation 29
   - 1.3.2.9 Malignancy 29

2. OBJECTIVES AND ENDPOINTS 29

3. STUDY DESIGN 30
   - 3.1 Description of the Study 30
   - 3.1.1 Internal Monitoring Committee and Scientific Oversight Committee 32
   - 3.2 End of Study and Length of Study 32
   - 3.3 Rationale for Study Design 33
   - 3.3.1 Rationale for GDC-0853 Dose and Schedule 33
   - 3.3.2 Rationale for Open-Label Design 34

3.3.3 Rationale for PK Sample Collection Schedule 34
3.3.4 Rationale for Other Study Design Elements 34
3.3.4.1 Efficacy Measurements 34
3.3.4.2 Corticosteroid Taper 35
3.3.4.3 Additional Clinical Outcomes Assessments 35
3.3.4.4 Concomitant Medication Rationale 35
4. MATERIALS AND METHODS 36
4.1 Patients 36
4.1.1 Inclusion Criteria 36
4.1.2 Exclusion Criteria 37
4.2 Study Treatment 39
4.2.1 Formulation, Packaging, and Handling 39
4.2.2 Dosage, Administration, and Compliance 39
4.2.2.1 GDC-0853 Dose and Administration 39
4.2.2.2 GDC-0853 Compliance 40
4.2.2.3 Background Standard of Care Therapy 40
4.2.2.4 Background Standard of Care Therapy Compliance 43
4.2.3 Investigational Medicinal Product Accountability 43
4.2.4 Continued Access to GDC-0853 43
4.3 Concomitant Therapy, Prohibited Food, and Additional Restrictions 44
4.3.1 Permitted Therapy 44
4.3.1.1 Antimalarials 45
4.3.1.2 Mycophenolate Mofetil/Mycophenolic Acid 45
4.3.1.3 Azathioprine 45
4.3.1.4 Methotrexate 45
4.3.1.5 Non-Steroidal Anti-Inflammatory Drugs 45
4.3.1.6 ACE Inhibitors and ARBs 45
4.3.1.7 Dietary Supplements 45
4.3.1.8 Acid Reducing Agents 46
4.3.2 Prohibited Therapy 46
4.3.2.1 Live or Attenuated Vaccinations 47

4.3.2.2 CYP3A Inhibition 47
4.3.3 Prohibited Food 48
4.3.4 Additional Restrictions 48
4.4 Study Assessments 48
4.4.1 Informed Consent Forms and Screening Log 48
4.4.2 Physical Examinations 49
4.4.3 Vital Signs 49
4.4.4 Tuberculin Purified Protein Derivative Skin Test 49
4.4.5 SLE Disease Activity Assessments 49
4.4.5.1 BILAG-2004 Index 50
4.4.5.2 SLEDAI-2K and SELENA-SLEDAI Flare Index 50
4.4.5.3 Glucocorticoid Toxicity Change Index 51
4.4.5.4 SLICC/ACR Damage Index for Systemic Lupus Erythematosus 51
4.4.5.5 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) 51
4.4.5.6 Physician's Global Assessment (PGA) 51
4.4.5.7 Patient's Global Assessment 51
4.4.6 Systemic Lupus Erythematosus Responder Index (SRI) 52
4.4.6.1 Optional Photography 52
4.4.7 Laboratory, Biomarker, and Other Biological Samples 52
4.4.8 Electrocardiograms 54
4.4.9 Patient-Reported Outcomes 55
4.4.10 Samples for Research Biosample Repository 55
4.4.10.1 Overview of the Research Biosample Repository 55
4.4.10.2 Approval by the Institutional Review Board or Ethics Committee 56
4.4.10.3 Sample Collection 56
4.4.10.4 Confidentiality 56
4.4.10.5 Consent to Participate in the Research Biosample Repository 57
4.4.10.6 Withdrawal from the Research Biosample Repository 57

4.4.10.7 Monitoring and Oversight 57
4.5 Treatment, Patient, Study, and Site Discontinuation 58
4.5.1 Study Treatment Discontinuation 58
4.5.2 Patient Discontinuation from Study 59
4.5.3 Study Discontinuation 59
4.5.4 Site Discontinuation 60
5. ASSESSMENT OF SAFETY 60
5.1 Safety Plan 60
5.1.1 Safety Plan for Potential Risks Associated with GDC-0853 60
5.1.1.1 Infections 60
5.1.1.2 Vaccinations 61
5.1.1.3 Bleeding 62
5.1.1.4 Cytopenias 63
5.1.1.5 Gastrointestinal Effects 64
5.1.1.6 Hepatotoxicity 64
5.1.1.7 Cardiovascular Effects 65
5.1.1.8 Vascular Inflammation 65
5.1.1.9 Malignancy 66
5.1.2 Management of Study Treatment in Patients Who Experience Specific Adverse Events 66
5.2 Safety Parameters and Definitions 70
5.2.1 Adverse Events 71
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 71
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 72
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 72
5.3.1 Adverse Event Reporting Period 73
5.3.2 Eliciting Adverse Event Information 73
5.3.3 Assessment of Severity of Adverse Events 73
5.3.4 Assessment of Causality of Adverse Events 74

5.3.5 Procedures for Recording Adverse Events 75
5.3.5.1 Diagnosis versus Signs and Symptoms 75
5.3.5.2 Adverse Events That Are Secondary to Other Events 75
5.3.5.3 Persistent or Recurrent Adverse Events 76
5.3.5.4 Abnormal Laboratory Values 76
5.3.5.5 Abnormal Vital Sign Values 77
5.3.5.6 Abnormal Liver Function Tests 78
5.3.5.7 Deaths 78
5.3.5.8 Preexisting Medical Conditions 78
5.3.5.9 Lack of Efficacy or Worsening of Lupus 79
5.3.5.10 Hospitalization or Prolonged Hospitalization 79
5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration 79
5.3.5.12 Patient-Reported Outcome Data 80
5.4 Immediate Reporting Requirements from Investigator to Sponsor 80
5.4.1 Emergency Medical Contacts 80
5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 81
5.4.2.1 Events That Occur prior to Study Drug Initiation 81
5.4.2.2 Events That Occur after Study Drug Initiation 81
5.4.3 Reporting Requirements for Pregnancies 81
5.4.3.1 Pregnancies in Female Patients 81
5.4.3.2 Pregnancies in Female Partners of Male Patients 82
5.4.3.3 Congenital Anomalies/Birth Defects and Abortions 82
5.5 Follow-Up of Patients after Adverse Events 82
5.5.1 Investigator Follow-Up 82
5.5.2 Sponsor Follow-Up 83
5.6 Adverse Events That Occur after the Adverse Event Reporting Period 83
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 83

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 84
6.1 Determination of Sample Size 84
6.2 Summaries of Conduct of Study 84
6.3 Summaries of Demogaphic and Baseline Characteristics 84
6.4 Safety Analyses 84
6.5 Efficacy Analyses 84
6.6 Pharmacokinetic Analyses 85
6.7 Interim Analysis 85
7. DATA COLLECTION AND MANAGEMENT 85
7.1 Data Quality Assurance 85
7.2 Electronic Case Report Forms 86
7.3 Source Data Documentation 86
7.4 Use of Computerized Systems 86
7.5 Retention of Records 87
8. ETHICAL CONSIDERATIONS 87
8.1 Compliance with Laws and Regulations 87
8.2 Informed Consent 87
8.3 Institutional Review Board or Ethics Committee 88
8.4 Confidentiality 89
8.5 Financial Disclosure 89
9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 90
9.1 Study Documentation 90
9.2 Protocol Deviations 90
9.3 Site Inspections 90
9.4 Administrative Structure 90
9.5 Publication of Data and Protection of Trade Secrets 90
9.6 Protocol Amendments 91
10. REFERENCES 92

LIST OF TABLES

Table 1 Objectives and Corresponding Endpoints 29
Table 2 Permitted Dose Ranges for Immunosuppressant and Antimalarial Medications 44
Table 3 Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events 67
Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE 74
Table 5 Causal Attribution Guidance 75

LIST OF FIGURES

Figure 1 Study Schema 32

LIST OF APPENDICES

Appendix 1 Schedule of Activities 96
Appendix 2 Types and Doses of Standard Oral Treatments for Systemic Lupus Erythematosus Permitted in Study 101
Appendix 3 Glucocorticoid Toxicity Change Index 102
Appendix 4 Suggested Prednisone Taper Schedule Achieving < 10 mg/day by 12 Weeks 109
Appendix 5 Childbearing Potential, Pregnancy Testing, and Contraception 110
Appendix 6 Bottle and Label Configuration for GDC-0853 Administration 112
Appendix 7 Concomitant Medications (Including Foods and Herbal Products) 113
Appendix 8 Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus 115
Appendix 9 BILAG-2004 Index Glossary 119
Appendix 10 Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) 138
Appendix 11 SELENA-SLEDAI Flare Index (SFI) 150

Appendix 12 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) 151
Appendix 13 Physician's Global Assessment 154
Appendix 14 Patient's Global Assessment 156
Appendix 15 Concomitant Medications (Including Foods and Herbal Products) 157

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE II, OPEN-LABEL EXTENSION STUDY OF PATIENTS PREVIOUSLY ENROLLED IN STUDY GA30044 TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS**
PROTOCOL NUMBER:	GA30066
VERSION NUMBER:	1
EUDRACT NUMBER:	2017-001764-37
IND NUMBER:	130011
TEST PRODUCT:	GDC-0853 (RO7010939)
MEDICAL MONITOR:	[redacted], M.D.
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, OPEN-LABEL EXTENSION STUDY OF PATIENTS PREVIOUSLY ENROLLED IN STUDY GA30044 TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF GDC-0853 IN PATIENTS WITH MODERATE TO SEVERE ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS**
PROTOCOL NUMBER:	GA30066
VERSION NUMBER:	1
EUDRACT NUMBER:	2017-001764-37
IND NUMBER:	130011
TEST PRODUCT:	GDC 0853 (RO7010939)
PHASE:	Phase II
INDICATION:	Systemic Lupus Erythematosus
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This open-label extension (OLE) study will evaluate the long-term safety and efficacy of GDC-0853 in patients with moderate to severe active systemic lupus erythematosus (SLE). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Objective (Safety)	
• To evaluate the long-term safety of GDC-0853 over an extended treatment period of up to 48 weeks	• The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results during and following GDC-0853 administration
Secondary Objective (Efficacy)	
• To evaluate the clinical efficacy of GDC-0853 in combination with SOC over time	• SRI-4 response up to Week 48
Exploratory Efficacy Objectives	
• To evaluate if GDC-0853 leads to decreased steroid usage and is steroid sparing	• Change in cumulative steroid dose use up to Week 48 • To assess glucocorticoid toxicity at Weeks 12, 24, 36, and 48 using the GTCI
• To evaluate the ability of GDC-0853 to prolong the time to first SLE flare and reduce the number of total SLE flares	• Flares as defined by the SFI and BILAG during the OLE study

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives (cont.)	
• To evaluate the ability of GDC-0853 to prevent systemic damage	• Change in SLICC/ACR Damage Index up to Week 48
• To evaluate the ability of GDC-0853 to improve cutaneous manifestations of SLE	• Change in CLASI Total Activity Score up to Week 48
• To evaluate the ability of GDC-0853 to improve Patient's Global Assessment	• Change in Patient's Global Assessment of disease activity up to Week 48
Pharmacokinetic Objective	
• To characterize the pharmacokinetics of GDC-0853 in patients using a population PK approach	• Steady-state PK parameters: $AUC_{0\text{-}t}$, C_{trough}, $t_{1/2}$, and apparent CL/F
Exploratory Pharmacokinetic Objective	
• To evaluate the relationship between measures of drug exposure and efficacy and safety of GDC-0853	• 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

ACR = American College of Rheumatology; $AUC_{0\text{-}t}$ = area under the concentration–time curve from time 0 to time *t*; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CL/F = apparent clearance; C_{trough} = steady-state concentration at the end of a dosing interval; GTCI = Glucocorticoid Toxicity Change Index; OLE = open-label extension; PK = pharmacokinetic; SFI = Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index Flare Index; SLE = systemic lupus erythematosus; SLICC = Systemic Lupus International Collaborating Clinics; SOC = standard of care; SRI = SLE Responder Index; $t_{1/2}$ = half-life.

Study Design

Description of Study

This is a Phase II, multicenter, OLE study to evaluate the long-term safety and efficacy of GDC-0853 in patients with SLE who have completed Study GA30044 up to 48 weeks. The population for this study consists of patients with moderate to severe active SLE who have been taking SOC therapy in combination with study medication in Study GA30044.

