Study Title:	A Phase 1b, Multiple Ascending-dose Study of EQ001 in Subjects with Systemic Lupus Erythematosus with or without Active Proliferative Lupus Nephritis
Protocol Number:	EQ001-19-002
Investigational Product(s):	EQ001
Sponsor:	Equillium, Inc.
Development Phase:	Phase 1b
NCT Number:	NCT04128579
Document Version Date:	03 Mar 2022

CONFIDENTIAL

Clinical Study Protocol

Study Title:	A Phase 1b, Multiple Ascending-dose Study of EQ001 in Subjects with Systemic Lupus Erythematosus with or without Active Proliferative Lupus Nephritis
Protocol Number:	EQ001-19-002
IND Number:	143830
Investigational Product(s):	EQ001
Sponsor:	Equillium, Inc. [redacted]
Development Phase:	Phase 1b
Sponsor's Responsible Medical Officer:	[redacted]

[redacted]

CONFIDENTIAL

4 TABLE OF CONTENTS

[redacted]

5 SYNOPSIS AND SCHEDULE OF EVENTS

5.1 Synopsis

Title of Study Protocol: A Phase 1b, Multiple Ascending-dose Study of EQ001 in Subjects with Systemic Lupus Erythematosus with or without Active Proliferative Lupus Nephritis

Protocol Number: EQ001-19-002

Name of Sponsor Company:
Equillium, Inc.
[redacted]

Name of Finished Product: EQ001 (itolizumab)

Phase of Development: Phase 1b

Objectives:

Primary Objective

Characterize the safety and tolerability of EQ001 (itolizumab) in subjects with Systemic Lupus Erythematosus (SLE) with or without active proliferative Lupus Nephritis (apLN)

Secondary Objectives

1. Characterize the pharmacokinetic (PK) profile of EQ001
- [redacted]
- [redacted]

4. Characterize the clinical activity of EQ001 in Type B Cohort subjects

Exploratory Objectives

- [redacted]

2. Characterize the clinical activity of EQ001 in Type A Cohort subjects

Endpoints:

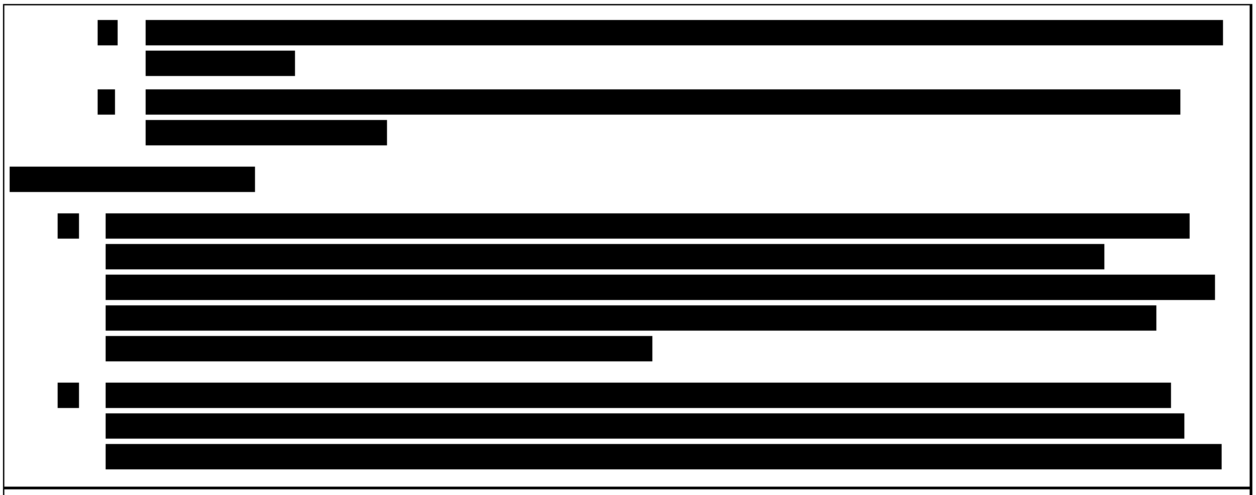
Primary Endpoints

Safety and tolerability of EQ001, as assessed by treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), clinical laboratory values, vital signs, 12-lead electrocardiogram (ECG), and physical examinations.

Secondary Endpoints

1. Pharmacokinetics of EQ001, as assessed by EQ001 serum concentrations at specified timepoints.
- [redacted]
- [redacted]

4. Clinical activity of EQ001 in subjects with apLN, as assessed by the following variables):
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]



Study Design:

This is a Phase 1b, multiple ascending-dose study to evaluate the safety, tolerability, PK, [redacted] and clinical activity of EQ001, a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively targets CD6 on effector T cells (T_{eff}), in subjects with SLE. Approximately 30 subjects with active or inactive SLE who do not have apLN are anticipated to be studied in dose escalation cohorts of 6 subjects each in Type A Cohorts. Up to approximately 20 subjects with apLN are anticipated to be studied in a Type B Cohort. Additional subjects may be added at the maximum-tolerated dose (MTD) cohort and/or to an additional cohort at an intermediate or lower dose in Type A. The exact numbers of each type of cohort will be determined by emerging data during the study.

To qualify for enrollment in the study, all subjects must have a diagnosis of SLE. Additionally, to qualify for enrollment in a Type B Cohort, subjects must have apLN, defined as proliferative LN (International Society of Nephrology [ISN]/Renal Pathology Society [RPS] Class III or IV with or without Class V) diagnosed by renal biopsy within 12 months prior to Day 1 or during Screening and previous evidence of serologic and clinical disease activity. Type B Cohort subjects may require induction treatment for apLN for newly diagnosed disease or relapsing/flaring disease or need additional treatment for incomplete response. Restricted SLE treatments (e.g., immunosuppressive medications and antimalarials) are required to be stable and/or washed out [redacted] Subjects in the Type B Cohort may have glucocorticoids administered and tapered [redacted]. Investigators will adhere to the protocol steroid taper schedule unless a safety concern (including concern related to insufficient response) necessitates departures from the schedule. Such planned departures must be discussed with the Medical Monitor, preferably in advance of the change in medication.

Type A

Type A will utilize a cohort dose escalation design. If < 2 of the 6 evaluable subjects in a Type A dose-escalation cohort experience a dose-limiting toxicity (DLT) during the DLT evaluation period (Days 1-29), then escalation may occur to the next higher dose level. If 2 or more of the 6 initial subjects in a Type A dose-escalation cohort experience a DLT, then no further dose escalation will occur. That dose will then be considered to have exceeded the MTD and the next-lower dose may be declared the MTD. Once a dose has been determined to have exceeded the MTD, the Data Review Committee (DRC) may recommend continuation of the study (with or without modification) and may expand enrollment to evaluate additional subjects at the MTD and/or in an additional cohort at an intermediate lower or dose to better define the MTD.

Type A Cohort enrollment will proceed in a sequential manner to evaluate escalating dose levels of EQ001. The first dose level to be studied, Dose Level 1, will be 0.4 mg/kg and the maximum dose level to be studied will be 3.2 mg/kg. Intermediate dose levels of 0.8, 1.6, and 2.4 mg/kg are planned for Type A Cohorts, but other intermediate doses may be chosen based on emerging PK, [redacted] and safety data. Subjects in Type A Cohorts will receive a total of 2 doses, 2 weeks apart.

The MTD determination will be made based only on Type A Cohorts. Dose escalation is allowed to proceed if no predefined stopping criteria are met and the DRC recommends that it is safe to proceed.

Type B

Up to approximately 20 subjects will be enrolled and dosed in the Type B Cohort. Subjects will receive a total of 13 doses of EQ001 1.6 mg/kg administered SC every 2 weeks over 24 weeks. All subjects must be on a stable dose of mycophenolate mofetil (MMF) or mycophenolic acid (MPA) for the duration of the study. Subjects that require induction treatment with pulse steroid treatment of methylprednisolone ≥500 mg or equivalent will undergo a rapid steroid taper with a 20% reduction per week. The targeted goal is to reach a prednisone dose of 10 mg or less per day by Week 10[redacted]

[redacted]

The study will be conducted in 3 defined periods, described below:

1. Screening Period
   a. **Type A Cohorts:** The Screening Period for Cohort A subjects will be up to 4 weeks in duration, starting with the first screening procedure in the Schedule of Events (SOE; excluding the informed consent), and completed prior to Study Day 1 (Section 5.2)
   b. **Type B Cohort:** The Screening Period for Cohort B subjects will be up to 6 weeks in duration (excluding the informed consent) and completed prior to Study Day 1 and may be completed over the course of multiple clinic visits. (Section 5.3).
2. Treatment Period
   a. **Type A Cohorts**: The Treatment Period for Cohort A subjects will be 4 weeks in duration, beginning on Day 1 with the first study drug dose. During the Treatment Period, 2 doses of study drug will be

administered subcutaneously (SC), 1 dose each on Days 1 and 15. Subjects will return to the study site for follow-up evaluations according to the SOE (Section 5.2).

b. **Type B Cohort**: The Treatment Period for Cohort B subjects will be 24 weeks in duration, beginning on Day 1 with the first study drug dose. During the Treatment Period, 13 doses of study drug will be administered SC, 1 dose each on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. Subjects will return to the study site for follow-up evaluations according to the SOE (Section 5.3 and Section 5.4).

3. Follow-up Period

a. **Type A Cohorts**: The Follow-up Period for Cohort A subjects will end approximately 6 weeks after the last dose of study drug (Section 5.2)

b. **Type B Cohort**: The Follow-up Period for Cohort B subjects will end approximately 12 weeks after the last dose of study drug (Section 5.4)

Note: Contraception requirements must be continued for 130 days after the last dose of study drug for Type A and B Cohorts.

Written informed consent for study participation may be obtained up to 4 weeks prior to the Screening Visit for Type A Cohort subjects and 8 weeks prior to the Screening Visit for Type B Cohort subjects. Evaluation of eligibility will be based on laboratory results, medical history, concomitant and prior medications, vital signs, 12-lead ECG, physical examination, pregnancy testing (if applicable), and, in Type B Cohort, renal biopsy results.

Subjects will be evaluated for eligibility to receive the next dose based on laboratory and clinical criteria prior to each dose. The pre-dose laboratory evaluations may be performed at a local or central laboratory up to 14- days prior to the next target dosing day or on the target dosing day. If a subject discontinues study drug treatment prior to the last dose, they will be asked to return to the clinical study site to complete all follow up visits, as described in the SOE.

If a subject withdraws from the study, they should complete an Early Termination Visit.

[redacted]

[redacted]

Number of Subjects Planned:

Approximately 50 subjects with SLE are planned to be enrolled in the study: approximately 30 subjects in Type A (subjects without apLN) and up to approximately 20 subjects in Type B (with apLN). Additional subjects may be added based on emerging data to meet the objectives of the study.

Inclusion Criteria:

Type A Cohort Inclusion Criteria. Subjects will be required to meet all of the following inclusion criteria in order to be eligible for study enrollment:

1. Is male or female, age ≥ 18 and ≤ 75 years
2. [redacted]
3. Has previously been documented to have met or currently meets Systemic Lupus International Collaborating Clinics (SLICC) and/or American College of Rheumatology (ACR) criteria for SLE [redacted]
4. Received at least 1 immunosuppressive or immunomodulatory treatment (including antimalarials) for SLE at any time in the past or currently
5. [redacted]
6. Has documented elevation of antinuclear antibodies (ANA) in the past or during Screening
7. Restricted SLE treatments (e.g., other immunosuppressive medications, glucocorticoids, and antimalarials) are stable and/or washed out at Screening [redacted]
8. Changes in SLE drug treatment(s), including increased doses of glucocorticoids or other SLE treatments, are not anticipated during the study
9. During Screening, has adequate hematologic function [redacted]

[redacted]

Type B Cohort Inclusion Criteria. Subjects will be required to meet all of the following inclusion criteria in order to be eligible for study enrollment:

1. Is male or female, age ≥ 18 and ≤ 75 years
3. Has a diagnosis of SLE
4. Kidney biopsy with a histologic diagnosis of LN (ISN/RPS 2003 classification of LN) Classes III, IV-S or IV-G, (A) or (A/C); subjects with Class III or IV and concomitant Class V will be permitted.
5. Has a urine protein to creatinine ratio of > 1000 mg/g
6. Requires induction treatment due to newly diagnosed LN or relapsing/flaring disease.
8. has adequate hematologic function
11. Has documented elevation of ANAs in the past or currently

[redacted]

14. Most recent eGFR ≥ 40 mL/min/1.73m^2 during Screening

[redacted]

[redacted]

Exclusion Criteria:

[redacted]

- [redacted]
- [redacted]

3. Acute or chronic infections requiring systemic antibacterial, antifungal, or antiviral therapy within 21 days of Screening or active infection during Screening
4. History of or Screening lab test positive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)

[redacted]

- [redacted]

6. Active tuberculosis (TB) or a positive interferon-gamma release assay (IGRA) TB test

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

3. Acute or chronic infections requiring systemic antibacterial, antifungal, or antiviral therapy within 21 days of the Screening Visit or active infection during Screening
4. History of or Screening lab test positive for HBV, HCV, or HIV

[redacted]

6. Active TB or untreated latent TB (as determined by the treating physician and local practice and requirements)

[redacted]

Investigational Products, Dosage, and Mode of Administration:

The investigational product is EQ001 (itolizumab), a humanized recombinant IgG1 mAb that selectively targets the extracellular scavenger receptor cysteine-rich- (Sc) membrane-distal domain 1 of human CD6. [redacted]

[redacted]

The planned doses and dosing regimen at each dose level [redacted]. The planned doses may be substituted for lower doses (including previously studied doses) based on accruing data. The highest dose level that will be studied is 3.2 mg/kg.

[redacted]

Measurements:

- Evaluation of safety will be performed by assessing adverse events, vital signs, 12-lead ECGs, physical examinations, and laboratory tests.
- Pharmacokinetics [redacted].
- Anti-drug antibodies (ADA) will be assessed, as well as neutralizing ADA in subjects that test positive for ADAs.
- [redacted]
- Evaluation of clinical activity will be performed in all subjects using the SLEDAI-2K, patient-reported outcomes, serological markers, spot urine PCR, urinalysis, and serum complement. Clinical activity in apLN subjects will be evaluated with urine PCR (including 24-hour urine collections), eGFR, and doses of prednisone (or equivalent).

Statistical Methods:

All safety, PK, [redacted] and efficacy endpoints will be tabulated with descriptive statistics by cohort for Type A and for Type B portions of the study. Data may be pooled across cohorts.

Analysis Populations:

The study consists of the following analysis populations:

Safety Population: All subjects who receive any study drug.

PK Population: Subjects in the safety population who have at least one measurable post-EQ001 exposure serum concentration.

[redacted]

Efficacy Population: Subjects in the safety population who have at least 1 post-treatment assessment for a marker of clinical activity.

[redacted]

Safety Analyses:

Extent of exposure to the study treatment as measured by number of doses administered and duration of exposure to the study drug will be summarized using descriptive statistics. Adverse events (including DLTs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v 20.1, or higher version and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v 5.0) for the purposes of data summarization. Incidence of TEAEs, TESAEs, TEAEs leading to study drug discontinuation, [redacted] TEAEs with an outcome of death will be summarized by MedDRA system organ class (SOC) and preferred term. Adverse events will also be summarized by worst CTCAE severity grade and causality relationship to study drug. [redacted]

Clinical laboratory data will be descriptively summarized, including observed values at collection timepoints and change from baseline. All laboratory parameters that can be graded using CTCAE v 5.0 will be graded. For selected parameters, the following summaries may be produced:

- Worst post-baseline severity grade
- Shift summary of baseline grade to worst post-baseline severity grade

Safety evaluations may also include changes in the subject's vital signs, and ECG results. The incidence of treatment-emergent anti-EQ001 binding and neutralization antibodies will be reported.

PK Analyses:

Serum concentrations will be listed and summarized for each EQ001 dose using descriptive statistics for each cohort.

Efficacy Analyses:

apLN Subjects:

The geometric mean fold change from baseline in UPCR from a urine collection to FU1 and FU2 will be summarized descriptively, along with their 2-sided 95% CI for the fold change. The geometric mean fold change from baseline over time by visit will also be described.

The proportion of subjects with a > 30% and > 50% decline in UPCR and those with a UPCR < 500 mg/g at FU1 and FU2 will be described, along with their 2-sided 95% CI.

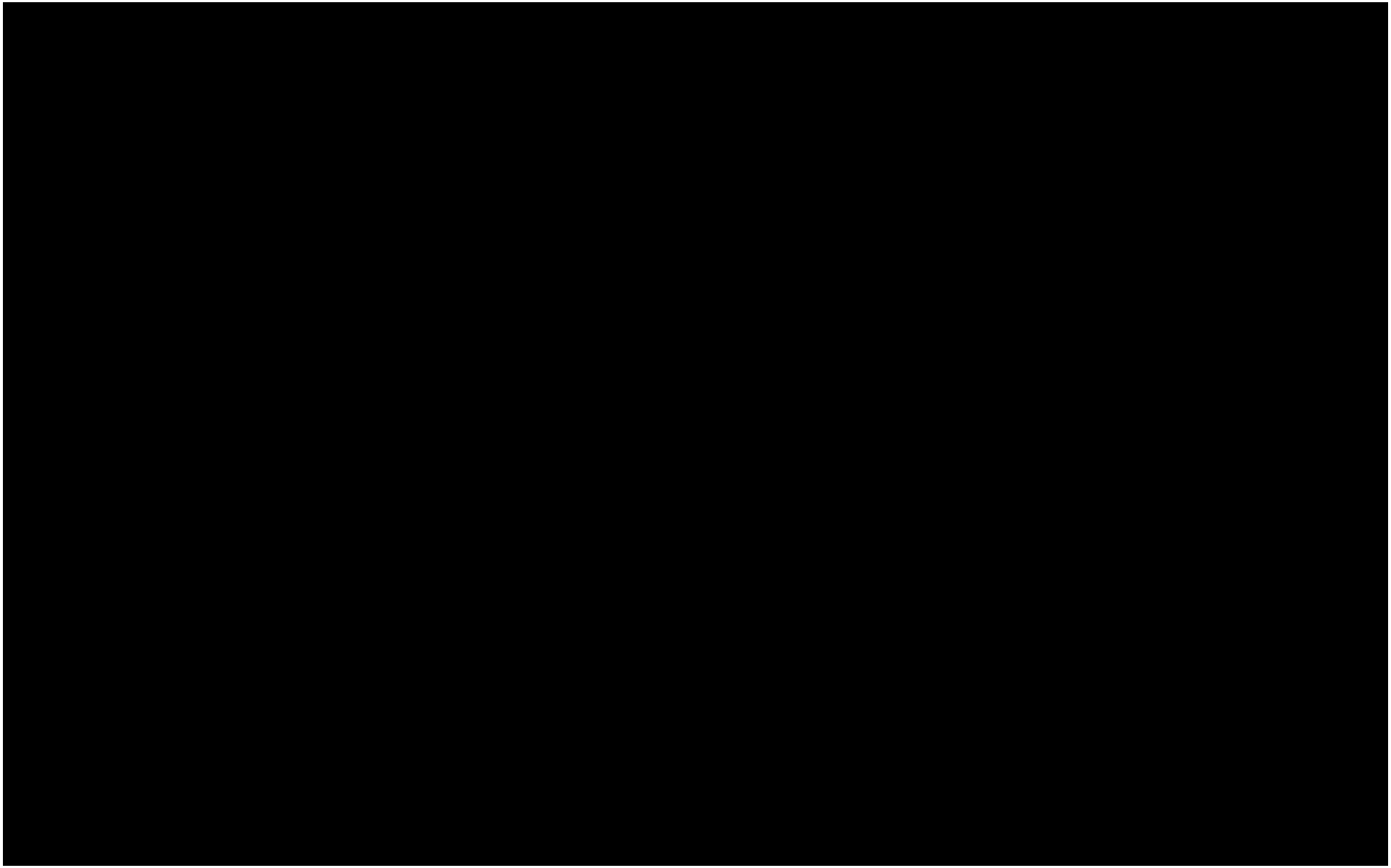
Time to UPCR decrease of > 50%, > 30%, and to a level of < 500 mg/g from baseline will be summarized using the Kaplan-Meier method. Baseline proteinuria is defined as the mean of the 2 UPCR measurements from 24-hour urine collections prior to Day 1 dosing. Descriptive analyses of serologic markers, eGFR, and prednisone use will be performed.

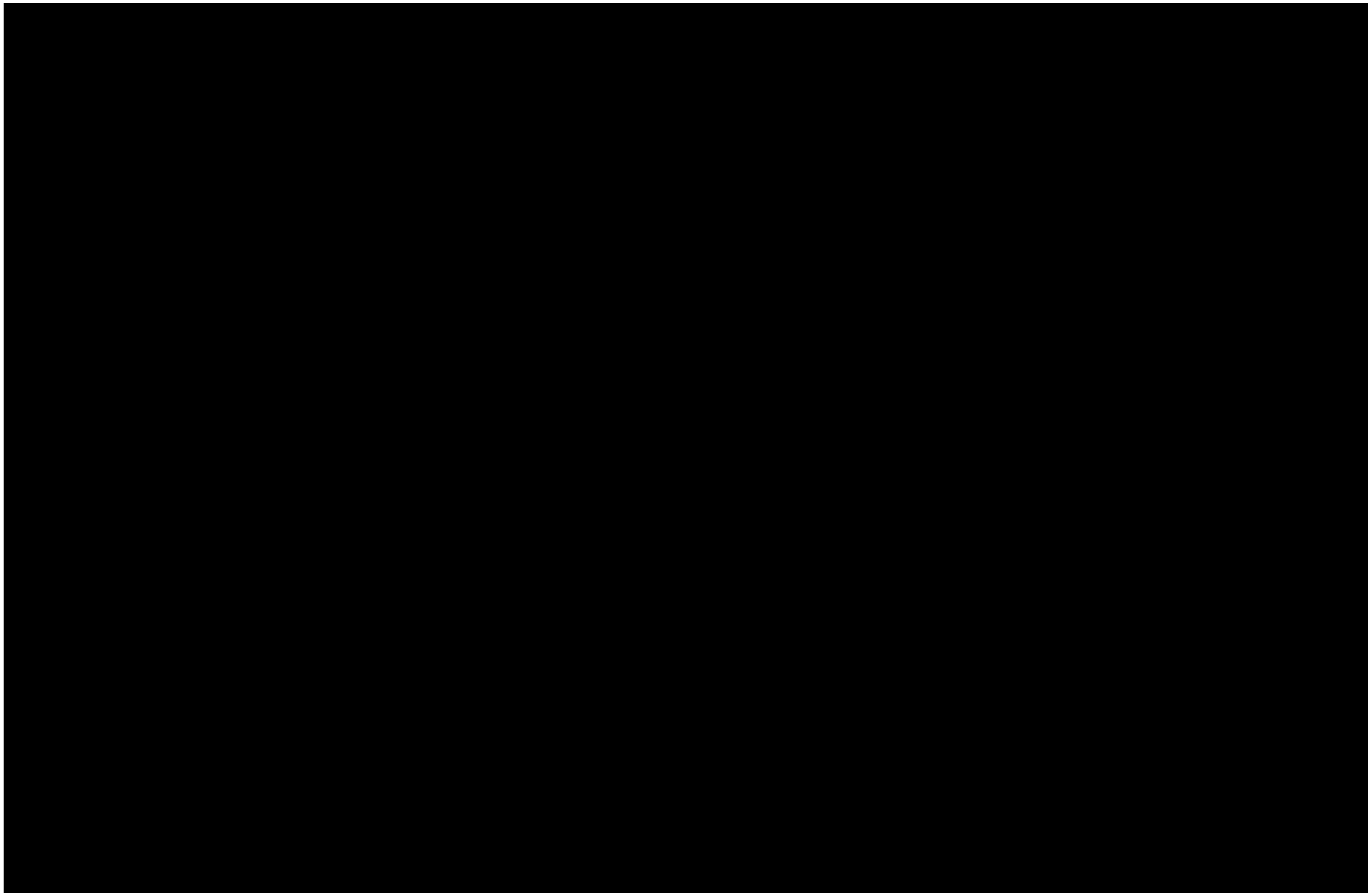
Subjects may be assessed based on the time since they had been on apLN treatment, such as MMF/MPA or time since pulse corticosteroids (i.e., >12 weeks vs < 12 weeks, or by quartiles). Additional subgroup analyses may be performed based on the data collection such as severity of lupus nephritis, baseline proteinuria or previous treatments.

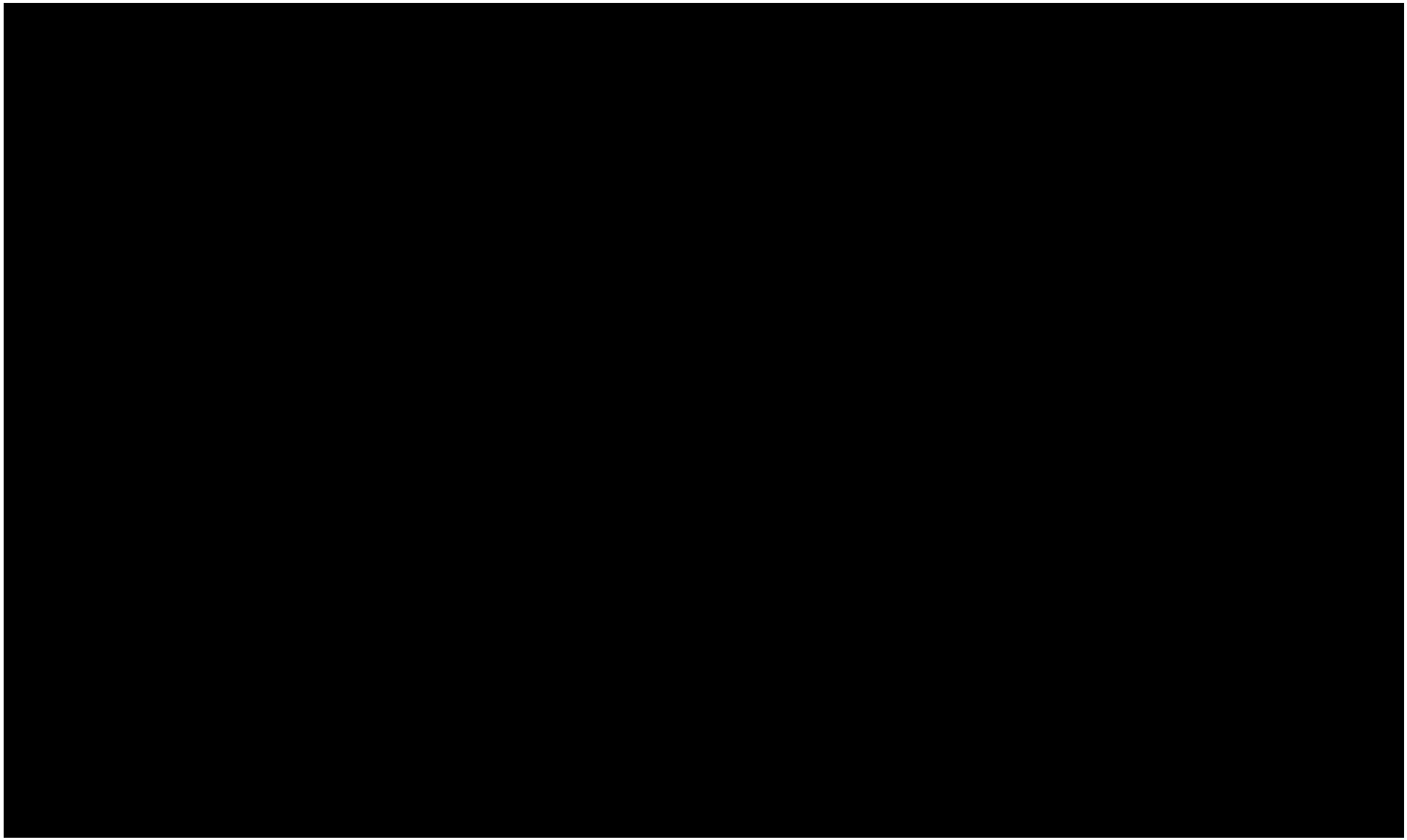
All Subjects: The changes in SLEDAI-2K scores from baseline will be summarized in both continuous and binary scale (e.g., decrease from baseline of ≥ 4 or < 4) with their 95% exact confidence intervals. Other measures of clinical activity of EQ001, such as change from baseline in autoantibody titers, serologic markers, and serum complement, will be summarized descriptively.

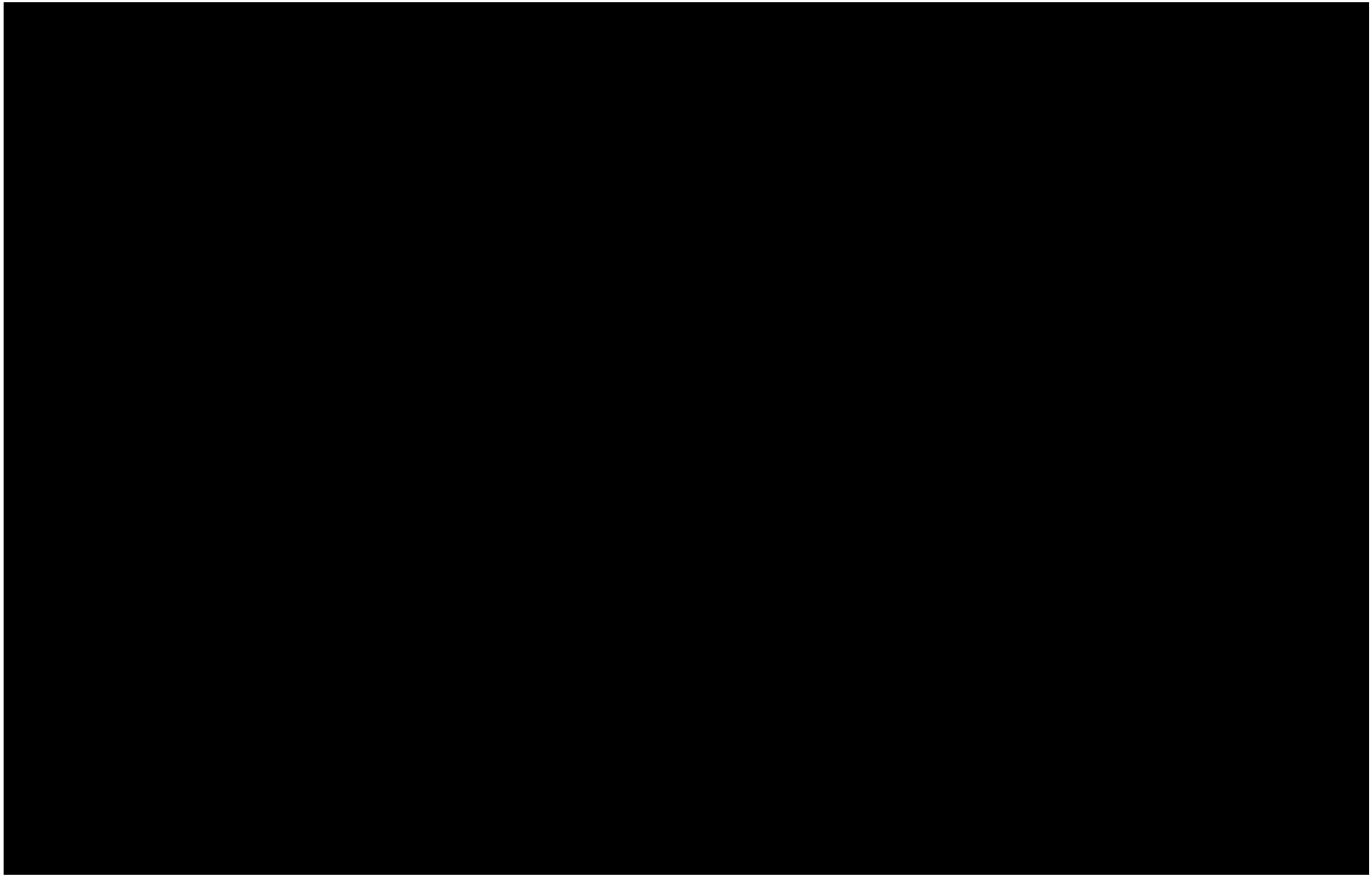
A detailed description of data analyses and statistical methods will be outlined separately in the Statistical Analysis Plan.