This OLE study will be conducted at sites that have enrolled patients in the double-blind, Phase II Study GA30044. The maximum number of patients enrolling in this study will be approximately 240 patients. Patients will be assigned the same patient number they had in Study GA30044.

Eligible patients who elect to participate will be enrolled directly into Study GA30066 after completing 48 weeks of study treatment in Study GA30044 rather than enrolling in the safety follow-up period for the blinded study. Patients will receive open-label GDC-0853 at 200 mg BID for 48 weeks, followed by a safety follow-up period of 8 weeks.

Dose reductions or discontinuations of GDC-0853 will occur, either temporarily or permanently, for specific safety reasons. Dose reductions may also be permitted on the basis of other clinical safety concerns of the investigator, only after discussion with the Medical Monitor. Investigators

are encouraged to call the Medical Monitor before discontinuing GDC-0853. If GDC-0853 dosing is reduced or interrupted during the OLE, it may be resumed or increased back to baseline if permitted by the Medical Monitor, based on the clinical context.

Patients should be encouraged to remain stable on their background therapies (e.g., antimalarials, immunosuppressants), but they will be allowed to change doses, discontinue, and/or switch to other permitted immunosuppressant therapies during the OLE if clinically indicated. Certain doses and combinations of immunosuppressants are not allowed with GDC-0853. Patients requiring escape therapy may switch to or add certain other permitted therapies (IV or oral corticosteroids [OCSs], or permitted immunosuppressants while continuing GDC-0853. If any prohibited medications are used, GDC-0853 must be discontinued.

Patients who enter the OLE study on prednisone $>$ 10 mg/day or equivalent OCS should be encouraged to taper their OCS, with the goal of achieving an OCS dose of $<$ 10 mg/day prednisone or equivalent.

Number of Patients

Up to approximately 240 patients from Study GA30044 can be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–76 years, inclusive, at time of signing Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Completion of Study GA30044 up to 48 weeks
- Acceptable safety and tolerability during Study GA30044 as determined by the investigator
- Women of childbearing potential must have a negative urine pregnancy test at baseline

  A serum pregnancy test is needed on Day 1 only if the urine pregnancy test is positive.
- For women of childbearing potential (including those who have had a tubal ligation): Agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<$ 1% per year during the treatment period and for at least 60 days after the last dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 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, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. 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 postovulation 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 (including those who have had a tubal ligation) 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.

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 postovulation 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:

- Met protocol-defined treatment-stopping criteria during Study GA30044
- An adverse event in Study GA30044 that required permanent discontinuation of study drug
- During Study GA30044, treatment with any therapy that is prohibited in this study
- In the opinion of the investigator, any new (since initially enrolling in the Phase II Study GA30044), significant, uncontrolled comorbidity or new clinical manifestation (related to SLE or not) that 1) requires medications not allowed in this protocol or 2) could put the patient at undue risk from a safety perspective

  If the Principal Investigator has questions related to exclusion, he or she should consult the Medical Monitor.
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of study drug
- Any uncontrolled or clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study in the opinion of the investigator in consultation with the Medical Monitor
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within the last 4 weeks of Study GA30044
- Evidence of active, latent, or inadequately treated infection with *Mycobacterium tuberculosis* (TB) as defined as follows:
  - A positive QuantiFERON®–TB Gold (QFT) or T-SPOT® TB test or a Mantoux purified protein derivative (PPD) skin test (performed per Centers for Disease Control and Prevention [CDC] guidelines using 5 tuberculin units per 0.1 mL) result of $\geq$ 5 mm of induration, performed at the Week 44 visit of Study GA30044 or later, prior to entry into Study GA30066
  - Patients with a history of bacillus Calmette-Guérin vaccination should be screened using the QFT test only.
  - A positive QFT test should be considered a positive diagnostic TB test.
  - If initial QFT is indeterminate, perform a confirmatory test with either QFT or T-SPOT. The Principal Investigator 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 borderline or positive T-SPOT test should be considered a positive diagnostic TB test.
- Patients who experienced a de novo or reactivated serious viral infection, such as hepatitis B virus or hepatitis C virus (HCV) during Study GA30044

  Positive hepatitis B surface antigen (HBsAg) or hepatitis C serology (regardless of treatment status) or positive hepatitis B core antibody (HBcAb) (tested at Week 44 of Study GA30044 or later, prior to entry into Study GA30066) are exclusionary.

- Patients who developed a malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin) during the Phase II Study GA30044
- 12-lead ECG at the Week 48 visit of Study GA30044 that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including the following:

  QTcF > 440 msec demonstrated by at least two ECGs > 30 minutes apart
- Current treatment with medications that are well known to prolong the QT interval 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 CredibleMeds® Web site: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf.
- 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
- Laboratory values from the Week 44 visit of Study GA30044 (which may be repeated once at a later unscheduled visit, if necessary) that meet the following criteria:
  - AST or ALT > 1.5 × ULN (unless due to known autoimmune hepatitis)
  - Total bilirubin > 1.2 ULN
  - Amylase or lipase > 2 × ULN
  - Hemoglobin < 7 g/dL
  - ANC < 1.5×10^9/L
  - Absolute lymphocyte count (ALC) < 0.5×10^9/L
  - Platelet count < 50,000/μL

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur 56 weeks after the last patient is enrolled.

Length of Study

The maximum time in the study for a patient is 56 weeks, including treatment for 48 weeks and an 8-week safety follow-up period after the last dose of GDC-0853. The total length of the study, from enrollment of the first patient to the end of the study, is expected to be approximately 3.5 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

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

Non-Investigational Medicinal Products

Corticosteroids

Patients who enter the OLE study on prednisone > 10 mg/day or equivalent OCS should be encouraged to taper their OCS, with the goal of achieving an OCS dose of < 10 mg/day prednisone or equivalent.

Burst Treatment

In the case of increased disease activity, the patient will have the opportunity to receive burst treatment (defined as an increase or new dose of oral prednisone or equivalent), in addition to the study treatment. 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:

- A burst is defined as an increase or new dose of oral prednisone up to 40 mg/day (or equivalent).

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 Immunosuppressant Review and/or Corticosteroid Medication eCRFs. Patients receiving the following escape therapies, after informing the Medical Monitor, will be allowed to remain on study drug but will be considered a protocol-defined “non-responder” in the secondary efficacy analysis:

- IV steroids
- OCS doses exceeding the limits described in the study

New or increased doses of an immunosuppressant medication up to the maximum allowed in the study.

Statistical Methods

Primary Analysis

The analyses will include all patients who received at least one dose of the study drug during this OLE study. Safety will be analyzed based on reported/documented adverse events including AESIs, and changes in laboratory results, ECGs, physical findings, and vital signs.

Determination of Sample Size

No formal sample size calculations were performed for this OLE study. The maximum number of patients eligible for enrollment is approximately 240 (i.e., all patients enrolled in Study GA30044).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	angiotensin converting enzyme
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ARB	angiotensin receptor blocker
ARC	American College of Rheumatology
AUC_{0-24}	area under the concentration–time curve from time 0 to 24 hours
BCR	B-cell receptor
BID	twice a day
BILAG	British Isles Lupus Assessment Group
BTK	Bruton's tyrosine kinase
C_{max}	maximum concentration observed
CDC	Centers for Disease Control and Prevention
CIA	collagen-induced arthritis
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CTCAE	Common Terminology Criteria for Adverse Events
DLAE	dose-limiting adverse event
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FcγR	Fc gamma receptor
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GTCI	Glucocorticoid Toxicity Change Index
H_2RA	H_2-receptor antagonist
HbA1c	glycosylated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
ICH	International Council for Harmonisation
IFN	interferon
IL	interleukin
IMC	Internal Monitoring Committee

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IxRS	interactive voice or Web-based response system
MAD	multiple-ascending dose
MCH	mean corpuscular hemoglobin
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NZB	New Zealand Black
NZW	New Zealand White
OCS	oral corticosteroid
OLE	open-label extension
PD	pharmacodynamic
PGA	Physician's Global Assessment
PK	pharmacokinetic
PPD	purified protein derivative
PPI	proton pump inhibitor
PRO	patient-reported outcome
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
QFT	QuantiFERON®–TB Gold
QD	once a day, daily
RA	rheumatoid arthritis
RBR	Research Biosample Repository
SAD	single-ascending dose
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SFI	SELENA-SLEDAI Flare Index
SLE	systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOC	standard of care
SRI	SLE Responder Index
TB	tuberculosis

Abbreviation	Definition
TLR	toll-like receptor
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
VAS	visual analogue scale
WGS	whole genome sequencing
XLA	X-linked agammaglobulinemia

1. BACKGROUND

1.1 BACKGROUND ON SYSTEMIC LUPUS ERYTHEMATOSUS

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 people 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. Antimalarial 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 immunosuppressant 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 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. Patients with XLA 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.

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 Fc gamma receptor (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, and Waldenstrom 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 toll-like receptor (TLR) 4-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 Fc epsilon receptor leads to activation and upregulation 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 the GDC-0853 Investigator's Brochure).

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 (IFN)-alpha–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 IFN signature in peripheral blood mononuclear cells.

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 systems; 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 (QTc) interval in dogs (7 msec or 3%; extrapolated unbound maximum observed concentration [C_{max}] of 3.17 μM). Fetal malformations in rats (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 parent Study GA30044 and the current study (GA30066).

1.2.3 Clinical Experience with GDC-0853

As of 10 May 2017, GDC-0853 or placebo has been administered to 406 subjects (i.e., 203 healthy subjects, 24 patients with hematological malignancies, 172 patients with RA, and 7 patients with SLE) 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), 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 the SAD and MAD healthy volunteer studies, there were no DLAEs, serious 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 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 9 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 2 deaths during the study due to complications of confirmed influenza (H1N1 influenza and influenza pneumonia). As of May 2017, 6 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).

GDC-0853 is also being investigated in two ongoing Phase II trials in RA (blinded, placebo-controlled Study GA29350 and open-label extension [OLE] Study GA30067) and in SLE (blinded, placebo-controlled Study GA30044). As of 10 May 2017, 172 patients with RA had received GDC-0853/placebo in Study GA29350; 53 of these patients have entered Study GA30067 and received open-label GDC-0853. An additional 7 patients with SLE have received GDC-0853/placebo in Study GA30044. Reported adverse events in the three trials have been mostly non-serious, mild, and self-limiting. In the blinded trials, there has been one reported severe adverse event (infection) and two Grade 3 adverse events (elevations in ALT/AST).

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 the parent Phase II study (GA30044) is to evaluate the safety and efficacy of GDC-0853 in combination with standard of care (SOC) in patients with moderate to severe SLE. The study tests two dose levels of GDC-0853 in comparison with placebo when added to background SOC. The study was powered to detect a meaningful clinical benefit in a composite measure of disease activity across multiple organ systems (see Section 3.3.4.1) and includes multiple safety assessments and monitoring by an unblinded Internal Monitoring Committee (IMC) and a Scientific Oversight Committee.

This OLE Study GA30066 will evaluate the long-term safety and efficacy of GDC-0853 in patients with SLE who have completed the ongoing, blinded Phase II Study GA30044. In this study, all patients will receive GDC-0853 starting at a dose of 200 mg twice a day (BID) for up to 48 weeks of treatment. Patients will be allowed to continue and adjust their background SOC therapy.

Inhibition of BTK offers a promising mechanism for the treatment of autoimmune diseases, such as RA and SLE (see the GDC-0853 Investigator's Brochure); 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 long-term treatment of patients will induce depletion. Therefore, IgG levels will be carefully 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. Ongoing clinical studies include Phase II studies in SLE (GA30044), RA (GA29350 and GA30067), and chronic spontaneous urticaria (GS39684), as well as clinical pharmacology studies in healthy volunteers. Based on the compelling mechanism for BTK inhibition in SLE and the promising results in NZB/NZW lupus-prone mice, the benefit–risk 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. 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 are 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 Igs 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 were 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 ALT, 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, 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 patient exposure is limited, so the safety profile in patients with SLE is unknown. However, there are several potential risks on the basis of the expected mechanism of action of GDC-0853, published literature for similar molecules, and nonclinical and clinical studies with GDC-0853. 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). 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 patients with marked baseline lymphopenia. Total Ig concentrations will also be measured regularly throughout the study. During this study, any serious infection, any infection requiring IV antimicrobials, or any opportunistic infection will be considered an adverse event of special interest (AESI) and will require expedited reporting to the Sponsor (see Section 5.4.2).