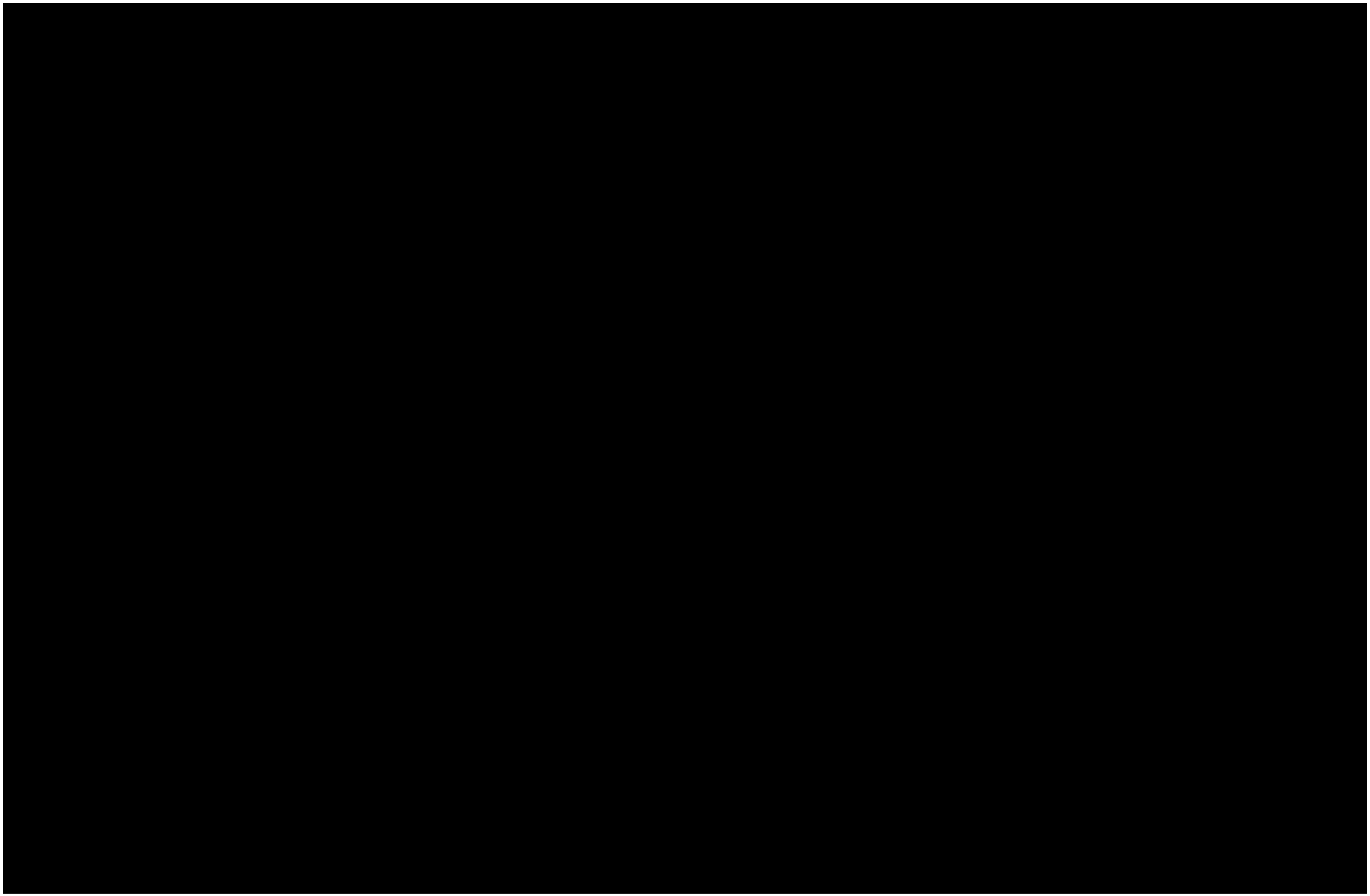
[redacted]











6 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	angiotensin converting enzyme
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
aGVHD	acute graft versus host disease
ALC	absolute lymphocyte count
ALCAM	activated leukocyte cell adhesion molecule
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
APAC	Asia-Pacific
apLN	active proliferative lupus nephritis
ARB	angiotensin-receptor blockers
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the curve from time 0 to infinity
$AUC_{0\text{-}t}$	area under the curve at time 0 to t
Bmab 600	itolizumab; EQ001
BUN	blood urea nitrogen
CCL	chemokine (C-C motif) ligand
CD6	cluster of differentiation 6 molecule
CFR	Code of Federal Regulations
CH50	Total hemolytic complement
Cl	clearance
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
C_{max}	maximum serum drug concentration
C_{min}	minimum serum drug concentration
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CXCL	C-X-C motif chemokine
DLT	dose-limiting toxicity
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form

eGFR	estimated glomerular filtration rate
ET	early termination
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
FU	Follow up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal(ly)
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HbsAg	hepatitis B virus surface antigen
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFNg	Interferon gamma
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IGRA	interferon-gamma release assay
IL-	interleukin-
IRB	Institutional Review Board
ISN	International Society of Nephrology
IUD	intrauterine device
IV	intravenous(ly)
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LN	lupus nephritis
mAb	monoclonal antibody
MCP	monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MTD	maximum tolerated dose

NCI	National Cancer Institute
OVA	ovalbumin
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PGA	Physician Global Assessment
Ph.Eur.	*European Pharmacopoeia*
PK	pharmacokinetic(s)
QoL	quality of life
RANTES	regulated on activation, normal T cell expressed and secreted
RBC	red blood cell
RNA	ribonucleic acid
RO	receptor occupancy
RPS	Renal Pathology Society
SAE	serious adverse event
SC	subcutaneous(ly)
Sc	scavenger receptor cysteine-rich
SF-36	The Short Form 36 Health Survey
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOC	system organ class
SOE	Schedule of Events
$t_{½}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
T_{eff}	effector T cell
TESAE	treatment-emergent serious adverse event
Th	T helper
T_{max}	time to maximum concentration
TNF-α	tumor necrosis factor alpha
TNF(R)	tumor necrosis factor (receptor)
T_{reg}	regulatory T cells
UPCR	urine protein creatinine ratio
USP	United States Pharmacopeia
V_d	volume of distribution
WBC	white blood cell

7 INTRODUCTION

7.1 Background

Systemic Lupus Erythematosus (SLE) is an autoimmune chronic inflammatory disease predominantly affecting women in the reproductive age range. The prevalence of SLE varies considerably by race, ethnicity, and geographical location [redacted] Prevalence of SLE in the United States has been reported to be between 20 to 150 cases per 100,000 (but as high as 406 per 100,000 among African American women) [redacted]

Lupus nephritis (LN) is a serious complication of SLE that results in significant morbidity and mortality. Despite the use of currently available anti-inflammatory and immunosuppressive treatments, progression of LN to chronic kidney disease is common and 10% of patients develop end-stage kidney disease [redacted] A number of risk factors affect the likelihood of progression of LN to end-stage kidney disease, including histologic class [redacted]. The presence of Class III (focal segmental) or Class IV (diffuse proliferative) LN increases mortality by 6 fold compared to the general population [redacted] Patients who achieve disease remission have improved overall survival and renal survival; however, in a study of patients with Class IV LN (diffuse glomerulonephritis), only 43% achieved a complete remission, with 24% achieving a partial remission, and 32% achieving no remission [redacted]). Ten-year patient survival for patients with complete, partial, and no remission in this study was 95%, 76% and 46%, respectively. The corresponding 10-year renal survival was 94%, 45%, and 19%, respectively. Patient survival with freedom from end-stage kidney disease at 10 years was 92%, 43%, and 13% for patients with complete, partial, and no remission, respectively.

T cells are a major factor in driving the immune pathology associated with LN [redacted] One important regulator of T cell activity is CD6, a tightly-regulated, co-stimulatory receptor that serves as a key checkpoint in regulating T_{eff} cells that are central to autoimmune responses [redacted] CD6 is highly expressed on CD4+ T_{eff} cells but not on regulatory T cells [T_{reg}] [redacted] Via interactions with its ligand, activated leukocyte cell adhesion molecule (ALCAM), CD6 plays an integral role in modulating T cell activation and trafficking. Preclinical data and clinical studies in other autoimmune diseases (psoriasis and rheumatoid arthritis) have demonstrated that blockade of CD6 co-stimulation leads to selective inhibition of pathogenic T_{eff} cell activity and trafficking, while preserving the essential regulatory function of T_{reg} cells [redacted]

7.2 Itolizumab

Itolizumab (Bmab 600; EQ001) is a humanized recombinant immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively targets the extracellular scavenger receptor cysteine-rich (Sc) membrane-distal domain 1 of human CD6 [redacted] a co-stimulatory membrane glycoprotein associated with T cell modulation and

implicated in several autoimmune and inflammatory diseases, including psoriasis, multiple sclerosis, rheumatoid arthritis, and Sjögren's disease [redacted].

EQ001 binds to domain-1 of human CD6 and is believed to sterically hinder the optimal engagement of ALCAM with domain-3, modulating both co-stimulation and trafficking without causing T cell depletion. [redacted]

The binding of ALCAM to CD6 also facilitates lymphocyte trafficking, and disruption of this interaction, as demonstrated through the use of CD6KO mice and/or anti-CD6 mAbs, results in reduced T cell infiltration into inflamed tissues [redacted] Additionally, in clinical trials with itolizumab, skin biopsies exhibited significantly reduced levels of infiltrating CD3 positive T cells [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.4 Clinical Findings

[redacted].

Three clinical studies of itolizumab have been performed in India in subjects with rheumatoid arthritis and chronic plaque psoriasis. A total of 368 subjects were exposed to T1h at doses of 0.1 to 1.6 mg/kg. T1h demonstrated preliminary evidence of efficacy in rheumatoid arthritis and definitive evidence of efficacy in plaque psoriasis [redacted] leading to approval of itolizumab in India for the treatment of plaque psoriasis. A conditional approval for itolizumab for the treatment of plaque psoriasis was also granted by Centro de Immunologia Molecular, Cuba on 16 May 2014.

[redacted]

[redacted]

[redacted]

7.5 Rationale for Evaluating EQ001 for the Treatment of LN

LN is a serious disease that affects roughly half of the patients with SLE; patients with LN have a substantially increased risk for end stage renal disease and death. Despite the presence of autoantibodies and inflammatory cytokines in SLE and LN, B-cell-directed and single cytokine targeted therapies have largely failed in clinical development. More recent evidence has demonstrated that T_{eff} cells play a crucial and central role in the pathogenesis of both SLE and LN in that they mediate tissue damage and also enhance the production of autoantibodies by promoting B cell differentiation, proliferation, and maturation [redacted] Multiple T_{eff} cells/cytokines, such T_h1/IFN-γ, T_h2/IL-4 and T_h17/IL-17, have all been implicated in the immune pathogenesis of both SLE and LN, highlighting the complex nature of the disease. However, T_h17 cells are emerging as key targets as it has been demonstrated that high levels of IL-17 predict poor histopathological outcome after immunosuppressive therapy in patients with LN [redacted]. Elevated levels of T_h17 cells are accompanied by a decrease of T_{reg} cells, suggesting that loss of this functional immune balance may be involved in the pathogenesis of renal damage in SLE patients [redacted] Therefore, targeting T_{eff} cells, or molecules that modulate T_{eff} cell activity, while preserving T_{reg} activity, could prove to be a successful therapeutic strategy for patients with SLE and LN.

The unique mechanism of action of EQ001 can selectively target elements of the underlying pathogenesis of LN by: (a) inhibiting multiple pathogenic T_{eff} cells and cytokine secretion; (b) inhibiting trafficking of T_{eff} cells into kidney tissues; and (c) reducing the T_h17:T_{reg} ratio associated with LN. Given the central role that T_{eff} cells play in the immunopathogenesis of SLE and LN, EQ001, which blocks the CD6-ALCAM pathway and inhibits both the activity as well as the trafficking of T_{eff} cells, represents a promising therapeutic approach in this disease. [redacted]

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a Phase 1b, multiple ascending-dose study to evaluate the safety, tolerability, PK, [redacted] and clinical activity of EQ001, a humanized IgG1 mAb that selectively targets CD6 on T_{eff} cells, in subjects with SLE.

Approximately 30 subjects with active or inactive SLE who do not have apLN are anticipated to be studied in dose escalation cohorts of 6 subjects each in Type A Cohorts. Up to approximately 20 subjects with apLN are anticipated to be studied in a Type B Cohort. Additional subjects may be added at the maximum-tolerated dose (MTD) cohort and/or to an additional cohort at an intermediate or lower dose in Type A. The exact numbers of each type of cohort will be determined by emerging data during the study.

To qualify for enrollment in the study, all subjects must have a diagnosis of SLE. Additionally, to qualify for enrollment in a Type B Cohort, subjects must have apLN, defined as proliferative LN (International Society of Nephrology [ISN]/Renal Pathology Society [RPS] Class III or IV with or without Class V) diagnosed by renal biopsy within 12 months prior to Day 1 or during Screening, and previous evidence of serologic and clinical disease activity. Type B Cohort subjects may require induction treatment for apLN for newly diagnosed disease or relapsing/flaring disease or need additional treatment for incomplete responders. Restricted SLE treatments (e.g., immunosuppressive medications and antimalarials) are required to be stable and/or washed out [redacted] Subjects in the Type B Cohort may have glucocorticoids administered and tapered [redacted]). Investigators will adhere to the protocol steroid taper schedule unless a safety concern (including concern related to insufficient response) necessitates departures from the schedule. Such planned departures must be discussed with the Medical Monitor, preferably in advance of the change in medication.

8.1.1 Type A

Type A will utilize a cohort dose escalation design. If < 2 of the 6 evaluable subjects in a Type A dose-escalation cohort experience a dose-limiting toxicity (DLT) during the DLT evaluation period (Days 1-29), then escalation may occur to the next higher dose level. If 2 or more of the 6 initial subjects in a Type A dose-escalation cohort experience a DLT, then no further dose escalation will occur. That dose will then be considered to have exceeded the MTD and the next-lower dose may be declared the MTD. Once a dose has been determined to have exceeded the MTD, the Data Review Committee (DRC) may recommend continuation of the study (with or without modification) and may expand enrollment to evaluate additional subjects at the MTD and/or an additional cohort at an intermediate or lower dose to better define the MTD.

Type A Cohort enrollment will proceed in a sequential manner to evaluate escalating dose levels of EQ001. The first dose level to be studied, Dose Level 1, will be 0.4 mg/kg and the maximum

dose level to be studied will be 3.2 mg/kg. Intermediate dose levels of 0.8, 1.6, and 2.4 mg/kg are planned, but other intermediate doses may be chosen based on emerging PK, PD, and safety data. Subjects in Type A Cohorts will receive a total of 2 doses, 2 weeks apart.

The MTD determination will be made based only on Type A Cohorts. Dose escalation is allowed to proceed if no predefined stopping criteria are met and the DRC recommends that it is safe to proceed.

[redacted]

8.1.2 Type B

Up to approximately 20 subjects will be dosed in the Type B Cohort. Subjects will receive a total of 13 doses of EQ001 1.6 mg/kg administered SC every 2 weeks over 24 weeks. This dose was selected based on the totality of evidence from the PK, [redacted] safety, and efficacy data of itolizumab from Type A subjects in SLE and in other indications (Section 8.4.2). [redacted]

8.2 Study Periods

The study will be conducted in 3 defined periods, Screening Period, Treatment Period, and the Follow-up Period (Section 5.2, Section 5.3, and Section 5.4). The Treatment Period for Type A Cohort subjects will be 4 weeks in duration and the Treatment Period for Type B Cohort subjects will be 24 weeks in duration. During the Treatment Period, subjects in Type A Cohorts will receive 2 doses of study drug (SC, 2 weeks apart) and subjects in the Type B Cohort will receive 13 doses of study drug (SC, every 2 weeks). Following the last dose of study drug received, subjects will enter the Follow-up Period. Each Type A Cohort subject who completes the study will undergo 4 weeks of treatment and 4 weeks of follow up, for a total of 8 weeks on study after the initiation of study drug. Each Type B Cohort subject who completes the study will undergo 24 weeks of treatment and 12 weeks of follow up, for a total of 36 weeks on study after the initiation of study drug. In addition, contraception requirements must be continued for 130 days after the last dose of study drug for Type A and B Cohorts.

Evaluation of safety will be performed by assessing adverse events, vital signs, 12-lead ECGs, physical examinations, and laboratory tests, including ADA and neutralizing ADA. Pharmacokinetics will be described by measuring EQ001 serum concentrations.

[redacted] Evaluation of clinical activity will be performed in all subjects using the SLEDAI-2K, patient-reported outcomes, serological markers, spot urine PCR, urinalysis, and serum

complement. Clinical activity in apLN subjects will be evaluated with urine PCR (including 24-hour urine collections), eGFR, and doses of prednisone (or equivalent).

8.3 Safety Monitoring and Considerations

Study subjects will be under close medical supervision by the investigator throughout the study. Study drug administration will be in the clinic. Scheduled visits for safety assessments will occur every 2 weeks during the treatment period. Blood counts will be measured and reviewed prior to each dose. Type A Cohorts will be the first cohorts to be studied at any new higher dose and will receive only 2 doses (over 4 weeks). Only once a dose is determined to not have exceeded the MTD will that dose be allowed to be studied in an expansion cohort of Type B subjects over a longer treatment duration (24 weeks).

Ongoing review of safety data for adverse trends will occur throughout the study. A DRC with expertise in nephrology and rheumatology will review data prior to dose escalations and will provide recommendations to the Sponsor as described in the DRC Charter and in Section 8.8.1. In addition, the Sponsor and/or Medical Monitor will perform regular ongoing review of safety data during the study.

Clinical experience with EQ001 has identified lymphopenia and injection-site (hypersensitivity) reactions such as fever as potential adverse drug reactions related to study drug administration.

8.3.1 Lymphopenia

[redacted]

[redacted]

Based on these findings and because the subject population of this study (SLE) is at risk for cytopenias from their underlying disease state, measurement of blood counts will be performed frequently in this study. [redacted]

To be eligible for the study, subjects are also required to have adequate hematologic function during Screening.

To mitigate against the potential risk of infectious complications, subjects will be specifically tested for human immunodeficiency virus (HIV), Hepatitis B and C, and tuberculosis (TB) during Screening and excluded if there is evidence of infection. Subjects with clinical evidence of active or recent bacterial, viral, or fungal infections or recent live-attenuated virus vaccinations will also be excluded.

Doses will be escalated by cohort only after review of safety data by the [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.3.3 Systemic Reactions

8.3.3.1 Systemic Hypersensitivity Reactions

Therapeutic protein products may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions that have often been described as "infusion reactions" in the past. Infusion reactions may encompass a wide range of clinical events, including anaphylaxis and other events that may not be directly related to antibody responses, such as cytokine release syndrome. All monoclonal antibodies have the potential for infusion/injection site and hypersensitivity reactions; therefore, these reactions are regarded as class-specific toxicities for monoclonal antibody drugs.

8.3.3.2 Fever and other Injection-Related Reactions

Potential systemic manifestations of infusion/injection-related/hypersensitivity reactions including urticaria, pruritus, and fever have been observed following treatment with EQ001.

For this study, in which the study drug will be administered SC, injection-related reactions are defined as acute onset of an illness (other than those limited to the injection-site, which are described above) occurring within 48 hours of study drug administration that is otherwise unexplained (e.g., by an intercurrent event or the subject's medical history) but does not meet the definition of anaphylaxis [redacted]. Signs of possible injection-related reactions include: fever, chills, pruritus, urticaria, chest pain, dyspnea, hypotension, and hypertension.

In this study, dosing will be done at the study site, and subjects will be monitored for evidence of such reactions. Because individual signs and symptoms of hypersensitivity such as fever are non-specific, investigators are required to clinically evaluate symptoms for etiology to guide management. Guidance for symptomatic and supportive treatment of presumed signs and symptoms of hypersensitivity are included in the protocol (Section 10.7). Subjects experiencing Grade 3 or higher injection-related reactions will be discontinued from study drug treatment. Specific information about such reactions will be collected in the eCRF to fully characterize them.

8.3.3.3 Anaphylaxis

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as an investigational product. Anaphylaxis will be evaluated using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (see Appendix D). Subjects with a history of anaphylaxis to foods or drugs will be excluded from the study. Any subject experiencing anaphylaxis considered

related to the study drug by the investigator will be discontinued permanently from study drug treatment.

Doses will be escalated by cohort only after review of safety data by the DRC, with special attention to hypersensitivity dose-limiting toxicities. Systemic hypersensitivity reactions (Injection-related reactions and anaphylaxis) have also been defined as AESIs, and thus are to be reported with clinical details of the event within 24 hours (Section 12.6) for review by the Sponsor or designee.

8.4 Rationale for Study Design

The open-label study design will ensure subject safety by allowing frequent ongoing assessment of safety by the Sponsor, investigators, and the DRC. All subjects will receive EQ001. The dose levels selected (from 0.4 to 3.2 mg/kg) will allow an assessment of the full dose-response curve of EQ001. Dose escalation will occur by cohort following review of data by the DRC to allow emerging safety, PK, and other data to inform dose-escalation decisions based on pre-defined DLT criteria and stopping rules.

The Type A Cohort subjects will receive 2 doses of study drug, which are expected to have pharmacodynamic effects for approximately 4 weeks. The multiple ascending dose data from Type A Cohorts is expected to provide sufficient safety and pharmacokinetic data to allow the study of a dose (1.6 mg/kg) determined not to exceed the MTD in the apLN population (Type B Cohort subjects) over a longer duration. Type B Cohort subjects will receive 13 doses over 24 weeks as prolonged treatment may be needed for subjects with chronic disease. This is reflective of lupus nephritis induction treatments, which generally require at least 6 months of treatment as noted in the Kidney Disease Improving Global Outcomes (KDIGO) glomerulonephritis guidelines (https://kdigo.org/guidelines/gn/). Prolonged treatment will also enable a better understanding of the exposure-response relationship, long-term safety, dose selection, and the effect size.

This design feature is intended to minimize risk to subjects and to allow exploration of a safe range of doses over relatively short treatment duration as well as to explore doses associated with PD and clinical activity.

8.4.1 Rationale for Evaluating EQ001 for the Treatment of Patients with Systemic Lupus Erythematosus with or without Active Proliferative Lupus Nephritis

Current treatment for Class III and IV LN are non-targeted immunosuppressive medications: cyclophosphamide and/or mycophenolate with glucocorticoids [redacted] For patients who do not achieve remission with these treatments or who are unable to tolerate them, there is no standardized approach to management because there is a general lack of evidence-basis [redacted] This study will enroll subjects with biopsy-proven active proliferative Class III or IV (with or without Class V) LN who have proteinuria (> 1000 mg/g) and evidence of serologic activity who require induction treatment for apLN for newly diagnosed disease or

relapsing/flaring disease. In this study, we will enroll patients with apLN who are, by definition, at high risk for adverse renal outcomes (Section 7). Further, the study population will consist of subjects who continue to have LN activity clinically and serologically despite induction treatment. This is a patient population for whom there is a clear unmet medical need and for whom the risk-benefit for the addition of an investigational agent to standard treatments is justifiable, particularly with close and careful monitoring that is required as part of this protocol.

In order to select EQ001 doses to examine in the apLN population for a 24-week treatment period, the safety, pharmacokinetics, and pharmacodynamics effects of EQ001 of each dose will first be studied in patients with SLE with or without active disease (and who do not have apLN) over a 4-week treatment period. This sequential approach of first evaluating each dose in a shorter treatment period in a less ill population allows for the initial evaluation of safety with multiple doses, optimization of dose selection for study in the apLN population, and also is intended to mitigate risk by initially exposing subjects treated at a given dose to a shorter course of treatment.

8.4.2 Rationale for Selection of Starting Dose of EQ001

A robust body of clinical data exists to inform the selection of a starting dose and dose regimen for EQ001 in this study.

A starting dose of 0.4 mg/kg administered SC was chosen for evaluation in the initial group of 6 subjects, with additional cohorts receiving the planned doses of 0.8, 1.6, 2.4, and 3.2 mg/kg EQ001, based on safety, tolerability, PK, [redacted] and clinical activity. [redacted]

The present study is designed to assure adequate trough levels while assessing the potential for accumulation in this short-term study. Because the study population is at increased risk for lymphopenia due to the underlying disease condition (SLE) and concomitant background treatment(s) (e.g. mycophenolate mofetil), and because of the potential risk of EQ001 causing a decrease in lymphocyte counts, the starting dose of EQ001 in this study will be lower (0.4 mg/kg) than the lowest dose studied in the Phase 1 healthy volunteer study (0.8 mg/kg).

Based on the safety, PK, [redacted] results from Type A cohorts in conjunction with data from other EQ001 studies such as in aGVHD, the 1.6 mg/kg was selected as the starting dose for the Type B cohorts. This dose was well tolerated in Type A subjects, and there was evidence of reduced cell surface level of CD6 on T cells, a PD marker for cellular activity. [redacted]

8.5 Study Objectives

8.5.1 Primary Objectives

Characterize the safety and tolerability of EQ001 in subjects with SLE with or without apLN

8.5.2 Secondary Objectives

In subjects with SLE with or without apLN,

1. Characterize the PK profile of EQ001
- [redacted]
- [redacted]
4. Characterize the clinical activity of EQ001 in Type B Cohort subjects

8.5.3 Exploratory Objectives

- [redacted]
2. Characterize the clinical activity of EQ001 in Type A Cohort subjects

8.6 Endpoints

8.6.1 Primary Endpoints

Safety and tolerability of EQ001, as assessed by TEAEs, treatment emergent-serious adverse events (TESAEs), clinical laboratory values, vital signs, 12-lead ECG, and physical examinations.

8.6.2 Secondary Endpoints

1. Pharmacokinetics of EQ001, as assessed by EQ001 serum concentrations at specified timepoints.
- [redacted]
- [redacted]
4. Clinical activity of EQ001 in subjects with apLN, as assessed by the following variables:
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]

[redacted]

8.6.3 Exploratory Endpoints

[redacted]

2. For Type B cohort subjects: Change from baseline in the Short-Form 36 Health Survey (SF-36) and FACIT-F (Additional Concerns domain) total score to FU1 and FU2 and change from baseline in the Lupus Quality of Life (QoL), patient global assessment, and physician global assessment (PGA) to FU2

8.7 Cohort Dose Escalation (Type A Cohorts)

The study will utilize a dose escalation design for Type A Cohorts. If < 2 of the 6 evaluable EQ001-treated subjects in a Type A dose-escalation cohort experience a DLT during the DLT evaluation period (Days 1-29), then escalation may occur to the next higher dose level. If 2 or more of the 6 initial subjects in a Type A dose-escalation cohort experience a DLT, then no further dose escalation will occur. That dose will then be considered to have exceeded the MTD and the next-lower dose may be declared the MTD. Once a dose has been determined to have exceeded the MTD, the DRC may recommend continuation of the study (with or without modification) at doses at or below the MTD. Alternatively, an additional cohort at an intermediate lower dose may be added to better define the MTD.

Type A Cohort enrollment will proceed in a sequential manner to evaluate escalating dose levels of EQ001. The first dose level to be studied, Dose Level 1, will be 0.4 mg/kg and the maximum dose level to be studied will be 3.2 mg/kg. Intermediate dose levels of 0.8, 1.6, 2.4 mg/kg are planned, but other intermediate doses or doses lower than 0.4 mg/kg may be chosen based on emerging PK, PD, and safety data. Subjects in Type A Cohorts will receive a total of 2 doses, 2 weeks apart. [redacted]

The MTD determination will be made based only on Type A Cohorts. Dose escalation is allowed to proceed if no predefined stopping criteria are met and the DRC recommends that it is safe to proceed.

Based on emerging data, the DRC may recommend expanding a dose cohort that has not exceeded the MTD (up to 6 additional subjects) and/or adding a dose cohort at an intermediate lower dose level (with up to 6 subjects).

8.8 Data Review Committee,

8.8.1 Data Review Committee

The DRC membership will consist of 3 independent medical experts with expertise in rheumatology and/or nephrology (voting members), as well as an independent statistician, and 2 Sponsor representatives, which may include one clinical and one safety representative (non-voting members). The full description of the DRC structure and responsibilities are described in the Data Review Committee Charter.

The DRC will be responsible for reviewing data from Type A Cohorts throughout the study.

The MTD determination will be made based only on Type A Cohorts.

For Type A Cohorts, dose escalation is allowed to proceed if no predefined stopping criteria are met (Section 8.8.2) and the DRC recommends that it is safe to proceed. Enrollment at a higher dose level will not commence until all safety data from all Type A Cohort subjects from the

current dose level through Study Day 29 (or early termination) are reviewed by the DRC and approval is granted for dose escalation.

Additionally, the DRC will receive expedited safety reports from other ongoing trials with EQ001. The DRC will continue to meet periodically as defined in the DRC Charter after dose escalation has been completed to review emerging safety data on an ongoing basis. The DRC may also schedule additional ad hoc meetings at their discretion or at the Sponsor's request. The DRC will make recommendations based on protocol-defined subject and study-stopping criteria with consideration given to the totality of the available safety data. The DRC recommendation may include a recommendation to advance to the next higher dose level, no further dose escalation, discontinuation of dosing in a given cohort, modification of the study (including the doses to be tested), or discontinuation of the study.

Additional subjects may be enrolled in a cohort if considered necessary by the DRC to further characterize drug safety, tolerability, or efficacy. Also, the DRC may recommend modification of the doses to be evaluated, to not initiate specific dose cohorts, to initiate additional dose cohorts, or to terminate the study if it is deemed necessary. Appropriate regulatory approvals will be obtained prior to initiation of any DRC-recommended protocol changes, as required.

8.8.2 Dose-Limiting Toxicities

Any of the following events occurring in subjects in a dose escalation Type A Cohort who have received at least 1 dose of study drug and that are considered by the investigator to be at least possibly related to the study drug are considered DLTs during the DLT window, Study Days 1 through 29:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Adverse events related to the standard of care (e.g., glucocorticoids, etc.) are not considered DLTs. Adverse events related to SLE (e.g., anemia, thrombocytopenia, fatigue, changes in renal function, etc.) will not be considered DLTs, unless they are judged to be related (or also related) to EQ001. [redacted]

[redacted]

[redacted]

9 STUDY POPULATION

Each cohort will enroll unique subjects who may not be treated in more than 1 cohort. Subjects will have SLE without active proliferative LN in Type A cohorts. The subjects in Type B cohorts will have SLE with active proliferative LN.

9.1 Inclusion Criteria

9.1.1 Type A Cohort (Subjects Without Active proliferative LN) Inclusion Criteria.

Subjects will be required to meet all of the following inclusion criteria in order to be eligible for study enrollment:

1. Is male or female, age ≥ 18 and ≤ 75 years
2. Has provided written informed consent prior to participation in the study in accordance with federal, local, and institutional guidelines
3. Has previously been documented to have met or currently meets Systemic Lupus International Collaborating Clinics (SLICC) and/or American College of Rheumatology (ACR) criteria for SLE [redacted]
4. Received at least 1 immunosuppressive or immunomodulatory treatment (including antimalarials) for SLE at any time in the past or currently
5. If the subject is taking prednisone (or equivalent glucocorticoid), the dose should be ≤ 10 mg per day and stable for at least 2 weeks prior to Screening.
6. Has documented elevation of antinuclear antibodies (ANA) in the past or during Screening
7. Restricted SLE treatments (e.g., other immunosuppressive medications, glucocorticoids, and antimalarials) are stable and/or washed out at Screening [redacted]
8. Changes in SLE drug treatment(s), including increased doses of glucocorticoids or other SLE treatments, are not anticipated during the study
9. During Screening, has adequate hematologic function as defined by
   a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   b. ALC ≥ 1.0×10^9/L
   c. Platelet count > 75×10^9/L
   d. Hemoglobin > 8.5 g/dL

   Note: If a more recent central laboratory value is available at the time of enrollment, the most recent value should be used
10. eGFR ≥ 40 mL/min/1.73m^2 during Screening

    Note: If a more recent central laboratory value is available at the time of enrollment, the most recent value should be used
11. If the subject is a female of childbearing potential, she must be willing to practice complete abstinence, or she and any male partner are required to simultaneously use

2 effective contraceptive methods, from the following list of 5 methods below throughout the study and for 130 days after the last dose of study drug:

- A barrier (condoms, diaphragm or cervical cap) with or without spermicide;
- A second, different barrier method (condoms, diaphragm or cervical cap);
- Oral or similar contraceptive, which includes, but is not limited to: injectable, implanted, or patch hormone therapy, and hormone-containing intrauterine device (IUD);
- Non-hormonal IUD (must be used with another non-IUD method);
- Partner vasectomy at least 6 months prior to Screening.

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal (i.e., no menses for 2 years) or permanently sterilized (i.e., bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, hysterectomy, or bilateral tubal occlusion with confirmation of occlusion by hysterosalpingogram).

Male subjects must have had a vasectomy at least 6 months prior to the first dose of the study drug or agree with their partner to use one of the acceptable birth control methods as listed above throughout the study and for 130 days after the last dose of study drug.

12. Is willing and able to comply with all protocol procedures and assessments required for the study
13. Is deemed by the investigator to be likely to comply with the protocol for the duration of the subject's participation in the study

9.1.2 Type B Cohort (Subjects with Active proliferative LN) Inclusion Criteria.

Subjects will be required to meet all of the following inclusion criteria in order to be eligible for study enrollment:

1. Is male or female, age ≥ 18 and ≤ 75 years
2. Has provided written informed consent prior to participation in the study in accordance with federal, local, and institutional guidelines
3. Has diagnosis of SLE
4. Kidney biopsy within 12 months prior to baseline or during Screening with a histologic diagnosis of LN (ISN/RPS 2003 classification of LN) Classes III, IV-S or IV-G, (A) or (A/C); Subjects with Class III or IV and concomitant Class V will be permitted.
5. Has a urine protein to creatinine ratio of > 1000 mg/g based on the mean of two 24-hour urine collections or a single urine protein to creatinine ratio of > 2000 mg/g based on a single 24-hour urine collection. The 2 collections must be within 12 weeks from Day 1 with 1 collected and resulted within 6 weeks of Day 1.

6. (All Regions except Asia-Pacific [APAC]) All subjects must be on MMF/MPA 2 to 3 g/day. For subjects that require induction treatment due to newly diagnosed LN or relapsing/flaring disease, subjects can have pulse systemic corticosteroids administered as part of their induction treatment.

   (APAC) Requires induction treatment due to newly diagnosed LN or relapsing/flaring disease. Subjects need to be on MMF/MPA (2 to 3 g/day) and pulse systemic corticosteroids as part of their induction treatment. The MMF/MPA and pulse systemic corticosteroids can be started within 12 weeks prior to Day 1 or on Day 1.