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. 2011) 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, and varicella) within 6 weeks before planned dosing in Study GA30044.

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, 2 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 CBCs will be monitored regularly throughout the study.

1.3.2.5 Gastrointestinal Effects

Healthy subjects in the MAD 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 did not lead to study drug discontinuation. Patients will be monitored for GI side effects throughout this study.

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 the SAD study, the MAD study for 14 days in healthy subjects, and a study of hematologic malignancies with daily dosing for over 1 year in patients, there have been no adverse events of liver enzyme elevations or trends towards elevations in laboratory evaluations. In Study GA29350, there have been 2 cases of Grade 3 elevations in AST and ALT levels in RA patients on methotrexate, out of a total of 172 patients (as of data cutoff: 10 May 2017), but as the study is still blinded, association with GDC-0853 cannot yet be determined. 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 (see Section 4.1.1). 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 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 (QT interval corrected using Fridericia's formula) intervals. Cardiac safety will be evaluated in all patients at baseline and throughout the study with routine monitoring of vital signs, including pulse 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 (see Section 5.4.2).

2. OBJECTIVES AND ENDPOINTS

This OLE study will evaluate the long-term safety and efficacy of GDC-0853 in patients with moderate to severe active SLE. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective (Safety)	
• To evaluate the long-term safety of GDC-0853 over an extended treatment period of up to 48 weeks	• The nature, frequency, severity, and timing of adverse events • Changes in vital signs, physical findings, ECGs, and clinical laboratory results during and following GDC-0853 administration
Secondary Objective (Efficacy)	
• To evaluate the clinical efficacy of GDC-0853 in combination with SOC over time	• SRI-4 response up to Week 48
Exploratory Efficacy Objectives	
• To evaluate if GDC-0853 leads to decreased steroid usage and is steroid sparing	• Change in cumulative steroid dose use up to Week 48 • To assess glucocorticoid toxicity at Weeks 12, 24, 36, and 48 using the GTCI
• To evaluate the ability of GDC-0853 to prolong the time to first SLE flare and reduce the number of total SLE flares	• Flares as defined by the SFI and BILAG during the OLE study

Table 1 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives (cont.)	
• To evaluate the ability of GDC-0853 to prevent systemic damage	• Change in SLICC/ACR Damage Index up to Week 48
• To evaluate the ability of GDC-0853 to improve cutaneous manifestations of SLE	• Change in CLASI Total Activity Score up to Week 48
• To evaluate the ability of GDC-0853 to improve Patient's Global Assessment	• Change in Patient's Global Assessment of disease activity up to Week 48
Pharmacokinetic Objective	
• To characterize the pharmacokinetics of GDC-0853 in patients using a population PK approach	• Steady-state PK parameters: $AUC_{0\text{-}t}$, C_{trough}, $t_{1/2}$, and apparent CL/F
Exploratory Pharmacokinetic Objective	
• To evaluate the relationship between measures of drug exposure and efficacy and safety of GDC-0853	• 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

ACR=American College of Rheumatology; $AUC_{0\text{-}t}$=area under the concentration–time curve from time 0 to time *t*; BILAG=British Isles Lupus Assessment Group; CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; CL/F=apparent clearance; C_{trough}=steady-state concentration at the end of a dosing interval; GTCI=Glucocorticoid Toxicity Change Index; OLE=open-label extension; PK=pharmacokinetic; SFI=Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index Flare Index; SLE=systemic lupus erythematosus; SLICC=Systemic Lupus International Collaborating Clinics; SOC=standard of care; SRI=SLE Responder Index; $t_{1/2}$=half-life.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, multicenter, OLE study to evaluate the long-term safety and efficacy of GDC-0853 in patients with SLE who have completed Study GA30044 up to 48 weeks. The population for this study consists of patients with moderate to severe active SLE who have been taking SOC therapy in combination with study medication in Study GA30044.

This OLE study will be conducted at sites that have enrolled patients in the double-blind, Phase II Study GA30044. The maximum number of patients enrolling in this study will

be approximately 240 patients. Patients will be assigned the same patient number they had in Study GA30044.

Eligible patients who elect to participate will be enrolled directly into Study GA30066 after completing 48 weeks of study treatment in Study GA30044 rather than enrolling in the safety follow-up period for the blinded study. Patients will receive open-label GDC-0853 at 200 mg BID for 48 weeks, followed by a safety follow-up period of 8 weeks.

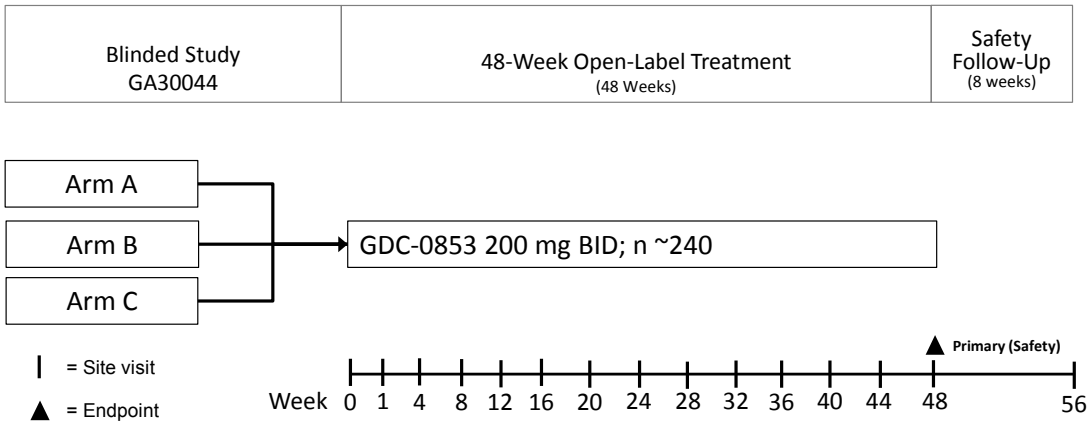
Dose reductions or discontinuations of GDC-0853 will occur, either temporarily or permanently, for specific safety reasons (see Section 5.1.2). Dose reductions may also be permitted on the basis of other clinical safety concerns of the investigator, only after discussion with the Medical Monitor. Investigators are encouraged to call the Medical Monitor before discontinuing GDC-0853. If GDC-0853 dosing is reduced or interrupted during the OLE, it may be resumed or increased back to baseline if permitted by the Medical Monitor, based on the clinical context.

Patients should be encouraged to remain stable on their background therapies (e.g., antimalarials, immunosuppressants), but they will be allowed to change doses, discontinue, and/or switch to other permitted immunosuppressant therapies during the OLE if clinically indicated (see Section 4.2.2.3.1). Certain doses and combinations of immunosuppressants are not allowed with GDC-0853 (see Section 4.3.2). Patients requiring escape therapy may switch to or add certain other permitted therapies (IV or oral corticosteroids [OCSs], or permitted immunosuppressants, see Section 4.1.1) while continuing GDC-0853. If any prohibited medications are used, GDC-0853 must be discontinued.

Patients who enter the OLE study on prednisone $>$ 10 mg/day or equivalent OCS (see Appendix 2), should be encouraged to taper their OCS, with the goal of achieving an OCS dose of $<$ 10 mg/day prednisone or equivalent.

A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



BID = twice a day.

3.1.1 Internal Monitoring Committee and Scientific Oversight Committee

Regular safety reviews for this OLE will be performed by the Sponsor's IMC in combination with the Scientific Oversight Committee as outlined in the IMC-Scientific Oversight Committee Agreement. If necessary, cumulative unblinded data for patients remaining in the parent Study GA30044 may also be made available to IMC and Scientific Oversight Committee members. This committee will include a clinical scientist, in conjunction with a safety scientist, biostatistician, two external SLE experts who are not investigators in this study and statistical programmers from the Sponsor who are not members of the Study Management Team. The committee members will not have direct contact with investigational staff or site monitors. The committee may request that additional Sponsor scientists (e.g., clinical pharmacologist, biomarker) participate in data analysis. This committee will review safety data and make recommendations to the Sponsor regarding continuation of the study and/or study drug dose modifications. After each meeting, either IMC or the 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 (based on analysis of the blinded Study GA30044), or 4) amend the study protocol. For further information, please see the IMC and Scientific Oversight Committee Agreement.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur 56 weeks after the last patient is enrolled.

The maximum time in the study for a patient is 56 weeks, including treatment for 48 weeks and an 8-week safety follow-up period after the last dose of GDC-0853. The total length of the study, from enrollment of the first patient to the end of the study, is expected to be approximately 3.5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for GDC-0853 Dose and Schedule

The GDC-0853 dose of 200 mg BID is the highest dose under evaluation in Study GA30044 and was selected in order to characterize its efficacy, safety, and tolerability profile in a larger patient population and for a longer treatment period. [redacted]

In the event of a safety (e.g., toxicity or intolerance) issue, dose reduction of GDC-0853 to 200 mg QD or lower for an individual patient is permitted in consultation with the Medical Monitor (see Section 5.1.2). This dose was selected because it is expected to reflect what may be a physician-initiated dose reduction in a real-world clinical setting (i.e., changing the dosing interval from BID to QD). [redacted]

In healthy subjects receiving GDC-0853 up to 600 mg in the single-dose Study GP29318 (SAD) and up to 250 mg BID and 500 mg QD for 14 days in the multiple-dose study GA29347 (MAD), the safety profile was acceptable and the drug was well tolerated. No maximum tolerated dose was identified, and there were no DLAEs; all adverse events were Grade 1 (mild) and transient.

Data from experiments evaluating the PD effects and anti-inflammatory activity of a tool BTK inhibitor compound (GDC-0834) in the rat model of CIA suggest that the amount of BTK inhibition anticipated in this study may be sufficient to achieve meaningful anti-inflammatory activity. These studies suggest that 70% BTK inhibition, as measured by phospho-BTK inhibition, is required for half-maximal activity (Liu et al. 2011). However, it is not known whether BTK inhibition in the rat CIA model accurately predicts efficacy in human RA.

Dose levels in this study are anticipated to result in exposures below 36 μM • hr (mean AUC_{0-24}), which is the NOAEL from nonclinical toxicology studies. The NOAEL (36 μM • hr) was defined in the 9-month dog study by vasculitis at higher doses (≥ 56 μM • hr). For further details, see the GDC-0853 Investigator's Brochure.

[redacted]

[redacted]

3.3.2 Rationale for Open-Label Design

The primary objective of Study GA30066 is to understand the long-term safety of GDC-0853 over an extended treatment period of up to 48 weeks. The open-label study design will allow all eligible patients originating from the blinded Study GA30044 to be treated with GDC-0853.

3.3.3 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 aid in exposure-response evaluations in this study and dose-regimen selection for future studies (see Appendix 1).

3.3.4 Rationale for Other Study Design Elements

3.3.4.1 Efficacy Measurements

The secondary efficacy endpoint in this study is the SLE Responder Index (SRI)-4 at Week 48 (see Appendix 10). The SRI-4 response criterion is commonly used in SLE

studies, is accepted by health authorities to measure reduction in SLE disease activity, and is a composite measure that includes the SLE Disease Activity Index 2000 (SLEDAI-2K), British Isles Lupus Assessment Group 2004 (BILAG-2004), and Physician's Global Assessment (PGA). 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 (Burness and McCormack 2011; Navarra et al. 2011; Furie et al. 2015; Khamashta et al. 2016).

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), SELENA-SLEDAI Flare Index (SFI), and patient-reported outcome (PRO) measures (i.e., Patient's Global Assessment). Each of these measures has been well established and validated in previous studies.

3.3.4.2 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 comorbidities and potential adverse events, including in patients in this trial. The Glucocorticoid Toxicity Change Index (GTCI) (Miloslavsky et al. 2017) will be used to determine the potential of GDC-0853 to reduce steroid-induced systemic side effects (see Appendix 3). In addition, 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). Although the investigators can adjust steroids per their discretion based on SLE disease activity to best determine the safety and efficacy of GDC-0853, corticosteroids should be tapered as tolerated during the OLE, with a goal of < 10 mg/day prednisone or equivalent.

3.3.4.3 Additional Clinical Outcomes Assessments

PRO and clinician-reported outcome data will be collected to more fully characterize the clinical profile of GDC-0853.

3.3.4.4 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. Open-label study drug GDC-0853 will be administered 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 for potential toxicities. Patients should be encouraged to remain stable on their background therapies (e.g., antimalarials, immunosuppressants), but they will be allowed to change doses, discontinue, and/or switch to other permitted immunosuppressant therapies during the

OLE if clinically indicated (see Section 4.2.2.3.1). Certain doses and combinations of immunosuppressants are not allowed with GDC-0853 (see Section 4.3.2).