7. Subjects that require induction treatment must receive at least 2 consecutive days of pulse systemic corticosteroids of methylprednisolone (≥500 mg) or equivalent and be able to receive it 12 weeks prior to Day 1 or start on Days 1 and 2; all induction subjects must be able to undergo a taper of systemic corticosteroids during the first 10 weeks of treatment.
8. Within 6 weeks of Day 1 has adequate hematologic function as defined by
   a. ANC $\geq 1.5 \times 10^9$/L
   b. ALC $\geq 1.0 \times 10^9$/L
   c. Platelet count $> 75 \times 10^9$/L
   d. Hemoglobin > 8.5 g/dL
9. Blood pressure ≤ 170/95 mm Hg without recent clinically significant changes per the investigator
10. The investigator considers the protocol-recommended steroid tapering schedule to be clinically appropriate for the subject based on the subject's current status and history
11. Has documented elevation of ANAs in the past or currently
12. The dose of MMF/MPA and other SLE drug treatments (other than glucocorticoids) are expected to remain stable during the study
13. Restricted SLE treatments (e.g., other immunosuppressive medications, antimalarials, ACE inhibitors, and angiotensin receptor blockers) are stable and/or washed out at Screening [redacted]
14. Most recent eGFR ≥ 40 mL/min/1.73m^2 during Screening
15. No recent clinically significant changes in eGFR (increases or decreases) per the investigator
16. If the subject is a female of childbearing potential, she must be willing to practice complete abstinence, or she and any male partner are required to simultaneously use 2 effective contraceptive methods, from the following list of 5 methods below throughout the study and for 130 days after the last dose of study drug:
    - A barrier (condoms, diaphragm or cervical cap) with or without spermicide;
    - A second, different barrier method (condoms, diaphragm or cervical cap);
    - Oral or similar contraceptive, which includes, but is not limited to: injectable, implanted, or patch hormone therapy, and hormone-containing IUD;

- Non-hormonal IUD (must be used with another non-IUD method);
- Partner vasectomy at least 6 months prior to Screening.

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal (i.e., no menses for 2 years) or permanently sterilized (i.e., bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy, hysterectomy, or bilateral tubal occlusion with confirmation of occlusion by hysterosalpingogram).

Male subjects must have had a vasectomy at least 6 months prior to the first dose of the study drug or agree with their partner to use one of the acceptable birth control methods as listed above throughout the study and for 130 days after the last dose of study.

17. Is willing and able to comply with all protocol procedures and assessments required for the study
18. Is deemed by the investigator to be likely to comply with the protocol for the duration of the subject's participation in the study
19. Has documented within 12 weeks of Day 1 one or more of the following, only if subject has a kidney biopsy > 6 months from Day 1:
    a. Anti-dsDNA immunoglobulin (IgG) above the reference range
    b. Complement C3 below the reference range
    c. Complement C4 below the reference range

[redacted]

9.2 Exclusion Criteria

9.2.1 Type A Cohort (Subjects Without Active proliferative LN) Exclusion Criteria.

Subjects will be ineligible for enrollment in the study if they meet any of the following criteria:

1. Active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Screening
2. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases that are not considered related to SLE (e.g., pulmonary [including congestive heart failure NYHA III/IV, myocardial infarction or stroke within 6 months, chronic obstructive pulmonary disease, pulmonary hypertension, and pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases) which, in the opinion of the investigator, could confound the results of the study, put the subject at undue risk, or interfere with protocol adherence or a subject's ability to give informed consent
3. Acute or chronic infections requiring systemic antibacterial, antifungal, or antiviral therapy within 21 days of Screening or active infection during Screening
4. History of or Screening lab test positive for hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV

   Note: Subjects with a history of HCV treatment who do not have detectable HCV ribonucleic acid (RNA) may be enrolled
5. Primary immunodeficiency other than complement deficiencies
6. Active TB or a positive interferon-gamma release assay (IGRA) TB test

   Note: Based on local practice and requirements, additional testing can be conducted with Medical Monitor approval to rule out active or untreated latent TB for eligibility
7. Receipt of a live-attenuated vaccine within 2 months prior to Screening or anticipated to be required during the study
8. Female subjects who are pregnant or breastfeeding
9. History of clinical manifestations of antiphospholipid syndrome (e.g., arterial, venous thrombosis, miscarriage, or pre-eclampsia) within 12 months of screening
10. History of apLN
11. History of cancer with signs of disease within the 5 years prior to Screening

    Note: Does not apply to subjects with in situ or non-melanoma skin cancer or in situ cervical carcinoma that has been completely excised or has been curatively treated.
12. Has a history of anaphylaxis to foods, drugs, or therapeutic biologic products
13. Has a history of substance abuse (including alcohol) that may, in the investigator's judgment, increase the risk to the subject of participation in the study

14. The subject has received an investigational drug within 30 days or within 5 half-lives prior to Screening, whichever is longer or is expected to receive any investigational product other than the study drug during the study.
15. Body mass index ≥ 40 kg/m^2

9.2.2 Type B Cohort (Subjects with Active proliferative LN) Exclusion Criteria

Subjects will be ineligible for enrollment in the study if they meet any of the following criteria:

1. Active CNS lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Screening
2. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases that are not considered related to SLE (e.g., pulmonary [including congestive heart failure NYHA III/IV, myocardial infarction or stroke within 6 months, chronic obstructive pulmonary disease, pulmonary hypertension, and pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases) which, in the opinion of the investigator, could confound the results of the study, put the subject at undue risk, or interfere with protocol adherence or a subject's ability to give informed consent
3. Acute or chronic infections requiring systemic antibacterial, antifungal, or antiviral therapy within 21 days or active infection during Screening
4. History of or Screening lab test positive for HBV, HCV, or HIV

   Note: Subjects with a history of HCV treatment who do not have detectable HCV RNA may be enrolled
5. Primary immunodeficiency other than complement deficiencies
6. Active TB or untreated latent TB (as determined by the treating physician and local practice and requirements)

   Note: Based on local practice and requirements, specific testing or additional testing can be conducted with Medical Monitor approval to rule out active or untreated latent TB for eligibility as required
7. Receipt of a live-attenuated vaccine within 2 months prior to Screening or anticipated to be required during the study
8. Female subjects who are pregnant or breastfeeding
9. History of clinical manifestations of antiphospholipid syndrome (e.g., arterial, venous thrombosis, miscarriage, or pre-eclampsia) within 12 months of screening
10. History of cancer with signs of disease within the 5 years prior to Screening.

    Note: Does not apply to subjects with in situ or non-melanoma skin cancer or in situ cervical carcinoma that has been completely excised or has been curatively treated.
11. Has a history of anaphylaxis to foods, drugs, or therapeutic biologic products

12. Has a history of substance abuse (including alcohol) that may, in the investigator's judgment, increase the risk to the subject of participation in the study
13. History of any concurrent illness (e.g., other than SLE or LN), that has required treatment with oral or parenteral glucocorticoids for more than a total of 2 weeks within the last 12 weeks prior to the Screening Visit
14. History or rapidly progressive glomerulonephritis and/or other renal disease not directly due to LN
15. The subject has received an investigational drug within 30 days or within 5 half-lives prior to Screening, whichever is longer or is expected to receive any investigational product other than the study drug during the study.
16. Body mass index ≥ 40 kg/m ^{2}

10 STUDY TREATMENTS

[redacted]

10.2 Study Drug: EQ001

All subjects will receive EQ001 (study drug). EQ001, containing the active ingredient itolizumab, is a humanized recombinant IgG1 mAb that selectively targets the extracellular Sc membrane-distal domain 1 of human CD6. [redacted]

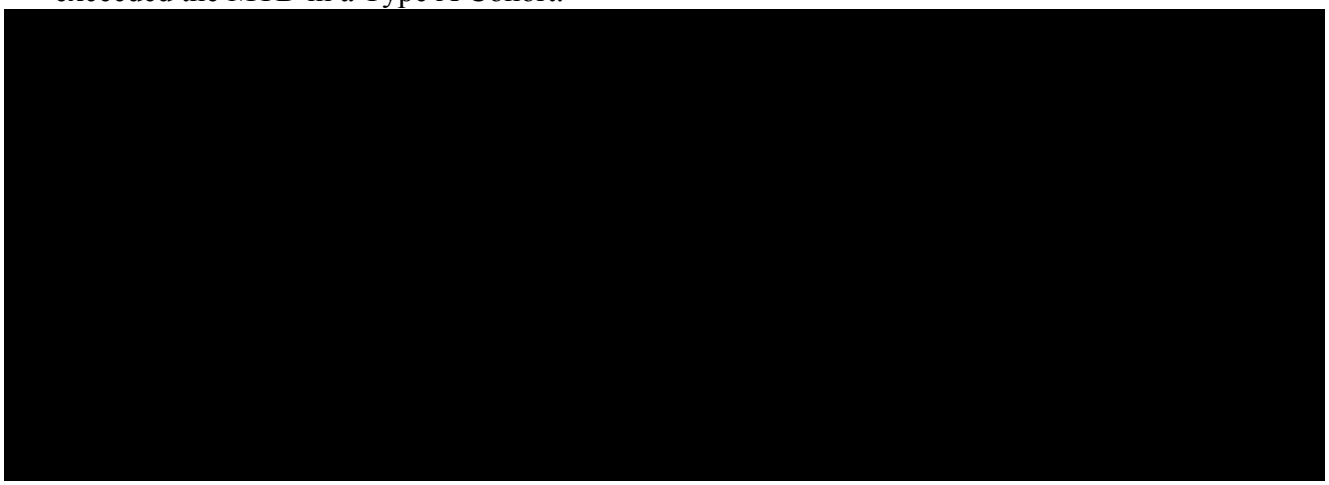
[redacted]

10.5 Study Drug Administration

EQ001 doses will be administered at the study site by a qualified staff member and the time of injection will be recorded; subjects will be observed for a minimum of 30 minutes after administration of the study drug. Study drug will be administered via SC injection into the abdomen.

In Type A Cohorts, study drug will be administered SC every 2 weeks for 4 weeks (a total of 2 doses). The first dose level to be studied, Dose Level 1, will be 0.4 mg/kg and the maximum dose level to be studied will be 3.2 mg/kg. Intermediate dose levels are currently anticipated to be 0.8, 1.6, and 2.4 mg/kg, but other intermediate doses or doses lower than 0.4 mg/kg may be chosen [redacted].

The dose level planned for the Type B Cohort is 1.6 mg/kg. Study drug will be administered SC every 2 weeks for 24 weeks (a total of 13 doses). This dose has been determined to not have exceeded the MTD in a Type A Cohort.



[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

10.7 Management of injection-site and hypersensitivity reactions

[redacted]

[redacted]

[redacted]

Injection-Related (Hypersensitivity) Reactions

For this study, in which the study drug will be administered SC, injection-related reactions are defined as acute onset of an illness (other than those limited to the injection-site, which are described in Section 8.3.3.2 occurring within 48 hours of study drug administration that is otherwise unexplained (e.g., by an intercurrent event or the subject's medical history) but does not

meet the definition of anaphylaxis [redacted] Signs of a possible injection-related reaction include fever, chills, pruritus, urticaria, chest pain, dyspnea, hypotension, and hypertension.

As clinically indicated, subjects may be treated for the reaction with antihistamines (H1 ± H2 blocker), glucocorticoids, supportive care, and any additional interventions. Subjects with Grade 1 or 2 reactions may continue treatment with study drug with prophylactic measures such as acetaminophen, NSAIDs, H1 or H2 blockers prior to each injection. The investigator and Medical Monitor should discuss and agree on a plan for prophylaxis for future doses. Grade 3 or higher-grade reactions require permanent discontinuation of study drug treatment.

Anaphylaxis

Anaphylaxis [redacted] determined to be related to the study drug by the investigator requires permanent discontinuation of study drug treatment. Immediate treatment and support should be given with oxygen, bronchodilators, steroids, epinephrine, etc. in accordance with investigator/local standard of care.

10.8 Prior and Concomitant Medications

Prior and concomitant medications and treatments will be collected at the time of enrollment and throughout the study. All prior treatments and treatment regimens for SLE and LN will be collected.

10.8.1 Permitted Therapies

Other than restricted medications described in Section 10.8.2, subjects may continue to take their chronic medications.

10.8.2 Restricted Medications

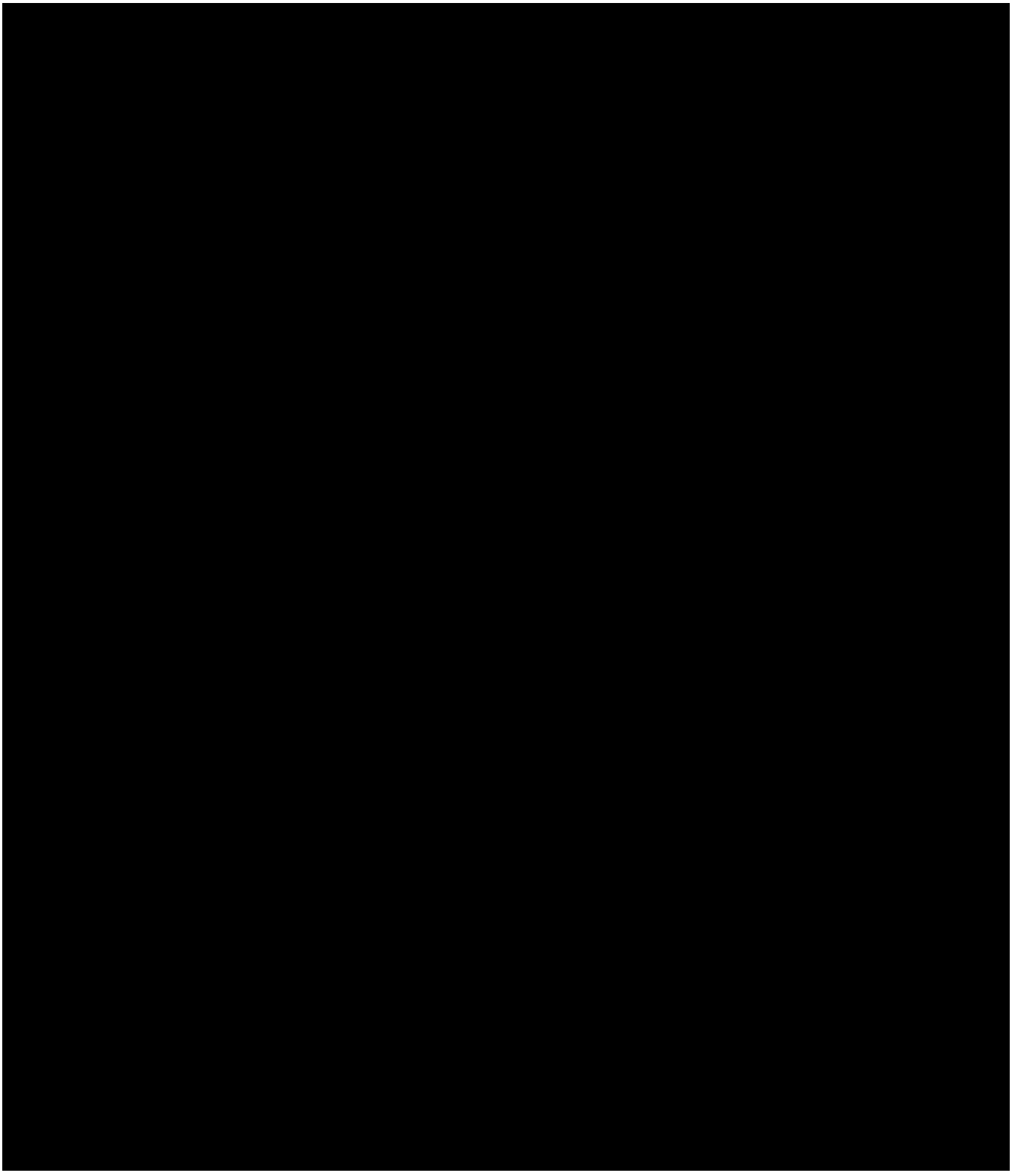
Treatments for SLE and its complications may need to be kept stable, washed out, or may be disallowed. [redacted]