For guidance on concomitant medications that are unrelated to background SOC therapy, please refer to Section 4.3.

4. MATERIALS AND METHODS

4.1 PATIENTS

Up to approximately 240 patients from Study GA30044 can be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (see Section 4.4.1)
- Age 18–76 years, inclusive, at time of signing Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Completion of Study GA30044 up to 48 weeks
- Acceptable safety and tolerability during Study GA30044 as determined by the investigator
- Women of childbearing potential must have a negative urine pregnancy test at baseline

  A serum pregnancy test is needed on Day 1 only if the urine pregnancy test is positive.
- For women of childbearing potential (including those who have had a tubal ligation): Agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<1\%$ per year during the treatment period and for at least 60 days after the last dose of study drug.

  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, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. 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 postovulation 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 (also see Appendix 5)

  Men with female partners of childbearing potential (including those who have had a tubal ligation) 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.

  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 postovulation 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:

- Met protocol-defined treatment-stopping criteria during Study GA30044
- An adverse event in Study GA30044 that required permanent discontinuation of study drug
- During Study GA30044, treatment with any therapy that is prohibited in this study (see Section 4.3.2)
- In the opinion of the investigator, any new (since initially enrolling in the Phase II Study GA30044), significant, uncontrolled comorbidity or new clinical manifestation (related to SLE or not) that 1) requires medications not allowed in this protocol (see Section 4.3.2) or 2) could put the patient at undue risk from a safety perspective

  If the Principal Investigator has questions related to exclusion, he or she should consult the Medical Monitor.
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of study drug
- Any uncontrolled or clinically significant laboratory abnormality that would affect safety, interpretation of study data, or the patient's participation in the study in the opinion of the investigator in consultation with the Medical Monitor
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within the last 4 weeks of Study GA30044
- Evidence of active, latent, or inadequately treated infection with *Mycobacterium tuberculosis* (TB) as defined as follows:
  - A positive QuantiFERON®–TB Gold (QFT) or T-SPOT® TB test or a Mantoux purified protein derivative (PPD) skin test (performed per Centers for Disease

Control and Prevention [CDC] guidelines using 5 tuberculin units per 0.1 mL) result of ≥ 5 mm of induration, performed at the Week 44 visit of Study GA30044 or later, prior to entry into Study GA30066

  - Patients with a history of bacillus Calmette-Guérin vaccination should be screened using the QFT test only.
  - A positive QFT test should be considered a positive diagnostic TB test.
  - If initial QFT is indeterminate, perform a confirmatory test with either QFT or T-SPOT. The Principal Investigator 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 borderline or positive T-SPOT test should be considered a positive diagnostic TB test.

- Patients who experienced a de novo or reactivated serious viral infection, such as hepatitis B virus or hepatitis C virus (HCV) during Study GA30044

  Positive hepatitis B surface antigen (HBsAg) or hepatitis C serology (regardless of treatment status) or positive hepatitis B core antibody (HBcAb) (tested at Week 44 of Study GA30044 or later, prior to entry into Study GA30066) are exclusionary.

- Patients who developed a malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin) during the Phase II Study GA30044
- 12-lead ECG at the Week 48 visit of Study GA30044 that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including the following:

  QTcF > 440 msec demonstrated by at least two ECGs > 30 minutes apart

- Current treatment with medications that are well known to prolong the QT interval 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 CredibleMeds® Web site: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf.

- 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
- Laboratory values from the Week 44 visit of Study GA30044 (which may be repeated once at a later unscheduled visit, if necessary) that meet the following criteria:
  - AST or ALT $> 1.5 \times$ ULN (unless due to known autoimmune hepatitis)
  - Total bilirubin > 1.2 ULN

- Amylase or lipase $> 2 \times$ ULN
- Hemoglobin < 7 g/dL
- ANC $< 1.5 \times 10^9$/L
- Absolute lymphocyte count (ALC) $< 0.5 \times 10^9$/L
- Platelet count $< 50{,}000/\mu$L

4.2 STUDY TREATMENT

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

4.2.1 Formulation, Packaging, and Handling

GDC-0853 will be provided by the Sponsor as 50-mg dose strength tablets.

Tablets will be supplied in bottles, which will be appropriately labeled for this study. GDC-0853 tablets should be stored between 2°C (35.6°F) and 8°C (46.4°F).

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

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 GDC-0853 Dose and Administration

The GDC-0853 dose regimen is oral 200 mg BID. Patients will receive GDC-0853 approximately every 12 hours for approximately 48 weeks. The first open-label dose of GDC-0853 should be the a.m. dose (taken in clinic) during the Week 48 visit of the GA30044 study (which is Day 1 of Study GA30066). 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 and Week 24), patients should be instructed that GDC-0853 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 on the bottle the dose that was missed and notify study staff of any missed doses. Doses that are vomited will be considered missed doses.

A dose reduction of GDC-0853 for specific safety events is permitted (see Table 3). For a potential dose reduction for other adverse events not listed in the table, please consult the Medical Monitor. If dose reduction is indicated, the dose of GDC-0853 may be reduced from 200 mg BID to 200 mg QD or lower (in consultation with the Medical Monitor). If the adverse event resolves and the patient has increased lupus disease activity, it is up to the discretion of the investigator in consultation with the Medical Monitor to decide if the patient can resume the 200 mg BID dosing.

Guidelines for dose reduction and treatment interruption or discontinuation are provided in Section 5.1.2.

GDC-0853 will be orally administered and may be taken with or without food except for the instances (see Appendix 1) where the dose of oral study drug is to be administered at the clinic visit while fasting (≥ 4 hours prior to the clinic visit). The dates and times of the most recent prior meal, last dose of GDC-0853 (prior to clinic visit), and timing of GDC-0853 administration in clinic should be recorded at clinic visits with PK and/or fasting lipid assessments. In addition, any use of PPIs, H_2-receptor antagonists (H_2RAs), and/or short-acting antacids (e.g., Maalox®, Pepto-Bismol®, Rolaids®) should be recorded as concomitant medications, including time and date of last administration prior to the PK clinic visits. Administration of GDC-0853 should be staggered with short-acting antacid use (i.e., GDC-0853 should be taken 2 hours before or 2 hours after the short-acting antacid).

At study visits, sufficient GDC-0853 tablets will be dispensed to complete dosing until the next scheduled visit. When GDC-0853 is administered at the site, it will be administered under supervision of study personnel, and the amount of GDC-0853 dispensed must be recorded.

4.2.2.2 GDC-0853 Compliance

The following measure will be taken to assess patient compliance with study drug: Patients will be directed to bring any used and unused bottles to each visit.

Sites will be responsible for prepopulating the dates on the dosing label (that should be affixed to the bottle) 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 on the affixed label. Refer to Appendix 6 for the bottle and label configuration. The number of tablets issued minus the number of tablets returned will be used to calculate the number of tablets taken and compliance.

Compliance will be documented on the source record.

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. If compliance is ≤80%, the investigator or designee is to counsel the patient and ensure steps are taken to improve compliance.

4.2.2.3 Background Standard of Care Therapy

4.2.2.3.1 Immunosuppressant Therapy

Patients should be encouraged to remain stable on their background therapies (e.g., antimalarials, immunosuppressants), but they will be allowed to change doses, discontinue, and/or switch to other permitted immunosuppressant therapies during the

OLE if clinically indicated (see Section 4.3.1). Certain doses and combinations of immunosuppressants are not allowed with GDC-0853 (see Section 4.3.2).

If dose modification (increase or decrease) of an immunosuppressant is required because of increased clinical disease activity or 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.

4.2.2.3.2 Corticosteroid

Patients who enter the OLE study on prednisone > 10 mg/day or equivalent OCS (see Appendix 2) should be encouraged to taper their OCS, with the goal of achieving an OCS dose of < 10 mg/day prednisone or equivalent. All steroid changes should be captured on the OCS diary (see Section 4.2.2.4).

Any change in steroid dose must be recorded on the Corticosteroid Medication eCRF.

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.

4.2.2.3.3 Burst Treatment

In the case of increased disease activity, the patient will have the opportunity to receive burst treatment (defined as an increase or new dose of oral prednisone or equivalent), in addition to the study treatment. 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:

- A burst is defined as an increase or new dose of oral prednisone up to 40 mg/day (or equivalent, see Appendix 2).

When using corticosteroids as a burst treatment, the investigator may temporarily increase the dose of corticosteroids, and then the investigator should attempt to taper the patient back down to his or her previous corticosteroid dose, ideally within 2 weeks. Patients will continue to receive their designated dose of study treatment (see Section 3.1) during the burst treatment. The previous corticosteroid dose is defined as the dose of corticosteroids taken prior to the burst. If the patient was not previously on corticosteroids, the investigator should attempt to 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 attempt to meet the target OCS dose (< 10 mg/day).

Any changes in steroid doses will be recorded in the Corticosteroid Medication eCRF.

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, the additional corticosteroid treatment in these cases should last no more than 7 days. After resolution of the acute emergent illness, the patient should resume his or her standard OCS dose and taper regimen.

Any dose of steroid higher than the maximum burst levels above 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 considered escape therapy (see Section 4.2.2.3.4) and will be recorded in the Corticosteroid Medication 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 this or any other reason, the Medical Monitor needs to be informed and the reason recorded on the Corticosteroid Medication eCRF (see Section 4.2.2.3.4).

4.2.2.3.4 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 Immunosuppressant Review and/or Corticosteroid Medication eCRFs. Patients receiving the following escape therapies, after informing the Medical Monitor, will be allowed to remain on study drug but will be considered a protocol-defined “non-responder” in the secondary efficacy analysis:

- IV steroids
- OCS doses exceeding the limits described in Section 4.2.2.3.3
- New or increased doses of an immunosuppressant medication up to the maximum allowed in the study (see Section 4.3.1)

NOTE: Any combination of azathioprine, methotrexate, mycophenolate mofetil, or mycophenolic sodium is prohibited during the study while the patient is receiving study treatment (see Section 4.3.2).

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 4.3.2 or any accepted immunosuppressant that exceeds the maximum dose as defined by the protocol or any increase in therapy not approved by the Medical Monitor), the patient should be discontinued from study treatment and return for the 8-week safety follow-up visit (see Section 4.5.1).

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.

4.2.2.4 Background Standard of Care Therapy Compliance

As in Study GA30044, all patients will be expected to continue to record their OCS intake using a diary and as instructed by study staff. Patients will record changes in their OCS dose using a paper diary and as instructed by study staff. OCS usage will be recorded in the Corticosteroid Medication eCRF.

4.2.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (GDC-0853) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the interactive voice and Web-based response system (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.

4.2.4 Continued Access to GDC-0853

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Sponsor study drug GDC-0853 or any other study treatments or interventions to patients who have completed Study GA30066. The Sponsor may evaluate whether to continue providing GDC-0853 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

4.3 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. 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 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.

4.3.1 Permitted Therapy

Concomitant immunosuppressant and antimalarial medications can be used up to the doses shown in Table 2.

Table 2 Permitted Dose Ranges for Immunosuppressant and Antimalarial Medications

Azathioprine	Up to 2.5 mg/kg/day
Methotrexate	Up to 25 mg/week
Mycophenolate mofetil	Up to 2500 mg/day
Mycophenolic sodium	Up to1800 mg/day
Hydroxychloroquine	Up to 400 mg/day
Chloroquine	Up to 250 mg/day
Quinacrine	Up to 200 mg/day
Other	—

Note: Other medications may be permitted (in consultation with the Medical Monitor).

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 4.3.2)

4.3.1.1 Antimalarials

Antimalarial medications (e.g., hydroxychloroquine, chloroquine, quinacrine), including combinations of up to two antimalarials, are permitted. Replacement of one antimalarial 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.

4.3.1.2 Mycophenolate Mofetil/Mycophenolic Acid

Patients who are taking mycophenolate mofetil (or mycophenolic acid) at permitted doses (see Table 2) will be eligible to participate in the OLE. 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 interact with oral contraceptives, decreasing 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.

4.3.1.3 Azathioprine

Prior to starting azathioprine, it is strongly recommended to test patients 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.

4.3.1.4 Methotrexate

To prevent methotrexate-associated adverse events, all patients on methotrexate are required to take folic acid or equivalent (e.g., 1 mg/day) at a stable dose of at least 5 mg/week or equivalent.

4.3.1.5 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).

4.3.1.6 ACE Inhibitors and ARBs

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 throughout the first half of the trial whenever possible.

4.3.1.7 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 7 for a list of prohibited concomitant medications, including herbal products, as well as Section 4.3.2.2). 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.

4.3.1.8 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 H_2RAs at up to the maximum recommended dose according to local labeling. The dose is recommended to remain stable throughout the study. At visits with scheduled PK assessments (see Appendix 1), any use of PPIs (see Section 4.2.2.1), H_2RA, and/or short-acting antacids should be recorded as concomitant medications, including the date and time of last administration prior to the clinic visit.

4.3.2 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 7. Biologic response modifiers and disease-modifying antirheumatic drugs other than 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 biological agents (e.g., tumor necrosis factor inhibitors, IL-17, IL-12/23, abatacept, denosumab) including 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
- 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
- Any combination of azathioprine, methotrexate, mycophenolate mofetil, or mycophenolic sodium

Please see Appendix 7 for additional prohibited therapies during this study.

4.3.2.1 Live or Attenuated Vaccinations

Immunization with a live or attenuated vaccine is prohibited within 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.

4.3.2.2 CYP3A Inhibition

In vitro studies suggest that GDC-0853 is a CYP3A inhibitor with inhibitory constant values of approximately 10 μM (Study 13-0384). [redacted]; however, it is possible that GDC-0853 inhibition of CYP3A may alter the metabolism of CYP3A substrates, including estrogen derivatives, such as ethinylestradiol, subsequently leading to an increase in plasma concentrations of these drugs (see the GDC-0853 Investigator's Brochure).

There is a moderate to high potential for a drug–drug interaction with any medication that is metabolized by CYP3A. Plasma concentrations of the medications in the following categories (listed in detail in Appendix 7) may increase; therefore, they should be used with caution unless otherwise specified in Section 4.3.2:

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

Ethinylestradiol is metabolized by CYP3A; therefore, plasma concentrations may increase in the presence of GDC-0853. The use of hormone-replacement therapy containing ethinylestradiol or hormonal contraceptives containing ethinylestradiol, with the concomitant use of a barrier method, is permitted during this study (see Appendix 5); however, these agents should be used with caution and 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 because CYP-mediated oxidation appears to be a relatively minor component of orally administered ethinylestradiol (Zhang et al. 2007). Although contraceptive efficacy is not expected to be impacted, increased ethinylestradiol plasma concentrations may lead to an increase in common side effects, such as nausea, breast tenderness, and headaches, and to a theoretical increase in rare dose-related events, such as thromboembolism (Inman et al. 1970).

In vitro data suggest that GDC-0853 is metabolized by CYP3A and there is a moderate to high 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 7 should be avoided until the last dose of study drug. 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.

- Moderate or strong CYP3A inhibitors
- Moderate or strong CYP3A inducers

The medications listed in Appendix 7 are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP3A. The investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

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

4.3.3 Prohibited Food

Use of the following foods is prohibited during the study due to their effects on the CYP450 3A4 enzyme, which is involved in GDC-0853 metabolism: grapefruit, Seville orange, pomegranate, or star fruit juice or products, which all contain furanocoumarin derivatives. Please refer to Appendix 7 for additional information.

4.3.4 Additional Restrictions

It is strongly recommended that patients be fasting ≥4 hours prior to fasting lipid draws as well as predose PK draws (see Appendix 1).

4.4 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

4.4.1 Informed Consent Forms and Screening Log

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. 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.

Patients entering the OLE study may be consented after meeting entry criteria for Study GA30066, which may include use of qualifying test results from the Week 44 visit or later from Study GA30044.

4.4.2 Physical Examinations

A complete physical examination should be performed on Day 1 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.

4.4.3 Vital Signs

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

4.4.4 Tuberculin Purified Protein Derivative Skin Test

Testing for TB should only be performed during Study GA30066 if it did not take place at the Week 44 visit or later in Study GA30044. The QFT should be used as the screening test for TB (if this was the initial method for testing in Study GA30044) 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 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.

4.4.5 SLE Disease Activity Assessments

The following applicable SLE disease activity assessments will be used in this study: BILAG-2004, SLEDAI-2K, SFI, GTCI, Systemic Lupus International Collaborating Clinics (SLICC), CLASI, PGA, and Patient's Global Assessment. Throughout the study, each assessment ideally should be conducted by the same assessor, 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 parent Study GA30044 for versions used in this study.

Investigators who have completed the disease assessment trainings during the main Study GA30044 or up to 2 years prior to the beginning of the Study GA30044 do not need to retake the training.

4.4.5.1 BILAG-2004 Index

The BILAG-2004 Index will be used as a method to assess disease activity in this study.

The BILAG-2004 assesses 97 clinical signs, symptoms, and laboratory parameters across 9 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 9 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-2004 will be provided as described in Appendix 9 and Section 4.4.5.

4.4.5.2 SLEDAI-2K and SELENA-SLEDAI Flare Index

SLEDAI-2K measures disease activity at the visit or within the preceding 28 days.

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

Detailed instructions and training on the use of the SLEDAI-2K will be provided during training sessions at each investigator meeting (for the parent Study GA30044) and through online resources. It is critical that investigators have a thorough understanding of both the SLEDAI-2K and the SFI and the differences between them. The investigators who trained during the Investigators Meeting for the main Study GA30044 and/or who are using the online resources available for the main Study GA30044 do not need to take the training again.

The SFI will be modified such that severe flares triggered only by an increase in SLEDAI-2K score to >12 alone 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.

4.4.5.3 Glucocorticoid Toxicity Change Index

The GTI is an exploratory standardized measure of damage related to use of glucocorticoids (see Appendix 3). 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 SOC and patient phenotype.

4.4.5.4 SLICC/ACR Damage Index for Systemic Lupus Erythematosus

The SLICC/American College of Rheumatology (ACR) Damage Index for SLE will be utilized to assess organ damage as opposed to the collection of disease activity (see Appendix 8). Damage is defined as non-reversible change not related to active inflammation.

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

The CLASI is an instrument designed to capture SLE-specific mucocutaneous disease manifestations (see Appendix 12). 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 activities 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 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 entering in the OLE study who has not completed the training during Study GA30044 or within 2 years from the beginning of Study GA30044.

4.4.5.6 Physician's Global Assessment (PGA)

The PGA (see Appendix 13) 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 that is gradated 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.

4.4.5.7 Patient's Global Assessment

The Patient's Global Assessment is a VAS (see Appendix 14). 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" (symptom-free) and the right–hand extreme as "Maximum."

4.4.6 Systemic Lupus Erythematosus Responder Index (SRI)

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 BILAG-2004, SLEDAI-2K, and PGA (Sections, 4.4.5.1; 4.4.5.2; 4.4.5.6 to measure response to treatment. The SRI-4 primary endpoint defines response as meeting each of the following criteria at Week 48 compared with baseline:

- $\geq$4 point reduction in SLEDAI-2K score, and
- No new BILAG A organ domain score or two new BILAG B organ domain scores, and
- No worsening (worsening defined as a $>$0.3 point increase) in the PGA.

4.4.6.1 Optional Photography

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 who sign the optional photography consent and is contingent on Institutional Review Board or Ethics Committee (IRB/EC) approval.

4.4.7 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments will be performed as indicated in the schedule of activities (see Appendix 1). 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 (e.g., pain questionnaires). On Week 24, PRO assessments will follow PK sample collection and treatment administration (see Appendix 1).

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

- ESR

  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

  Urine pregnancy tests will be performed at specified visits for women of childbearing potential (including those who have had a tubal ligation). 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

  The direct Coombs test will be performed at a local laboratory per the SOA and should be used if the patient develops anemia that may be autoimmune in etiology.

- T-SPOT test for TB

  The T-SPOT test may be performed at a local laboratory (optional, if not performed at the Week 44 visit or later in Study GA30044).

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

- Anti-double stranded DNA
- 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), blood urea nitrogen, creatinine, glucose, ALT, AST, amylase, lipase, total and direct bilirubin, ALP, GGT, albumin, globulin, total protein, calcium, uric acid
- CK, aldolase, and LDH
- Coagulation panel: INR, aPTT, PT
- High sensitivity C-reactive protein
- Fasting Lipids: triglycerides, HDL, LDL, glycosylated hemoglobin ($HbA1_C$), and total cholesterol
- Hematology: hemoglobin, hematocrit, RBC count, calculated indices (mean corpuscular volume, mean corpuscular hemoglobin [MCH], MCH concentration, red cell distribution width), platelets, WBC with differential
- Immunology: total Igs, IgG, IgM, IgE, and IgA
- T, B, and natural killer cells
- 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, hepatitis B surface antibody, and HCV antibody (if not performed at the Week 44 visit or later in Study GA30044)
- QFT; if QFT not available, a PPD skin test will be administered if clinically indicated (if not performed at the Week 44 visit or later in Study GA30044)

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

- Plasma samples for PK analysis and metabolite identification, as needed.

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 4.4.10), 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.

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. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

4.4.8 Electrocardiograms

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

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1). ECG recordings may be obtained at unscheduled and other timepoints as indicated.

ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) whenever possible. 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.

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 postdose timepoint, the mean QTcF is > 500 msec and/or 60 msec longer than the baseline value, triplicate ECGs 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. Triplicate ECG recordings will be obtained within approximately 2–5 minutes of each other. The Medical Monitor should be notified. SOC treatment for QT prolongation 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).

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

4.4.10 Samples for Research Biosample Repository

4.4.10.1 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.

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

4.4.10.2 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 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 (Section 4.4.10) will not be applicable at that site.

4.4.10.3 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 or diseases:

- Leftover blood, serum, plasma, and urine samples

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's 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 identification of important pathways, guiding the development of new targeted agents.

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).

4.4.10.4 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.

4.4.10.5 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.

4.4.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdawal of consent, results from those tests will remain as part of the overall research data. 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 GA30066 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 GA30066.

4.4.10.7 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.

4.5 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Study Treatment Discontinuation

Patients must discontinue study treatment and return for a safety follow-up visit if they experience any of the following (see Table 3):

- Requirement of any prohibited medication as defined in Section 4.3.2
- Treated with accepted immunosuppressant that exceeds the maximum dose as defined by the protocol (see Section 4.3.1)
- Combination immunosuppressant 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: 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 torsades de pointes

Patients must discontinue study treatment if they are receiving any treatments that are not specifically permitted in this protocol (see Section 4.3.1) and approved by the Medical Monitor.

Investigators may discontinue study treatment for:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

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.

4.5.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. 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
- Study termination or site closure

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 a patient discontinues the study prior to the Week 48 treatment completion visit, an early termination visit should be conducted. If possible, the investigator will clarify the following:

- If the patient withdrew consent for the remaining study procedures 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

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.

4.5.3 Study 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.

4.5.4 Site Discontinuation

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:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for 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 IMC in collaboration with a Scientific Oversight Committee will monitor safety throughout the study (see Section 3.1.1).

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 in 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 4.

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 Ig 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 that are primarily cleared by B-cell adaptive immune responses. This risk is likely independent of the patient's sex for 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 Igs 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) 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 [redacted] subject had asymptomatic bacteriuria, which resolved while study drug dosing continued.

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 TB, 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 and systemic viral infections, and episodes of suspicious or febrile diarrhea, should be evaluated using serology or polymerase chain reaction, if available, and cultured if feasible. Any identified organisms should be 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 AESI 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 a patient experiences an infection are provided in Table 3.

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 recommendations (van Assen

et al. 2011) or local guidelines be up to date before participation in Study GA30044. 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 injectable 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 (e.g., PT/PTT), 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 patients with XLA (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 patients receiving antiplatelet or anticoagulant therapies. As a precautionary safety measure, patients will be excluded from participation in the blinded Study GA30044 if they have a need for any of the following:

- 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 cerebrovascular accident
- Any history of spontaneous intracranial hemorrhage
- Traumatic intracranial hemorrhage within 10 years prior to the study
- 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, comorbidities, 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 symptoms

Any bleeding event Grade $\geq$2 is considered an AESI 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 3.

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 activities (see Appendix 1) 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 3.

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 MAD study (GA29347) reported events of mild self-limited nausea.

Throughout the study, patients will be monitored for GI side effects, including weight changes. Guidelines for management of study treatment in the event of GI side effects in patients are provided in Table 3.

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 blinded study GA30044, 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 the Week 44 visit or later (prior to entry into Study GA30066). 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 activities (see Appendix 1).