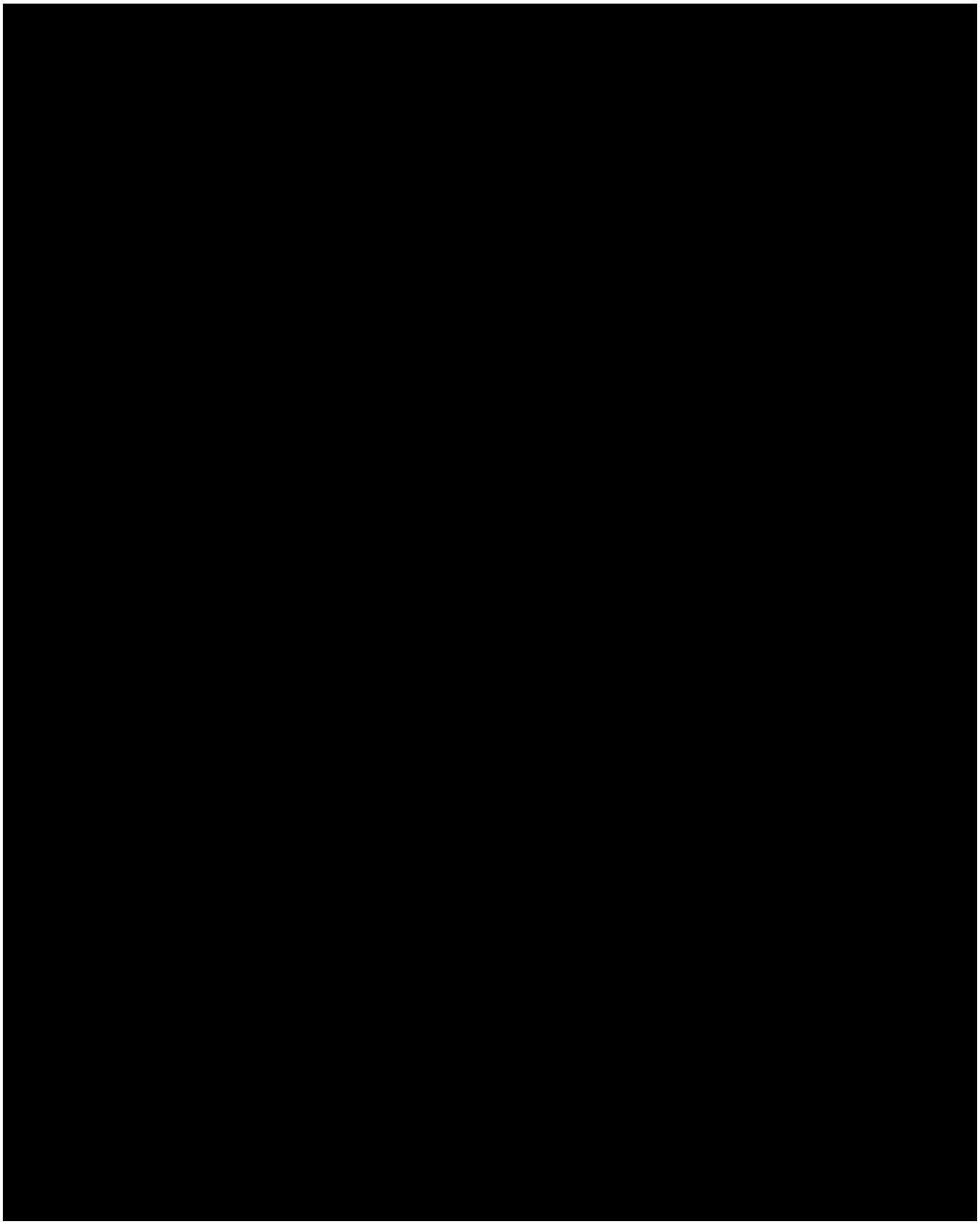
10.8.2.1 Glucocorticoids

In subjects in the Type A cohorts, the dose of glucocorticoids must be kept stable during the study [redacted]

Subjects in the Type B Cohort should be on a stable dose of MMF or MPA for the duration of the study. For subjects that are undergoing induction treatment, they may require additional pulse steroid treatment and receive methylprednisolone ≥500 mg or equivalent within 12 weeks prior to starting study treatment or receive a dose start on Day 1 and Day 2 and then undergo a rapid oral corticosteroid taper, which will be reduced by 20% per week targeting to reach prednisone of approximately <10 mg per day by Week 10. Prednisone or equivalent can be maintained at 7.5 mg per day for the duration of the study [redacted] Investigators will adhere to the protocol steroid taper schedule unless a safety concern (including

concern related to insufficient response) necessitates departures from the schedule. Such planned departures must be discussed with the Medical Monitor, preferably in advance of the change in medication.





[redacted]

10.9 Enrollment

It is the investigator's responsibility to ensure that subjects are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study. An IWRS will be used to ensure study drug inventory, accountability, and appropriate cohort allocation.

The study will be open label. After informed consent has been obtained, all screening procedures have been assessed, and study eligibility has been confirmed, subjects will receive EQ001 on Study Day 1. Subjects will be formally enrolled into the study on Day 1, as defined by completing the enrollment transaction within the IWRS.

The study pharmacist (or the designated site staff) will access the IWRS to receive the dose of study drug assigned, record drug accountability, and request resupply.

[redacted]

[redacted]

11 STUDY PROCEDURES

The following assessments will be conducted during screening and at the time points specified in the Schedule of Events (SOE) (Section 5.2, Section 5.3, and Section 5.4) and protocol Section 10. All missed visits must be documented in the subject's medical record and the appropriate eCRF.

11.1 Screening and Informed Consent

Each subject must sign and date the informed consent form (ICF) before participating in any study-specific activities. The ICF may be signed up to 4 weeks prior to the Screening Visit for Type A Cohort subjects and 8 weeks prior to the Screening Visit for Type B Cohort Subjects.

After the ICF is signed, the subject will be assigned a unique subject identification number by IWRS.

The subject number, assigned at the time of screening, will be used to identify the subject during the study and must be used on all study documentation related to that subject. The subject identification number will remain constant throughout the entire study and must not be changed after initial assignment. Each study site will maintain a list identifying all subjects by subject identification number and subject initials.

After completing the Screening Period, the subject will be evaluated by the investigator to confirm eligibility. A subject is considered to have started screening on the date that the Screening Visit is recorded in the IWRS. Screen failure subjects will be entered into the IWRS. Investigators will maintain a screening log of all potential study subjects that includes limited information about each candidate, including dates of screening and procedures, and the outcome of the screening process (e.g., enrolled into the study, reason for ineligibility, or withdrawal of consent).

At Baseline and before any study drug is administered, potential subjects will be reviewed by the site to reconfirm their eligibility.

11.2 Demographics and Medical/Surgical History

11.2.1 Demographics

Demographic data will be collected, including each subject's sex, age, race, and ethnicity. Where local regulations do not permit certain demographic data to be collected, collection of those data will not be required.

11.2.2 Medical and Surgical Histories

The investigator or designee will collect the subject's medical and surgical histories, including information on the subject's concurrent medical conditions. All findings will be recorded on the medical history and surgical history eCRFs. A *complete medical history* at the Screening Visit [redacted]

[redacted]

11.3 Physical Examination

The investigator or designee will conduct a complete physical examination as outlined in the SOE. Physical examination clinically significant findings prior to the first dose of study drug administration will be recorded on the medical history eCRF; clinically significant findings after the first study drug dose will be recorded as AEs.

[redacted]

11.4 Vital Signs

The following vital sign measurements will be performed: systolic and diastolic blood pressure, pulse, respiration rate, and temperature. Vital signs will be measured according to the SOE. On study drug dosing days, vital signs will be measured prior to the injection and approximately 15 and 30 minutes following the end of the injection. The subject must be seated or in a semi-recumbent position in a rested, calm state for at least 3 minutes before vital signs are collected. The position selected for a subject should be the same throughout the study and documented on the vital signs eCRF whenever possible. Height will be measured without shoes at Screening.

Weight without shoes will be obtained at Screening. On dosing days, weight will be obtained before dosing. The weight at Screening will be used to calculate all study drug doses, unless there has been a weight change of ≥ 20% from Baseline.

11.5 SLEDAI-2K Assessment

The investigator and/or appropriately qualified designee will complete the SLEDAI-2K data collection sheet [redacted] at specific time points, as specified in the SOE. The same individual should perform all SLEDAI-2K assessments for a given subject whenever possible.

11.6 Urine Protein Creatinine Ratio

The UPCR from a urine collection will be assessed at the timepoints specified in the SOE.

11.7 12-Lead Electrocardiography

12-Lead ECGs will be centrally read and obtained on standardized ECG equipment supplied for the study. The subject must be in a semi-recumbent or supine position in a rested, calm state for at least 10 minutes before ECG assessment is performed. Each 12-lead ECG should be performed prior to blood draws, dosing, or other invasive procedures whenever possible.

The investigator or designated study site physician will review, sign, and date all ECGs.

Any clinically significant abnormal ECG findings will be recorded as an AE.

11.8 Patient-Reported Outcomes Measures

The Medical Outcomes SF-36 [redacted] FACIT-F [redacted] Lupus QoL [redacted] and Patient Global Assessment [redacted] questionnaires will be completed by the subjects while they are at the study site. Subjects should be seated in a location away from others during the questionnaire completion. Subjects should not confer with anyone on what responses to give nor should anyone else suggest or imply the responses to give. Subjects should be told that there is no time limit for completion of the questionnaires. After the questionnaires are completed, the site staff should collect them and review them to ensure that all questions have been completed before the subject leaves the clinic.

11.9 Physician Global Assessment

At the visits during which the PGA [redacted] is assessed, investigators will score their global assessment of disease activity after reviewing the most recent laboratory results and completing the physical examination but before completing the SLEDAI-2K. The same investigator or sub-investigator should complete all the physician global assessment for a given subject whenever possible.

11.10 Kidney Biopsy (if needed and approved)

Kidney biopsies are required in Type B Cohort subjects to determine study eligibility. [redacted] If the most recent biopsy was performed more than 12 months prior to baseline, a new biopsy is required to confirm the diagnosis of apLN. This study biopsy may be performed only following approval of the Sponsor or designee based on key eligibility criteria including SLE markers (e.g. C3, anti-dsDNA antibodies), eGFR, UPCR, hematology, concomitant medications, and history of apLN. The biopsy will be read locally in accordance with the RPS/ISN classification system with an indicator of the activity and chronicity index, whenever possible. Slides should be submitted for future central reading.

11.11 Clinical Laboratory Tests

11.11.1 Safety Laboratory Tests

Blood and urine samples will be collected according to the SOE (Section 5.2, Section 5.3, and Section 5.4) and below. All scheduled laboratory tests, other than urine pregnancy testing and laboratory testing to evaluate hematology parameters prior to dosing, will be performed at the central or local laboratory. The pre-dose laboratory evaluations (ie, hematology for ALC) may be performed at a local or central laboratory up to 14 days prior to the next target dosing day or on the target dosing day. Blood testing for TB may be performed locally, at the investigator's discretion. Repeat laboratory testing will not be required if a test was already performed within the specified time window for collection. Samples may be analyzed for the tests outlined in this protocol and for any additional tests (with the Sponsor's approval) necessary to further evaluate subject safety. These may include, but are not limited to, investigation of unexpected results. Subjects will be in a seated, semi-recumbent, or supine position during blood collection. Collection procedures are described in the study Laboratory Manual.

[redacted]

[redacted]

[redacted]

[redacted]

11.11.1.1 Complement and Anti-dsDNA

Blood samples will be assayed for complement C3 and C4 and anti-dsDNA at selected time points (see SOE for details). Total hemolytic complement (CH50) may also be measured in the Type B Cohort.

11.11.1.2 Autoantibodies

Serum will be assayed for autoantibodies, including anti-nuclear antibodies (ANA) at selected time points (see SOE for details). Anti-C1q antibodies may also be analyzed.

11.11.1.3 Pharmacokinetics

Serum will be assayed for EQ001 concentrations using a validated assay. The PK samples will be collected at time points specified in the SOE.

11.11.1.4 Anti-Drug Antibody and Neutralizing ADA

Serum samples will be obtained for detection of ADA against EQ001 at the time points specified in the SOE, and, if required, a neutralizing ADA assay will be performed on the same samples. ADA sampling may be requested by the Sponsor at an unscheduled visit to further evaluate safety in individual patients.

[redacted]

[redacted]

[redacted]

[redacted]

12 ADVERSE EVENTS

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease or any worsening of a pre-existing condition temporally associated with the use of a study drug, whether or not related to study drug. The AEs that occur after the first dose of EQ001 or during the study treatment and safety follow-up periods will be documented on the AE eCRF. The investigator will assess AE severity and the causality relationship of the AE to study drug. The investigator will treat the subject as medically required to ensure the subject's safety.

Laboratory values that are outside the laboratory reference range should be reported as AEs only if the investigator considered those AEs to be clinically significant.

From the time of signing the ICF through the first study drug administration, all SAEs and nonserious AEs related to protocol-mandated procedures (including medication washout performed specifically for the study) will be recorded on the SAE/AE eCRF. All other untoward medical occurrences observed during screening, including exacerbation or changes in the medical and surgical history, will be captured on the medical and surgical history eCRF. Details on recording and reporting AEs are provided below. All AEs will be captured through the last required Follow-up visit or the ET Visit, whichever is later.

Investigators should use their clinical judgment to determine whether a subject is to be withdrawn due to an AE. In the event the subject discontinues study treatment or is withdrawn from the study due to an AE, the subject should be asked to complete all remaining FU study visits. In the event a subject is withdrawn from the study, an ET Visit should be completed.

All subjects experiencing AEs, including clinically significant abnormal laboratory values, whether or not associated with the study drug, must be monitored until the condition (1) returns to normal, (2) returns to the subject's baseline, (3) the investigator determines the AE has reached a stable outcome and is no longer clinically significant, or (4) the subject is considered lost to follow-up.

12.1 Severity

All AEs, both serious and nonserious, will be assessed for severity using the NCI CTCAE v 5.0. The CTCAE scale includes unique clinical descriptions of AEs categorized by anatomy and/or pathophysiology. Reference the following website:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

The CTCAE scale displays Grades 1 through 5 with unique clinical descriptions of severity for each AE (including abnormal laboratory values), based on this general guideline provided in the scale. For AEs not covered by CTCAE, the conventional definition of severity will be used, as follows:

- Grade 1 (mild) AE: Minor; no specific medical intervention; marginal clinical relevance.
- Grade 2 (moderate) AE: Minimal intervention; local intervention; noninvasive intervention.
- Grade 3 (severe) AE: Significant symptoms requiring hospitalization or invasive intervention.
- Grade 4 (life-threatening or disabling) AE: Complicated by acute, life-threatening complications; need for intensive care or emergent invasive procedure.
- Grade 5: Fatal AE

12.2 Causality Assessment

The investigator or qualified subinvestigator is responsible for assessing and assigning the causality relationship of the event to study drug or study-related procedures (e.g., invasive procedures, such as venipuncture) using clinical judgment and the following categories of relatedness:

- Related: There is at least some possibility that the AE could be related to study drug or a study-related procedure.
- Not related: There is a high degree of certainty that the AE is NOT related to study drug or a study-related procedure.

In making a causality assessment of an AE, it should be considered as to whether or not the AE is expected to occur due to the underlying disease, based on the investigator's clinical experience in managing SLE (Section 12.5.1).

12.3 Clinical Laboratory Adverse Events

The investigator is responsible for reviewing the results of all laboratory tests as they become available and determining whether an abnormal value in an individual subject is a clinically significant change from the subject's baseline value(s). The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, laboratory value changes that require treatment or adjustment in current therapy are to be considered AEs. When applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

12.4 Serious Adverse Events

A *serious adverse event* (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening AE (Note: A life-threatening AE is one that, in the view of the investigator places the subject at immediate risk of death from the reaction as it occurred)
- Hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

[redacted]

All SAEs, regardless of cause(s) or causal relationship to study drug, must be reported within 24 hours to the study Sponsor and/or designee. If an SAE occurs outside the reporting window of the subject's follow-up or ET visits and is considered related to study treatment, it must be reported to the Sponsor within 24 hours of the site's awareness.

12.5 Reporting Adverse Events

12.5.1 Reporting Procedures for Nonserious Adverse Events

The investigator is responsible for ensuring that all AEs observed by the investigator or designee or reported by the subject are reported using the AE eCRF.

The investigator will assign the following AE attributes:

- AE diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity
- Causality relationship to study drug or study-related procedures
- Action taken
- Outcome

Follow-up of nonserious AEs will continue through the last day on the study and/or until a definitive outcome (e.g., resolved, resolved with sequelae, lost to follow-up) is achieved.

When a subject is withdrawn from the study because of a nonserious AE, the Sponsor and/or designee must be notified by email or phone within 48 hours.

12.5.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject are promptly assessed and reported to the Sponsor and/or designee. The investigator must assess the causality relationship of the SAE to study drug or any study-related procedure.

The procedures for reporting SAEs are as follows:

- Within 24 hours of the investigator's knowledge of the event, enter data into the AE/SAE eCRF. If the EDC is not available, the paper SAE Report Form may be used, but all data must be entered into the EDC once the EDC is available.
- Additional contact numbers and AE/SAE reporting instructions will be provided in the eCRF Completion Guidelines.
- For fatal or life-threatening events and all SAEs, also email and/or fax redacted copies of hospital records, autopsy reports, and other documents, when requested and applicable. Transmission of such documents should occur with personal subject details de-identified (redacted), without losing the traceability of a document to the subject identifiers. Entry of the initial report of the event into EDC should not be delayed in order to include these additional documents.
- The Sponsor and/or designee may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The investigator must take all necessary therapeutic measures for resolution of the SAE. Any medications or therapies necessary for treatment of the SAE must be recorded in the event description section of the SAE form and the concomitant medication eCRF.

Follow-up of SAEs will continue through the last day on the study and/or until a definitive outcome (e.g., resolved, resolved with sequelae, lost to follow-up, fatal) is achieved.

While pregnancy is not considered an AE, all cases of fetal drug exposure via a maternal parent as study subject or pregnancy of a partner of a male study subject that occurs during the study or within 130 days after the last dose of study drug will be reported immediately to the Sponsor or its designee. Information related to the pregnancy must be documented on a Pregnancy Confirmation and Outcome Form, provided by the Sponsor or its designee, and the pregnancy should be followed until a definitive outcome has been determined.