Laboratory results of Grade ≥3 (>5×ULN) AST or ALT elevation, or ALT or AST elevations >3×ULN in combination with clinical jaundice (total bilirubin >2×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 3.

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 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 pulse rate and blood pressure), collection of routine safety ECGs, triplicate ECGs, 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 [from Study GA30044] 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 4.4.7 and Section 4.4.8).

Guidelines for management of study treatment in the event of cardiovascular effects in patients are provided in Table 3.

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 3.

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.

All malignancies are considered AESIs 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 3. 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 GDC-0853 in patients who experience specific adverse events are provided in Table 3. These guidelines do not cover all possible clinical scenarios; please consult the Medical Monitor when there are any questions about specific adverse events. For a potential dose reduction for other adverse events not listed in the table, please consult the Medical Monitor.

Table 3 Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events

Event	Action to Be Taken [a]
Infection [b]	
Serious infection or any infection requiring treatment with a prolonged oral or IV antimicrobial agent	Withhold GDC-0853. Once the infection has resolved consult with Medical Monitor to discuss potential resumption of GDC-0853.
Self-limited infections that require treatment	Withhold GDC-0853 during antimicrobial therapy.
Bleeding	Any Grade ≥ 2 bleeding event is considered an AESI and should be reported to the Sponsor in an expedited manner. For Grade 3 or higher bleeding events or any serious bleeding event, withhold GDC-0853 and consult with the Medical Monitor. Once the bleeding event has resolved, consult with Medical Monitor to discuss the potential resumption of GDC-0853.
Neutropenia [c]	
Grade 2: ANC >1000–1500/mm^3	Maintain GDC-0853 dosing.
Grade 3: ANC 500–1000/mm^3	**For the first occurrence** of a Grade 3 neutrophil count decreased, withhold GDC-0853 and recheck the CBC in 7 days. If the neutrophil count has recovered to Grade 1 ($>1500/mm^3$) or baseline, resume dosing at 200 mg BID unless there is a concurrent serious or Grade 3 infection. If still at Grade 2 (1000–1500/mm^3) and above baseline, consult with the Medical Monitor regarding further dosing instructions. If the Grade 3 neutropenia persists, discontinue GDC-0853. **For the second occurrence** of Grade 3 neutrophil count decreased, withhold GDC-0853 and recheck the CBC in 7 days. If the neutrophil count has recovered to Grade 1 ($>1500/mm^3$) or baseline, restart GDC-0853 at the lower dose of 200 mg QD for 1 week and recheck CBC after 1 week at the lower dose. If at Grade 2 (1000–1500/mm^3) and below baseline, consult with the Medical Monitor regarding further dosing instructions. If the Grade 3 neutrophil count persists, discontinue GDC-0853. **For the third occurrence** of Grade 3 neutrophil count decreased, withhold GDC-0853 and confirm. If Grade 3 neutrophil count decreased is confirmed, discontinue GDC-0853.
Grade 4: ANC $<500/mm^3$	Withhold GDC-0853 and confirm. If Grade 4 neutrophil count decreased is confirmed, discontinue GDC-0853.

Table 3 Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken a
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 occurrence** of treatment emergent Grade 3 lymphopenia, withhold GDC-0853 and recheck CBC in 7 days. If lymphocyte count has recovered to >500/mm^3 (Grade 2 or less severe), resume study treatment unless there is a concurrent serious or Grade 3 infection. If Grade 3 lymphopenia persists, discuss with the Medical Monitor. **For the second occurrence** of Grade 3 lymphopenia, withhold GDC-0853 and recheck CBC in 7 days. If lymphocyte count has recovered to $>500/mm^3$ (Grade 2 or less severe), restart GDC 0853 at the lower dose of 200 mg QD for one week and recheck CBC. If still at $<800/mm^3$ (Grade 2 or more severe), consult with medical monitor regarding further dosing instructions. **For the third occurrence** of Grade 3 lymphopenia, withhold GDC-0853 and confirm. If Grade 3 lymphopenia is confirmed, discontinue GDC-0853.
Grade 4 Lymphopenia**:** lymphocyte count $<200/mm^3$	Withhold GDC-0853 and confirm. If Grade 4 lymphopenia is confirmed, discontinue GDC-0853.
Thrombocytopenia [d]	
Treatment Emergent Grade 1: PLT $>75,000/mm^3$	In the absence of bleeding event(s), maintain GDC-0853 dosing.
Treatment emergent Grade 2: PLT 50,000–75,000/mm^3	**For the first occurrence**, in the absence of SLE flare, hold GDC-0853 and recheck CBC in 7 days. If platelet count has recovered to $>75,000/mm^3$ or to baseline, resume GDC-0853. If platelet count remains $<$ 75,000/mm^3, discuss with the Medical Monitor and consider reducing GDC-0853 dose to 200 mg QD. **For recurrence** in the absence of bleeding events, discuss with the Medical Monitor and consider reducing GDC-0853 dose to 200 mg QD.
Grade >3: PLT $<50,000/mm^3$	**For the first occurrence**, in the absence of SLE flare, hold GDC-0853 and recheck platelets in 7 days. If platelet count has recovered to baseline or above 75,000/mm^3 (Grade 1), resume study treatment. If platelet count has recovered to 50,000–75,000/mm^3 (and this is not baseline) in the absence of bleeding events, consider reducing GDC-0853 dose to 200 mg QD for 1 week and recheck platelets. If still at $<75,000/mm^3$, consult with Medical Monitor regarding further dosing instructions. **For further occurrences** or persistent Grade 3 treatment-emergent thrombocytopenia in the absence of SLE flare, after withholding or dose-reducing GDC-0853, and in the absence of bleeding events, discuss with the Medical Monitor or discontinue study treatment.
Grade 4: PLT < 25,000/mm³	Discontinue GDC-0853.

Table 3 Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken a
Gastrointestinal effects	
Nausea, vomiting, and/or diarrhea	Manage according to site institutional guidelines. Consider administration of GDC-0853 with food as possible mitigation strategy. Consider reducing GDC-0853 dose to 200 mg QD and discuss with Medical Monitor.
Malignancy	
Any malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin)	Discontinue GDC-0853. Report event as an AESI to the Sponsor in an expedited manner.
Hepatotoxicity	
Any AST or ALT $>3.0–5.0\times$ ULN	Withhold GDC-0853 and consult with the Medical Monitor.
AST or ALT elevation $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN, of which at least 35% is direct bilirubin, or clinical jaundice	Discontinue GDC-0853 and consult with the Medical Monitor. Recheck liver laboratory tests, including 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 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 AESI to the Sponsor in an expedited manner.
Any AST or ALT $>5\times$ ULN	Discontinue GDC-0853 and consult with the Medical Monitor. Recheck liver laboratory tests, including 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 for other causes of liver dysfunction (e.g., viral hepatitis, concomitant medications). Continue to monitor liver function tests until abnormalities resolve. Elevations of AST or ALT of $>5\times$ ULN should be reported as AESIs 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	Unless there is a clear alternative cause other than study drug, discontinue GDC-0853. [e]

Table 3 Guidelines for Management of GDC-0853 in Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken a
Sustained absolute QTcF that is >515 msec	Unless there is a clear alternative cause other than study drug, discontinue GDC-0853. [e]
An episode of torsades de pointes or a new ECG finding of clinical concern	Discontinue GDC-0853. [e]
Vascular Inflammation	
Vasculitis	Consult with the Medical Monitor.

AESI = adverse event of special interest; BID = twice a day; PLT = platelet count; QD = once a day; QTcF = QT interval corrected using Fridericia's formula; SLE = systemic lupus erythematosus; ULN = upper limit of normal.

[a] Any patient who discontinues GDC-0853 should enter safety follow-up if possible.

[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 because of a reduced neutrophil count must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, and must have a repeat WBC count with differential performed weekly until the ANC is above 1000 cells/mm³ (1.0×10^9/L). If the ANC does not return to above 1000 cells/mm³ (1.0×10^9/L) within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

[d] Patients withdrawn from the study because of a reduced platelet count must have a repeat platelet count weekly until the count is above 50,000 cells/mm³ (50×10^9/L); additional management and treatment should be as deemed appropriate by the investigator.

[e] In rare circumstances, it may be acceptable to resume GDC-0853, provided that any ECG abnormalities have resolved and that the patient is appropriately monitored. Clinical judgment should be applied and discussion with the Medical Monitor should occur.

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)

AESIs 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). AESIs for this study include the following:

AESIs 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

AESIs 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 Sections 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 patient receives.

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 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 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 5):

- 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 5 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 5.3.5.3 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 finding of an elevation in ALT or AST ($>5\times$ULN), even in the absence of elevation of total bilirubin ($>2\times$ULN) or clinical jaundice, is considered an AESI and subject to expedited reporting requirements.

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 AESI (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, refer to the eCRF reporting guidelines for recording onto 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 the parent Study GA30044. 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.

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)
- AESIs (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.

Telephone No: [redacted] [redacted], U.S.)

[redacted] Medical Monitor contact information:

Medical Monitor: [redacted], M.D.

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

Emergency Telephone Nos. [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 AESIs will be reported until 8 weeks after the last dose of study drug the patients receives either in Study GA30044 or in this study. 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 paper Clinical Trial 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 8 weeks after the last dose of study drug. A paper 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 paper 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. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will 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, email, 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 patient receives), 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 paper Clinical Trial 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

6.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations were performed for this OLE study. The maximum number of patients eligible for enrollment is approximately 240 (i.e., all patients enrolled in Study GA30044).

6.2 SUMMARIES OF CONDUCT OF STUDY

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 the study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, weight, and disease activity will be summarized using means or medians for continuous variables and proportions for categorical variables. Medical history including diagnoses and treatment will be tabulated.

6.4 SAFETY ANALYSES

The analyses will include all patients who received at least one dose of the study drug during this OLE study. Safety will be analyzed based on reported/documented adverse events including AESIs, and changes in laboratory results, ECGs, physical findings,and vital signs.

6.5 EFFICACY ANALYSES

Patient efficacy data will be summarized separated by treatment cohort during the blinded study (GA30044), in addition to overall summaries. Efficacy summary will be based on the intent-to-treat population, defined as all eligible patients enrolled into this OLE study. Analyses of additional study populations (e.g., completers and per protocol [excluding major protocol violators]) will be performed as supportive evaluations. Additional subgroup analyses may be conducted on an exploratory basis. Details will be provided in the data analysis plan.

6.6 PHARMACOKINETIC ANALYSES

The PK analyses will include patients with sufficient data to enable estimation of key parameters (e.g., area under the concentration–time curve, predose concentrations, and half-life).

Systemic GDC-0853 exposure will be evaluated using a population PK approach, and estimates of PK parameters will be generated. The extent of inter-patient variability will be evaluated, and potential sources of variability will be assessed. Relationships between exposure, efficacy, and safety endpoints will be explored and additional PK analyses will be conducted during and/or at the end of the study as appropriate.

6.7 INTERIM ANALYSIS

No formal interim analysis is planned. Data cuts may be performed at appropriate time points for inclusion in the submission with the main studies to support the safety profile.

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 and 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 and review 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 or paper 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 U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the 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 or the patient's legally authorized representative 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 (see definition of end of study in Section 3.2).

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:

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 Clinical Study Report. 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

	Treatment														SFU			
Study Week	0 [a, b]	1 [c]	4	8	12 [a]	16	20	24 [a]	28	32	36 [a]	40	44	48 [a]	56			
Day (Visit Window)	1	8 (±1)	29 (±4	57 (±4)	85 (±4)	113 (±4)	141 (±4)	169 (±4)	197 (±7)	225 (±7)	253 (±7)	281 (±7)	309 (±7)	337 (±7)	393 (±7)	UV [d]	FV [e]	ET
Informed consent [f]	x																	
Eligibility criteria	x																	
Concomitant medications [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [h]	x		x	x	x			x			x			x	x	x	x	x
Weight	x		x		x			x			x			x	x	x	x	x
Height	x																	
Complete PE [i]	x																	
Limited PE [j]			x	x	x			x			x			x	x	x	x	x
MTB screening [k]	x																	
Viral Serology [l]	x																	
12-Lead ECG [m]	x		x					x						x	x	x		x
CK, aldolase, and LDH [n]	x															x	x	
Direct Coombs test [o]	x		x	x	x			x			x			x	x	x	x	x
Hematology [p]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry panel [q]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation panel [r]	x							x						x		x		x

Appendix 1
Schedule of Activities (cont.)

	Treatment														SFU			
Study Week	0 [a, b]	1 [c]	4	8	12 [a]	16	20	24 [a]	28	32	36 [a]	40	44	48 [a]	56			
Day (Visit Window)	1	8 (±1)	29 (±4	57 (±4)	85 (±4)	113 (±4)	141 (±4)	169 (±4)	197 (±7)	225 (±7)	253 (±7)	281 (±7)	309 (±7)	337 (±7)	393 (±7)	UV [d]	FV [e]	ET
Total Ig, IgG, IgM, IgE, IgA [s]	x				x			x			x			x	x	x	x	x
CRP	x		x		x			x			x			x	x	x	x	x
Pregnancy test [t]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TBNK	x		x		x			x			x			x	x	x	x	x
ESR (on site or at local laboratory)	x		x					x			x			x		x	x	x
Urinalysis [u]	x		x	x	x			x			x			x	x	x	x	x
C3, C4, CH50 [v]	x		x	x	x			x			x			x	x	x	x	x
Autoantibody panel [w]	x							x						x				
Anti-dsDNA	x		x	x	x			x			x			x	x	x	x	x
Protein creatinine ratio [x]	x		x	x	x			x			x			x	x		x	x
Plasma PK sample [y]	x							x						x		x	x	x
BILAG-2004	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
GTCI and fasting lipids [z]	x				x			x			x			x				
SLICC damage index	x							x						x				
CLASI	x		x		x			x			x			x	x	x	x	x
Optional photographic documentation [aa]	x		x		x			x			x			x	x	x	x	x

Appendix 1
Schedule of Activities (cont.)

	Treatment														SFU			
Study Week	0 [a, b]	1 [c]	4	8	12 [a]	16	20	24 [a]	28	32	36 [a]	40	44	48 [a]	56			
Day (Visit Window)	1	8 (±1)	29 (±4	57 (±4)	85 (±4)	113 (±4)	141 (±4)	169 (±4)	197 (±7)	225 (±7)	253 (±7)	281 (±7)	309 (±7)	337 (±7)	393 (±7)	UV [d]	FV [e]	ET
PGA [bb]	x		x	x	x			x			x			x	x	x	x	x
Patient's Global Assessment [cc]	x		x	x	x			x			x			x	x	x	x	x
Drug dispensing	x		x	x	x	x	x	x	x	x	x	x	x					
GDC-0853 administration in clinic [dd]	x [ee]							x										

BID = twice a day; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CRP = C-reactive protein; dsDNA = double stranded DNA; EC = Ethics Committee; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; ET = early termination; FMV = first morning void; FV = flare visit; GGT = gamma-glutamyl transpeptidase; GTCI = Glucocorticoid Toxicity Index; $H_2RA = H_2$ receptor antagonist; $HbA1_C$ = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; IRB = Institutional Review Board; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MTB = mycobacterium tuberculosis; OCS = oral corticosteroid; OLE = open-label extension; PE = physical examination; PGA = Physician's Global Assessment; PK = pharmacokinetic; PPD = purified protein derivative; PPI = proton pump inhibitor; PRO = patient-reported outcome; QFT = QuantiFERON–TB Gold; RDW = red cell distribution width; SFI = SELENA-SLEDAI Flare Index; SFU = safety follow-up; SLE = systemic lupus erythematosus; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; TB = tuberculosis; TBNK = T, B, and natural killer cells; UV = unscheduled visit.

[a] A morning clinic visit (fasting ≥4 hours prior to PK blood draw) is strongly recommended for PK visits on Day 1 and Week 24. For other study visits, morning visits are recommended. In addition, the patient should be fasting ≥4 hours for fasting lipid assessments at Day 1, Weeks 12, 24, 36, and 48.

[b] Day 1 OLE assessments that overlap with Week 48 assessments in the blinded Study GA30044 do not need to be repeated. Therefore, Week 48 assessments in Study GA30044 should be used as the Day 1 assessments of Study GA30066.

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

[d] At an unscheduled visit, 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 unscheduled visit. If the patient returns for an unscheduled visit or regular study visit and has any evidence of increased SLE-activity requiring treatment, perform all assessments required for a flare visit.

[e] A flare visit 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 flare visit.

[f] Patients entering the OLE study may be consented after meeting entry criteria for Study GA30066, which may include use of qualifying test results from the Week 44 visit or later from Study GA30044 (see Section 4.4.1).

[g] Starting at Day 1, all patients must record their OCS use as instructed by study staff (see Section 4.2.2.4).

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

[i] Includes 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; and Appendix 12 CLASI) and of infections or other medical conditions, which could place the patient at increased risk.

[j] 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.

[k] MTB testing should be performed only for patients who did not complete testing at Week 44 or later of Study GA30044. Follow the same method of testing and assessment that was completed during screening period. In most cases, QFT is to be used as the initial TB screening test, and if indeterminate, this should be followed by either a repeat QFT or a T-SPOT test. A PPD skin test should be performed only if QFT is not available.

[l] Hepatitis B and C testing should be performed only for patients who did not complete testing at Week 44 or later of Study GA30044. Includes HBsAg, HBsAb, HBcAb, HCV Ab.

[m] ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to the other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) if possible. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart 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.

[n] May be collected throughout treatment period as needed to complete disease activity measures (e.g., SLEDAI-2K and BILAG-2004).

[o] If the Coombs test is needed, it should be performed at a local laboratory.

Appendix 1
Schedule of Activities (cont.)

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

[q] Includes electrolytes (Na, K, Cl, bicarbonate, phosphorus), blood urea nitrogen, creatinine, glucose, ALT, AST, amylase, lipase, total and direct bilirubin, ALP, GGT, albumin, globulin, total protein, calcium, and uric acid.

[r] Includes INR, aPTT, and PT.

[s] Includes total Igs, IgG, IgM, IgE, and IgA.

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

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

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

[w] Includes anti-Smith, anti-RNP, anti-Ro, anti-La, anti-cardiolipin, and anti-B2 glycoprotein.

[x] FMV urine samples should be collected at all 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.

[y] Collect prior to drug administration.

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

[aa] Photography is contingent upon the review and approval by each site's IRB/EC and, if applicable, an appropriate regulatory body.

[bb] The same clinician should complete the PGA throughout the study.

[cc] 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.

[dd] Patients will receive GDC-0853 BID starting on Day 1 and ending on the evening prior to the Week 48 visit of Study GA30066. GDC-0853 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 H_2RA, last dose of oral study drug (prior to clinic visit), and timing of study drug administration in clinic should be recorded at clinic visits with PK and/or fasting lipid assessments.

[ee] The last dose of blinded study drug in Study GA30044 is the p.m. dose on the evening before the Week 48 visit for all patients. For patients continuing into the OLE Study GA30066, the first open-label dose of GDC-0853 should be the a.m. dose on Week 48 (which is Day 1 of Study GA30066).

Appendix 2
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 antimalarials [b]	
Azathioprine	1 to 2.5 mg/kg/day
Methotrexate	7.5 to 25 mg/week
Mycophenolate mofetil	500 to 2500 mg/day
Mycophenolic sodium	360 to1800 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 3
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 3
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 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 3
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 3
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 3
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 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 3
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

Appendix 3
Glucocorticoid Toxicity Change Index (cont.)

- 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 4
Suggested Prednisone Taper Schedule Achieving < 10 mg/day by 12 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

Appendix 5
Childbearing Potential, Pregnancy Testing, and Contraception

For Women

All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test at baseline 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
- Injections for contraception (with prolonged release)

Appendix 5
Childbearing Potential, Pregnancy Testing, and Contraception (cont.)

- 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

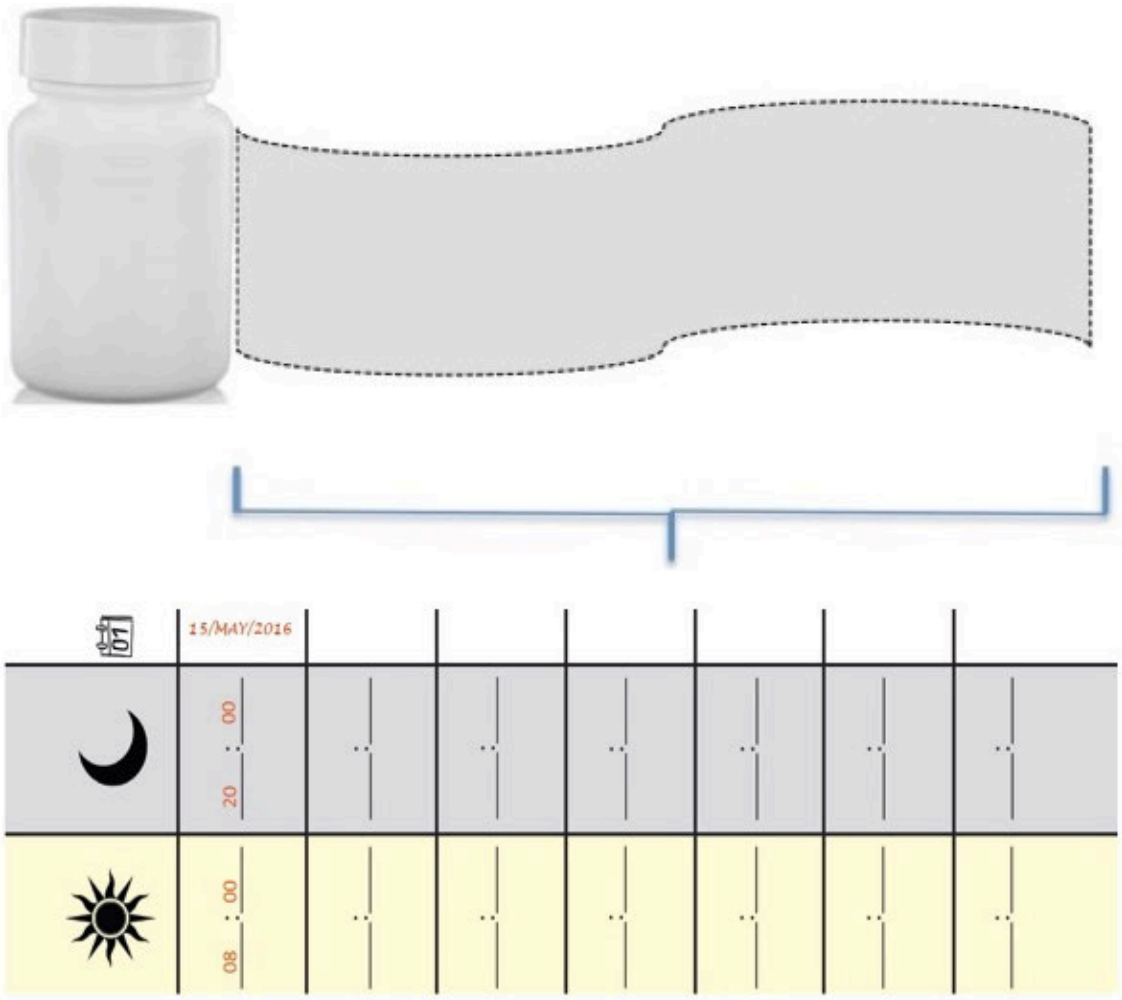
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix 6
Bottle and Label Configuration for GDC-0853 Administration

Label to be affixed on the study drug bottle shows a.m. (sun) versus p.m. (moon) dose.

Site will be responsible for prepopulating the **dates** on the label and affixing the label to the bottle.

Patients should record the **time** (in military time) of each dose on the label.



Appendix 7
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®
Moderate or strong 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) • Antihypertensive/cardiac (verapamil, diltiazem) • 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, lovastatin) • Migraine (eletriptan, ergotamine) • Steroids (budesonide, fluticasone) • Other (alfentanil, buspirone, conivaptan, darifenacin, dasatinib, dihydroergotamine, fentanyl, lurasidone, pimozide, quetiapine, sildenafil, tolvaptan, triazolam)

Appendix 7
Concomitant Medications
(Including Foods and Herbal Products) (cont.)

[a] The following list is not comprehensive. Please refer to the Web sites below for additional information and consult the Medical Monitor if necessary:

U.S. FDA Table of Substrates, Inhibitors, and Inducers (Tables 3-1, 3-2, and 3-3) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

Indiana University Department of Medicine P450 Drug Interactions Table (http://medicine.iupui.edu/clinpharm/ddis/clinical-table)

[b] Potential CYP3A-mediated interactions between GDC-0853 and concomitant medications will be reviewed by the Medical Monitor or delegate during the pre-enrollment adjudication process.