The Sponsor or its designee will report SAEs as required to regulatory authorities and investigators in compliance with all reporting requirements, according to local regulations and ICH Good Clinical Practice (GCP).

The investigator will notify the appropriate IRB/IEC of SAEs occurring at the study site and other AE reports received from the Sponsor, in accordance with local requirements. The investigator or designee at each study site is responsible for submitting safety reports (initial and follow-up) and other safety information [redacted] to the IRB/IEC and/or other applicable regulatory authorities for retaining a copy in the study files.

[redacted]

[redacted]

[redacted]

13.1 General Considerations

Data will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies and percentages for discrete variables. All data summaries will be displayed by cohort. Data may also be pooled across cohorts. Baseline values of variables are considered the last available non-missing value prior to receiving any study drug unless otherwise specified. By-subject listings of the data will also be provided. All data summaries and listings will be produced using the SAS® software, version 9.3 or higher.

[redacted]

[redacted].

13.3 Analysis Populations

13.3.1 Safety Population

The *safety population* consists of all subjects who receive any study drug.

13.3.2 Pharmacokinetic Analysis Population

The *pharmacokinetics population* includes those subjects in the safety population who have at least one measurable post-EQ001 exposure serum concentration.

[redacted]

[redacted]

13.3.4 Efficacy Population

Subjects in the safety population who have at least 1 post-treatment assessment for a marker of clinical activity will be included in the efficacy population.

13.4 Subject Disposition

Subject disposition data will be summarized and will include the number and percent of enrolled subjects; number and percent of subjects initiating and completing treatment; and number and percent of subjects discontinuing treatment and discontinuing the study, further broken down by

the reasons for discontinuation. Subject enrollment will also be summarized by study site. A summary of major protocol deviations will be tabulated for each cohort.

13.5 Demographics and Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the subjects in the safety population. Demographic data will include age, gender, race, and ethnicity. Baseline characteristics data will include (but not be limited to) renal function, proteinuria (UPCR), complement, and autoantibody titers. Medical history data will include (but not be limited to) time from diagnosis of SLE to Screening, prior and current medications used for SLE, including use of biologic therapy for SLE.

13.6 Statistical Analysis of Pharmacokinetic Variables

Serum concentrations will be listed and summarized for each EQ001 dose using descriptive statistics for each cohort.

[redacted]

13.7 Safety Analyses

All safety data summaries will use the safety population.

The number and percent of Type A subjects experiencing any DLTs will be presented by cohort. A listing of DLTs will also be provided.

Adverse events (including DLTs) will be coded using the Medical Dictionary for Regulatory Activities (v 20.1, or higher version) and will be graded by the investigator using the NCI CTCAE v 5.0. Subject incidence of TEAEs, TESAEs, TEAEs leading to treatment discontinuation, AESIs, and TEAEs with an outcome of death will be summarized by SOC and preferred term. Adverse events will also be further summarized by worst CTCAE severity grade and relationship to study drug. In addition, AESIs as described in Section 12.6 will also be summarized by SOC, preferred term, and worst severity grade.

Clinical laboratory data will be summarized descriptively, these summaries will include observed values at collection timepoints and their changes from baseline. All laboratory parameters that can be graded using the CTCAE v 5.0 will be graded. For selected parameters, the following summaries may be produced:

- Worst post-baseline severity grade
- Shift summary of baseline grade to worst post-baseline severity grade.

Safety evaluations may also include changes in the subject's vital signs and ECG findings.

[redacted]

[redacted]

[redacted]

[redacted]

13.9 Efficacy Analyses

All efficacy analyses will use the Efficacy population. Handling of efficacy data obtained after a subject receives new immunosuppressive or other treatments for LN or has an increase in glucocorticoids will be described in the Statistical Analysis Plan. [redacted]

[redacted]

Analyses will be performed by dose and with all doses combined.

13.9.1 Lupus Nephritis Subjects (Type B Cohort)

13.9.1.1 Proteinuria

The geometric mean fold change from baseline in UPCR from a 24-hour urine collection and spot collections to FU1 and to FU2 will be summarized descriptively, along with their 2-sided 95% CI for the fold change. The geometric mean fold change from baseline over time by visit will also be described. The proportion of subjects with a > 30% and > 50% decline in UPCR and those with a UPCR < 500 mg/g at FU1 and FU2 will be described, along with their 2-sided 95% CI.

Time to earliest response of UPCR with response defined as a decrease of > 50% from baseline, a decrease of > 30% from baseline, and a decrease to a level < 500 mg/g will be summarized using the Kaplan-Meier method.

[redacted]

[redacted]

13.9.1.2 Serologic Markers Associated with Active LN (C3, C4, anti-dsDNA)

The mean change from baseline in C3, C4, and anti-dsDNA to FU1 and FU2 will be summarized, along with their 2-sided 95% CI for the change. The mean change from baseline over time by visit will also be described.

13.9.1.3 eGFR

The change from baseline in eGFR (mean of all Screening and Day 1 values) will be summarized by time point. The proportion of subjects with a change from baseline to FU1 and FU2 of < 20%, < 30%, and < 40% will be summarized along with their 2-sided 95% CI.

13.9.1.4 Glucocorticoid Dose

The mean change from baseline in the daily prednisone equivalent dose during Screening to the mean daily prednisone dose during the period from FU1 to FU2 will be summarized along with the 2-sided 95% CI. The proportion of subjects (with the 2-sided 95% CI) who had a prednisone dose equivalent < 10.0 mg, < 7.5 mg and < 5.0 mg at FU1 and FU2 will be summarized. This analysis will also be performed for FU3 and FU4.

13.9.1.5 Responders

The proportion of subjects achieving a complete and partial renal response [redacted] will be summarized along with the 2-sided 95% CI at FU1 and FU2. Time to earliest response will be summarized using the Kaplan-Meier method.

[redacted]

13.9.1.6 PRO Endpoints

Analyses of patient-reported outcomes measures (SF-36, Lupus QoL, FACIT-F [redacted] and Patient Global Assessment) and the Physician Global Assessment will be described in the Statistical Analysis Plan.

13.9.2 All Subjects

The changes in SLEDAI-2K scores from baseline will be summarized in both continuous and binary scale (e.g., decrease from baseline of > 4 or ≤ 4) with their 95% exact confidence intervals. Other measures of clinical activity of EQ001, such as change from baseline in autoantibody titers, serologic markers, and serum complement, will be summarized descriptively.

14 ADMINISTRATIVE CONSIDERATIONS

14.1 Investigator Responsibilities

The investigator is responsible for complying with all regulatory requirements relating to performing clinical research with an investigational product. The investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator Agreement (FDA Form 1572, or equivalent), the approved protocol, and applicable regulations for protecting the rights, safety, and welfare of study subject under the investigator's care. The investigator is additionally responsible for the control of investigational product and for providing accurate and verifiable data to the Sponsor.

The investigator must obtain the written informed consent of each subject before participation in the study. The investigator must assure initial and continuing review of the study by an IRB/IEC that complies with applicable national and local regulations.

The investigator will ensure adequate documentation of the training of research study personnel for conduct of the study, including qualifications, experience, and study role.

The investigator will be given a copy of the most current version of the EQ001 Investigator's Brochure and appropriate study process manuals and plans. The investigator is obligated to become familiar with these documents prior to initiation of the study.

Other investigator responsibilities relative to the IRB/IEC include, but are not limited to, the following:

- Submit to the IRB/IEC for review any advertisements that will be used to recruit subjects, as applicable
- Submit all protocol amendments, revisions of the Investigator's Brochure, or revisions of the Informed Consent to the IRB/IEC for review
- If Sponsor notifies the investigator about SAEs reported in other studies associated with this investigational product, report that information to the IRB/IEC if required per local regulations
- Provide the IRB/IEC with any other information it requests before or during the conduct of the study
- Report to the IRB/IEC all adverse drug reactions that are serious, unexpected, and related to investigational product as per local regulations
- Maintain a file of study-related information
- Update the IRB/IEC on a minimum of a yearly basis as per local regulations

14.2 Independent Ethics Committee Approval

Before initiation of the study at a study site, the protocol, including the final version of the ICF, the subject information sheet (if applicable), and any other applicable/relevant study documentation will be submitted to the appropriate IRB/IEC. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study prior to use. Written approval of the study documentation must be obtained and sent to the Sponsor or its designee before the study drug can be released to the investigator.

The investigator is responsible for informing the IRB/IEC of any amendments to the protocol, ICF, written information provided to subjects, and/or other procedures in accordance with local requirements. The protocol must be re-approved by the IRB/IEC upon receipt of amendments, in accordance with applicable law. The investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor or its designee.

The investigator will report promptly to the IRB/IEC and the Sponsor any new information that may adversely affect the health or safety of past or current subjects or the conduct of the study, including deviations from the protocol or reports of any reportable SAEs, during and for one (1) year after study completion.

The investigator should submit written reports of clinical study status to their IRB/IEC annually or more frequently if required. A final study notification will also be forwarded to the IRB/IEC after the study is completed or in the event of premature termination of the study in accordance with the applicable regulations. After completion of the study, the investigator will provide the IRB/IEC with a report of the outcome of the study. Copies of all contacts with the IRB/IEC should be maintained in the study file. Copies of clinical study status reports (including termination) should be provided to the Sponsor.

14.3 Ethical Conduct of Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements (referred to herein as “applicable law”).

Investigators and all sub-investigators will comply with 21 Code of Federal Regulations (CFR), Part 54, 1998 and similar conflicts of interest laws requiring documentation of financial interests or arrangements with the Sponsor, or proprietary interests in the drug under study and any other local regulatory requirements as applicable. Any required documentation must be provided prior to the investigator’s (and any sub-investigator’s) participation in the study. The investigator and sub-investigator(s) will notify the Sponsor or its designee of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes all protocol-defined activities.

14.4 Subject Information and Consent

Prior to conducting any study-related procedures, the investigator must obtain written informed consent from each subject, in accordance with applicable law. Consent will be documented on a written ICF. The ICF must be approved both by the Sponsor and by the reviewing IRB/IEC prior to presenting it to a subject. Each ICF must comply with the ICH GCP Guidelines and applicable regulatory requirements.

Investigators may discuss study availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study. The investigator or qualified designee must explain to each subject the aims, methods, reasonably anticipated benefits, and potential hazards of the study.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), the approved ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF; the original will be retained in the study files. The investigator must document the consent interview and place the record in the study files. The investigator shall also maintain a log of all subjects who sign the ICF and indicate if the subject was enrolled into the study or reason for non-enrollment.

14.5 Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, age, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions (or in accordance with local regulations). NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. Subject data will be processed in accordance with all applicable regulations. (Some studies may require double-coding of samples).

The investigator agrees that all information received from the Sponsor, including but not limited to the EQ001 Investigator's Brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without

prior written consent from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain. In compliance with applicable law and/or ICH GCP Guidelines, the investigator will permit the Sponsor's representatives and, when necessary, representatives of the regulatory authorities, direct access to any medical records relevant to the study for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

Investigators will obtain authorization from the subject to permit access to study-related records, including personal information.

Authorization is required from each subject (e.g., specific permission granted by such individual to a covered entity for the use or disclosure of an individual's protected health information). The investigator and institution must obtain such waiver/authorization in writing from the subject. Valid authorization must meet the implementation specifications under the applicable privacy laws. Authorization may be combined in the ICF (approved by the IRB/IEC), or it may be a separate document (approved by the IRB/IEC) or provided by the investigator or Sponsor (without IRB/IEC approval).

14.6 Study Initiation

Before the study drug can be shipped to the study site and before enrollment can begin, all applicable documentation and approvals as per local regulations must be in place.

The Sponsor or designee will notify the site when they are activated.

14.7 Case Report Forms and Other Study Records

The investigator will comply with the requirements for all assessments and data collection for each subject, as specified in the protocol.

During each subject's visit to the study site, the investigator or qualified designee will record progress notes in the subject's medical record to document all significant observations. At a minimum, these notes will contain the following:

- Documentation of the informed consent process, including any revised consents.
- The date of the visit and the corresponding visit or day in the study schedule.
- General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any AEs and the investigator's assessment of relationship to study drug must also be recorded.
- Any changes in concomitant medications.
- A general reference to the procedures completed.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes, as described above.

Data for this study will be captured in electronic eCRFs. Study auditing, data entry, verification and validation, and subsequent analysis will be performed by the Sponsor, or its designees, in accordance with GCPs and established Standard Operating Procedures.

Clinical data (including AEs, concomitant medications, and applicable clinical laboratory data) will be entered into an electronic database. The creation and validation of the database, data entry, validation, and verification will be performed according to 21 CFR part 11 and other applicable local regulations. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

14.8 Study Monitoring

The Sponsor or designee will assign monitors who will perform on site monitoring as frequently as necessary and in accordance with ICH GCP.

Source documents and eCRFs will be reviewed at monitoring visits and any findings will be discussed with the investigational staff. The Sponsor expects that at monitoring visits study documents and staff will be available and a suitable space will be provided for review of the study documents. The monitor will meet with the investigator on a regular basis to provide feedback on the conduct of the study.

14.9 Access to Source Documentation

The study may be subject to audit by the Sponsor, its designee, or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required subject records. The investigator should notify the Sponsor promptly of regulatory authority audits that are scheduled and must forward copies of any findings or audit reports to the Sponsor promptly.

By signing this protocol, the investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring and review of all appropriate study documentation, as well as on-site review of the procedures employed in data collection, where clinically appropriate.

14.10 Study or Study Site Termination

The Sponsor may suspend or stop the study at all centers or at specific study centers due to (but not limited to) the discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study, a decision on the part of the Sponsor to suspend or discontinue development of the product, failure of the investigator to enroll subjects into the study at an acceptable rate, failure of the investigator to comply with regulatory authority or ICH Guidelines, or submission of knowingly false information.

[redacted]

14.13 Quality Assurance

Authorized representatives of the Sponsor, a regulatory authority, or IRB/IEC may visit the study site to perform audits or inspections, including source data verification. The purpose of any such audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any other applicable regulatory requirements.

The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

It is important that the investigator and relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

14.14 Retention of Data

When the study is completed, the investigator must retain the essential documents for as long as needed (up to 25 years) to comply with regulatory guidelines and Sponsor requirements. The investigator will notify the Sponsor prior to moving or destroying any of the study documents. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator should take measures to prevent any accidental or premature destruction of these documents.

14.15 Study Report and Publications

A clinical study report will be prepared and submitted to the appropriate regulatory agency or agencies. The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after written consent has been obtained from the Sponsor.

The investigator will submit to the Sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 60 days before submission of the publication or presentation.

No such communication, presentation, or publication will include the Sponsor's confidential information (see Section 14.5).