Appendix 8
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)	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
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
SKIN		
Scarring chronic alopecia		1
Extensive scarring or panniculum other than scalp and pulp space		1
Skin ulceration for > 6 months (excluding thrombosis)		1
PREMATURE GONADAL FAILURE (secondary amenorrhoea before age 40)		1
DIABETES MELLITUS (regardless of treatment)		1

Appendix 8
Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (cont.)

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.

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.

Appendix 8
Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (cont.)

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.

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.

Appendix 8
Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (cont.)

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 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 SIE 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

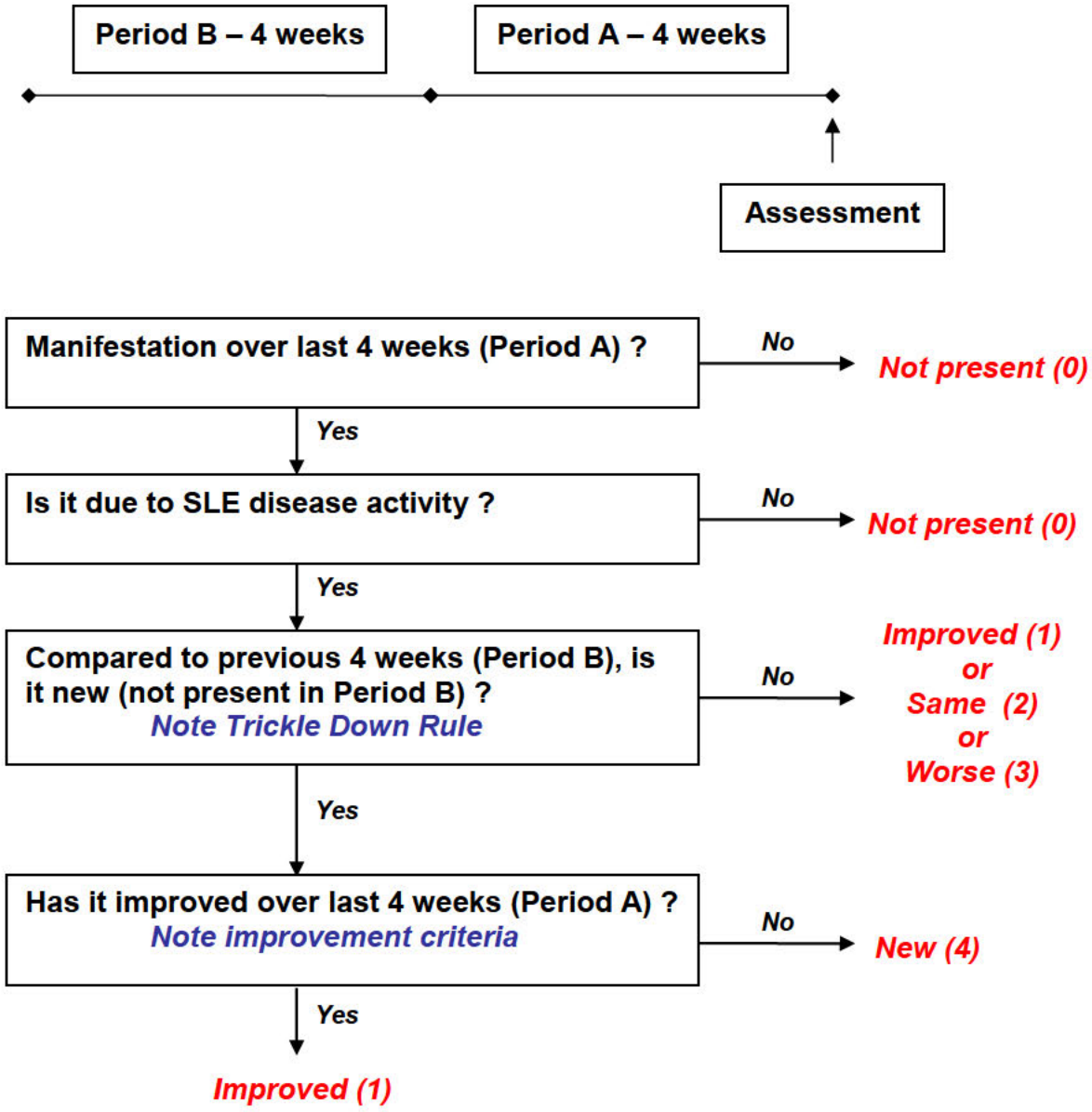
  Or as improving (1) if criteria for severe category has been met at some point over last 4 weeks

  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

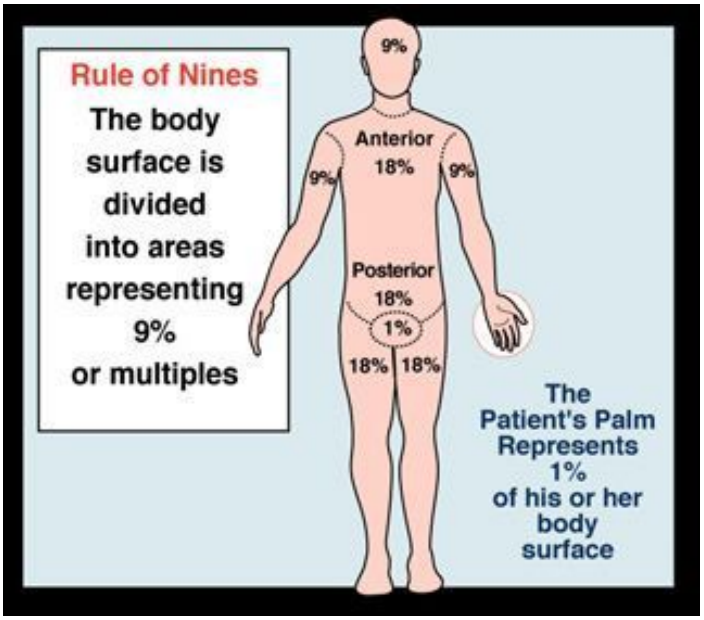
2. Unintentional weight loss > 5%

Appendix 9
BILAG-2004 Index Glossary (cont.)

3. Lymphadenopathy	lymph node more than 1 cm diameter 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



Appendix 9
BILAG-2004 Index Glossary (cont.)

6. Mild eruption	≤ 18% body surface area 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	

NEUROPSYCHIATRIC

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

Appendix 9
BILAG-2004 Index Glossary (cont.)

	supportive imaging required exclude multiple sclerosis
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

Appendix 9
BILAG-2004 Index Glossary (cont.)

29. Polyneuropathy	acute symmetrical distal sensory and/or motor deficit supportive electrophysiology study required
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

Appendix 9
BILAG-2004 Index Glossary (cont.)

	sufficiently severe to interfere with daily activities neuropsychological testing should be done or 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

Appendix 9
BILAG-2004 Index Glossary (cont.)

MUSCULOSKELETAL

39. Severe myositis	significantly elevated serum muscle enzymes with significant muscle weakness 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
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

Appendix 9
BILAG-2004 Index Glossary (cont.)

	inflammatory arthritis which does not fulfil the above criteria for moderate or severe arthritis
CARDIORESPIRATORY	
44. Mild myocarditis	inflammation of myocardium with raised cardiac enzymes &/or ECG changes and without resulting cardiac failure, arrhythmia or valvular dysfunction
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

Appendix 9
BILAG-2004 Index Glossary (cont.)

	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
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 measurement	acute reduction (>20% if previous 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

Appendix 9
BILAG-2004 Index Glossary (cont.)

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
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

Appendix 9
BILAG-2004 Index Glossary (cont.)

OPHTHALMIC

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
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

Appendix 9
BILAG-2004 Index Glossary (cont.)

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 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 ($\geq$ 3.5 g/day or protein-creatinine ratio $\geq$ 350 mg/mmol or albumin-creatinine ratio $\geq$ 350 mg/mmol) hypoalbuminaemia oedema
86. Plasma/Serum creatinine creatinine	exclude other causes for increase in (especially drugs)

Appendix 9
BILAG-2004 Index Glossary (cont.)

87. GFR	MDRD formula: GFR = 170 x [serum creatinine (mg/dl)]$^{-0.999}$ x [age]$^{-0.176}$ x [serum urea (mg/dl]$^{-0.17}$ x [serum albumin (g/dl)]$^{0.318}$ x [0.762 if female] x [1.180 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 exclude other causes for decrease in GFR (especially drugs)
88. Active urinary sediment	pyuria (> 5 WCC/hpf or > 10 WCC/mm^3 (μl)) OR haematuria (> 5 RBC/hpf or > 10 RBC/mm^3 (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

Appendix 9
BILAG-2004 Index Glossary (cont.)

	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	
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

Appendix 9
BILAG-2004 Index Glossary (cont.)

REFERENCES

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Appendix 10
Systemic Lupus Erythematosus Disease Activity Index 2000 (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 10 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

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

Item no.	SLEDAI SCORE	Descriptor	Definition
16	2	Alopecia	Abnormal, patchy or diffuse loss of hair
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.

- 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.

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.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

CRANIAL NERVE DISORDER

Definition: New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.

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.

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.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

The patient complains of muscle aching and/or weakness in the proximal muscles PLUS one of the following must be present:

1. elevated serum creatine phosphokinase and/or aldolase
2. abnormalities on electromyogram consistent with myositis
3. biopsy-proven myositis

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.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

PYURIA

Definition: >5 white blood cells/high power field. Exclude infection.

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.

Appendix 10
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (cont.)

LOW COMPLEMENT:

Definition: Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.

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:

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 to > 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 PGA by ≥ 1.0, but not to more than 2.5	Increase in PGA to > 2.5

NSAID = nonsteroidal anti-inflammatory drug; PGA = Physician's Global Assessment; SELENA = Safety of Estrogens in Lupus Erythematosus National Assessment; SFI = SELENA-SLEDAI Flare Index; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

REFERENCES

Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005;142(12 Pt 1):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
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 schedule of activities (Appendix 1) for any patient who has mucocutaneous manifestations of systemic lupus erythematosus (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. Wherever possible, digital images of the lesions should be obtained.

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 12
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 VP. Development of the CLASI as an outcome instrument for cutaneous lupus erythematosus. Dermatol Ther 2007;20:93–101.

Appendix 12
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

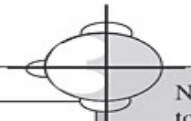
Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ 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 13
Physician's Global Assessment

The investigator's global assessment of the patient's current disease activity (using Physician's Global Assessment [PGA]) will be marked on a 100-mm horizontal visual analogue scale marked from "none" to "severe" and graded from 0 to 3 (see example that follows). 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 British Isles Lupus Assessment Group, the Safety of Estrogens in Lupus Erythematosus National Assessment, the Systemic Lupus Erythematosus Disease Activity Index, and (where appropriate) the Cutaneous Lupus Erythematosus Disease Area and Severity Index and 28-joint counts.

Pertinent laboratory values should be taken into account before completing the PGA rating. If relevant laboratory results are pending, the 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 is available.

Appendix 13
Physician's Global Assessment (cont.)

PHYSICIAN'S GLOBAL ASSESSMENT

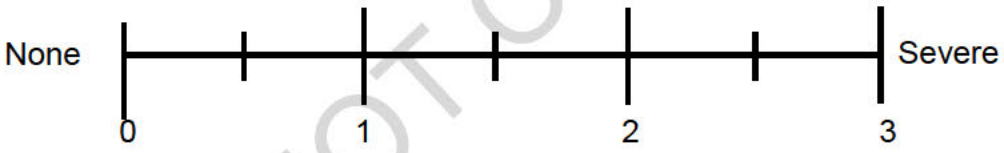
☐ Check if assessment was not done

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 14
Patient's Global Assessment

The patient is asked to rate her or his lupus over the previous 24 hours considering all aspects of the disease. This overall assessment of 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 the investigational medicinal product.

The investigator or study coordinator will measure the distance in millimeters from the left-hand end of the VAS line and record this measurement 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 15
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®
Moderate or strong 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) • Antihypertensive/cardiac (verapamil, diltiazem) • 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, lovastatin) • Migraine (eletriptan, ergotamine) • Steroids (budesonide, fluticasone) • Other (alfentanil, buspirone, conivaptan, darifenacin, dasatinib, dihydroergotamine, fentanyl, lurasidone, pimozide, quetiapine, sildenafil, tolvaptan, triazolam)

Appendix 15
Concomitant Medications (Including Foods and Herbal Products) (cont.)

[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, and 3-3) (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-mediated interactions between GDC-0853 and concomitant medications will be reviewed by the Medical Monitor or delegate during the pre-enrolment adjudication process