The investigator will comply with the Sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

[redacted]

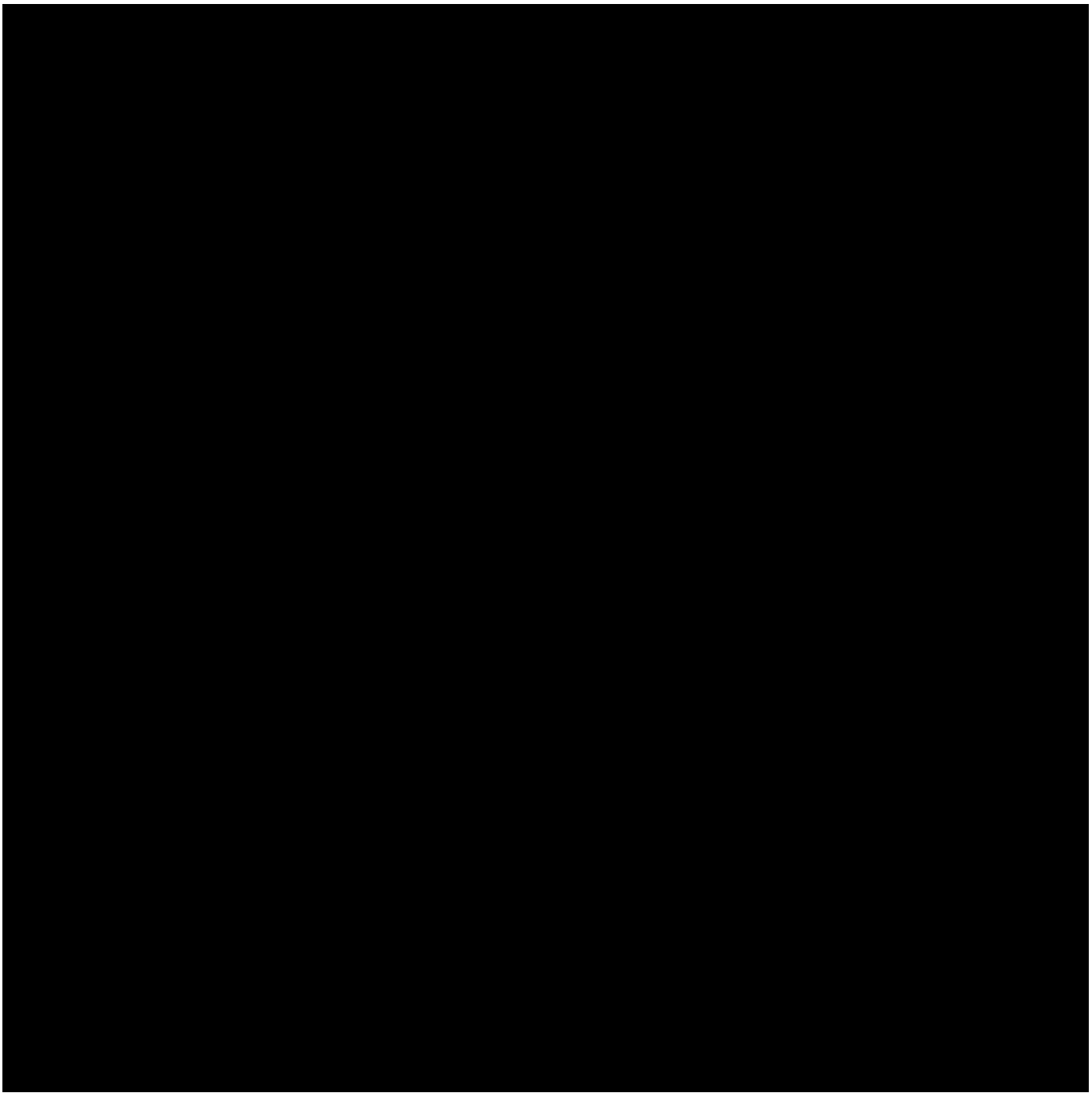
[redacted]

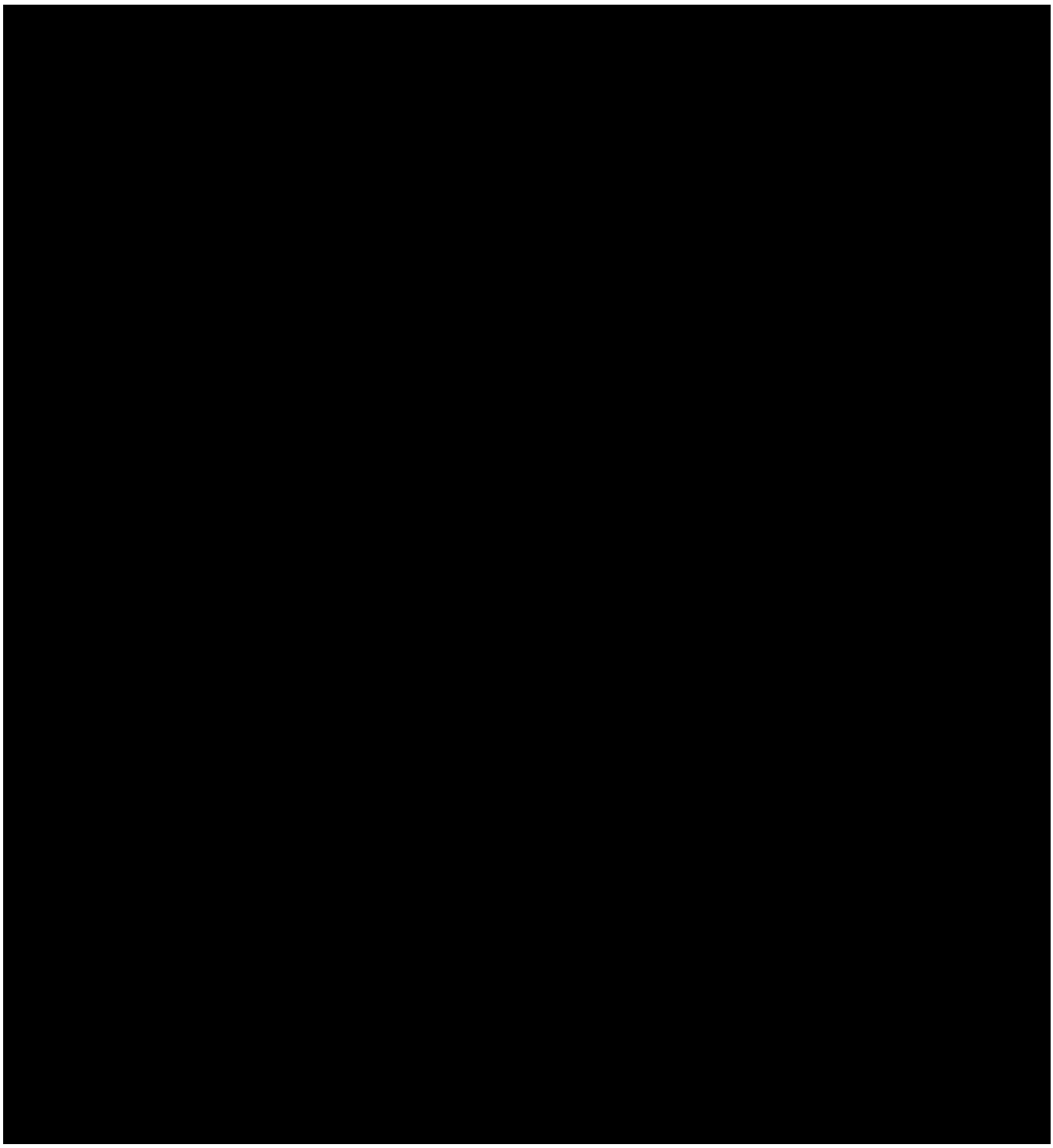
[redacted]

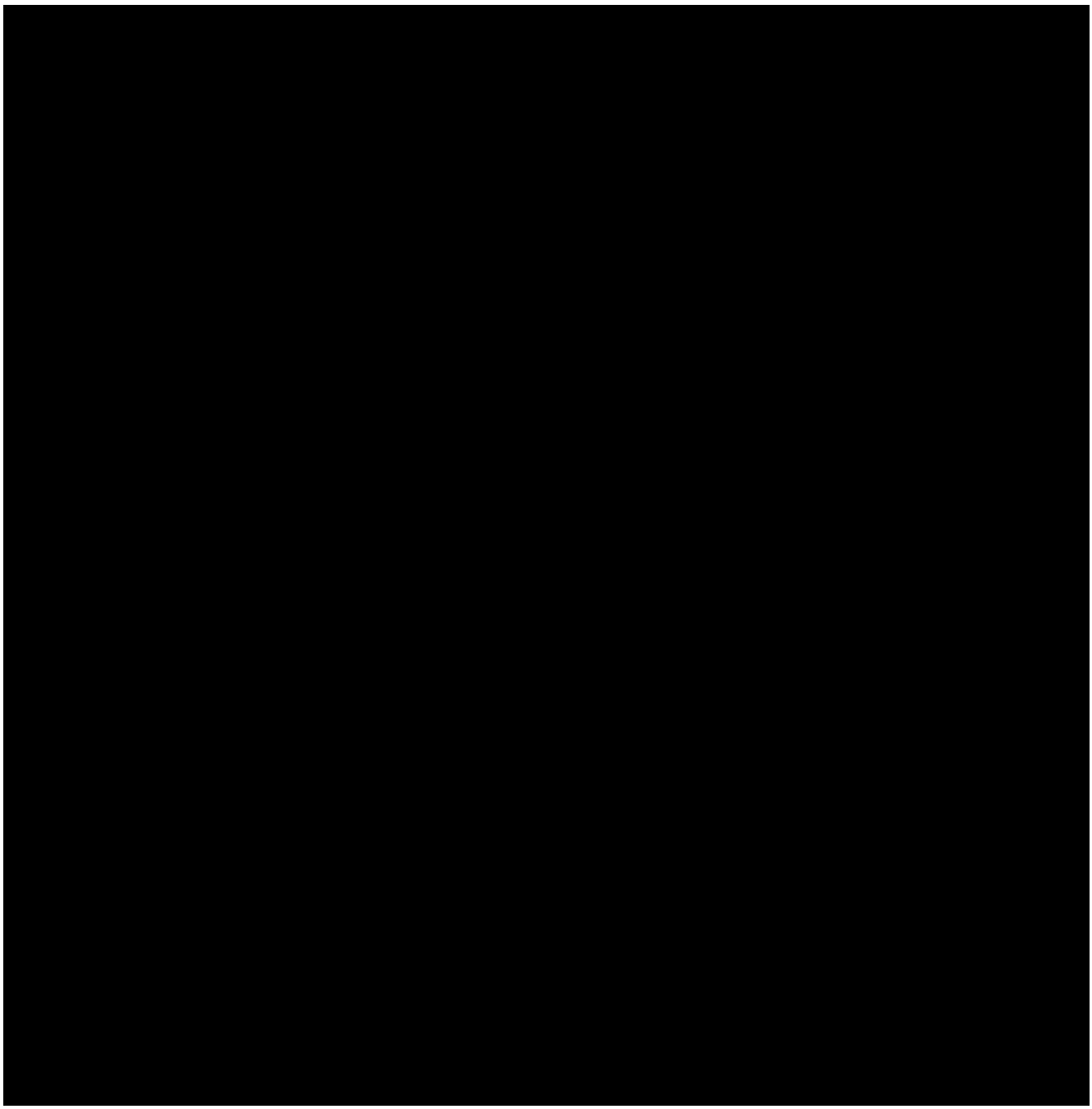
[redacted]

[redacted]

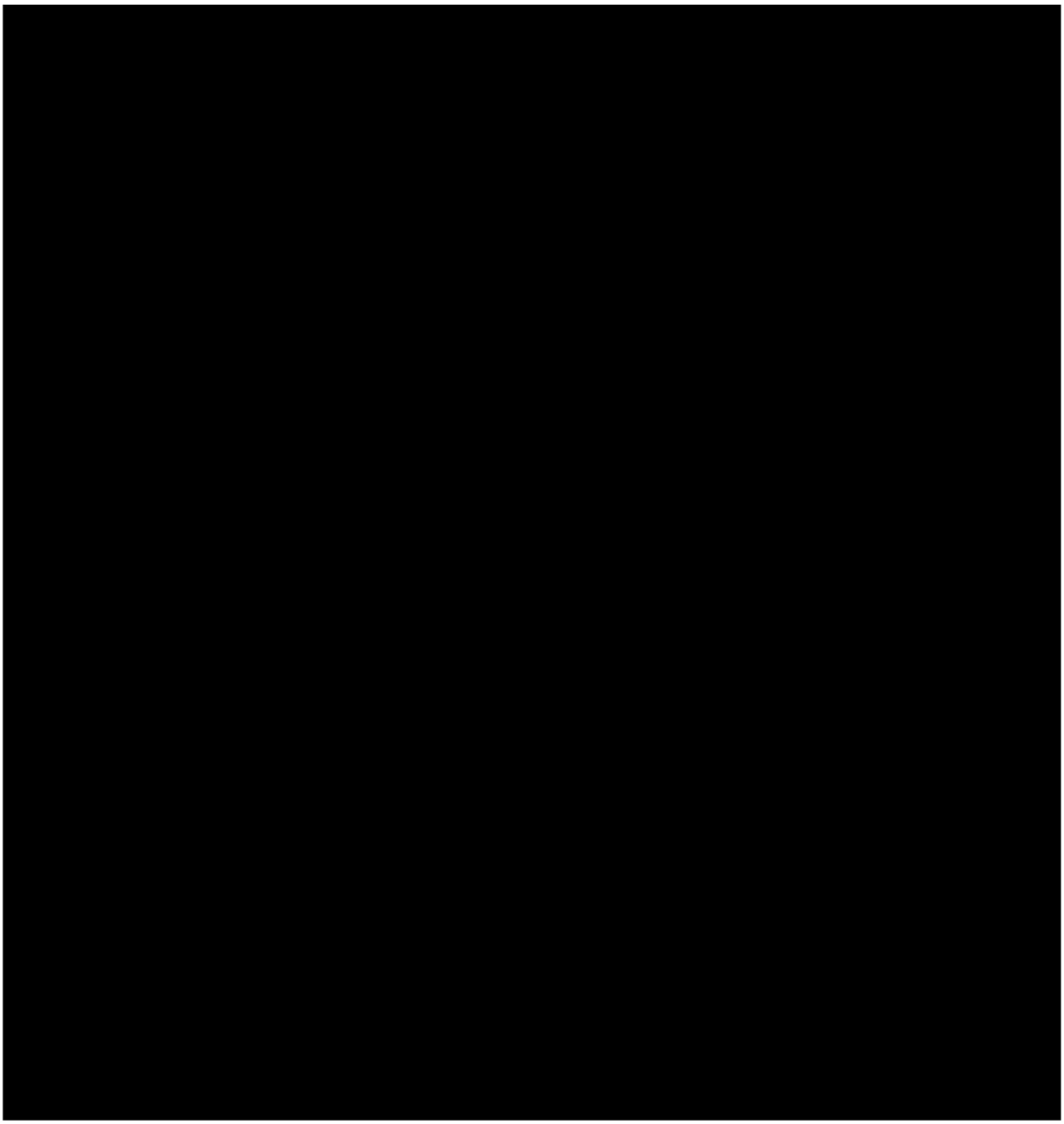
[redacted]

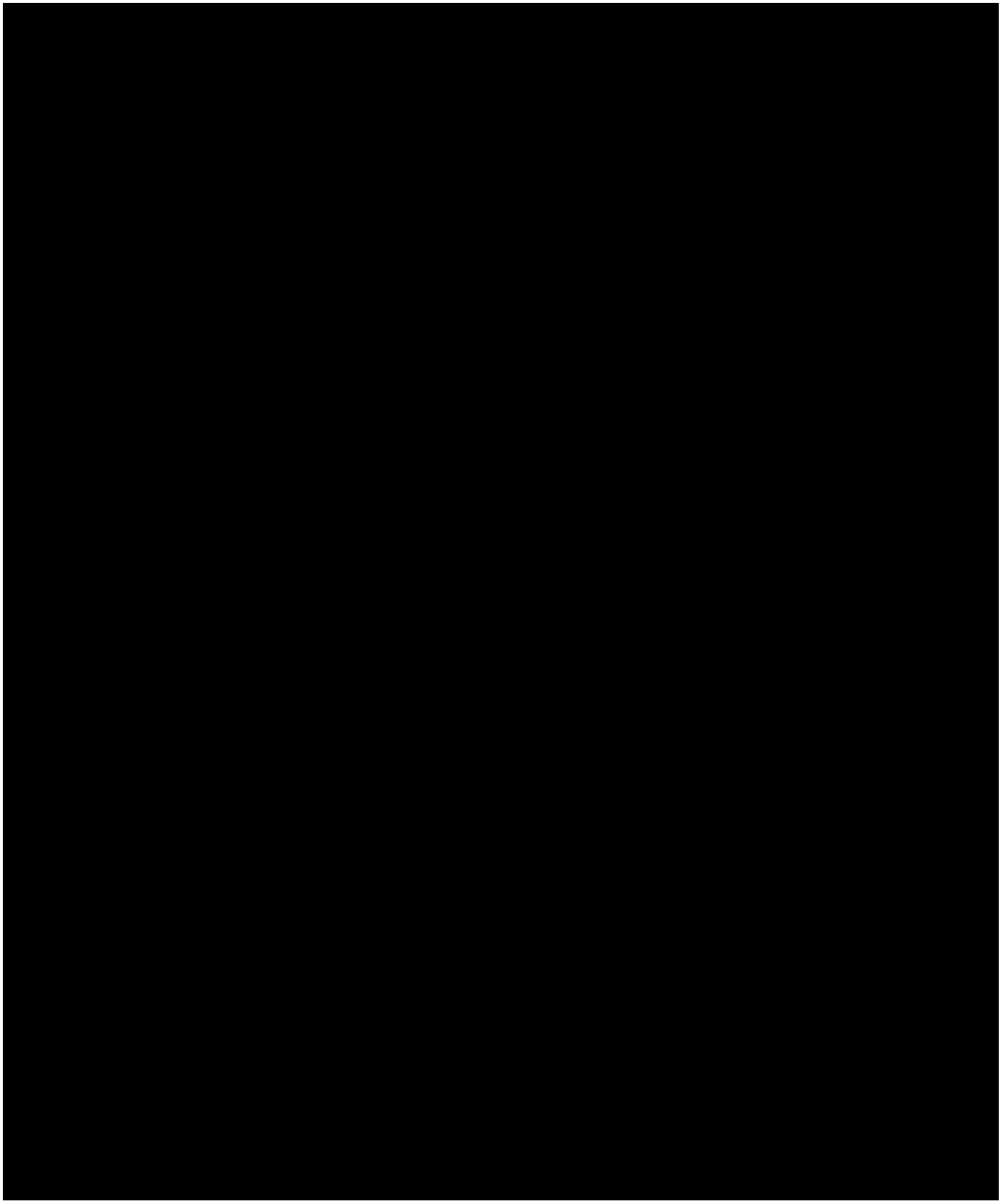






[redacted]





[redacted]

[redacted]

[redacted]

[redacted]