Protocol AC-064A201

A multicenter, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ACT-334441 in subjects with systemic lupus erythematosus

ClinicalTrials.gov Identifier: NCT02472795

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ACT-334441

Systemic Lupus Erythematosus

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A multicenter, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ACT-334441 in subjects with systemic lupus erythematosus

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SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

ACT-334441

Indication

Systemic Lupus Erythematosus

Protocol number, study title

AC-064A201, A multicenter, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ACT-334441 in subjects with systemic lupus erythematosus

I approve the design of this study.

Clinical Science Program Head	[redacted]
Clinical Project Statistician	

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

ACT-334441

Indication

Systemic Lupus Erythematosus

Protocol number, study title

AC-064A201, A multicenter, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ACT-334441 in subjects with systemic lupus erythematosus.

I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (eCRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Institutional Review Board or Independent Ethics Committee (IRB/IEC) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IRB/IEC and ensure approval by regulatory authorities (if applicable) have been obtained before the implementation of changes described in the amendment. I will allow direct access to source documents and study facilities to sponsor representative(s), particularly monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative. I will ensure that the study treatment(s) supplied by the sponsor are being used only as described in this protocol. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

	Country	Site number	Town	Date	Signature
Site Principal Investigator					

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LIST OF ABBREVIATIONS AND ACRONYMS

ACR	American College of Rheumatology
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANCOVA	Analysis of covariance
anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
anti-Sm	Anti-Smith
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-24}	Area under the curve from 0 to 24 hours
AV	Atrioventricular
BAFF	B-cell activating factor
BLyS	B-lymphocyte stimulator
BP	Blood pressure
bpm	Beats per minute
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CRA	Clinical research associate
CRO	Contract Research Organization
CRP	C-reactive protein
CSA	Cardiac safety assessor
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Measured plasma concentration at the end of one dosing interval
CTT	Clinical Trial Team

CV	Coefficient of variation
CYP	Cytochrome P450
CXCL10	C-X-C motif chemokine 10
CXR	Chest X-Ray
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
E_{max}	Maximum effect
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbant assay
EMA	European Medicines Agency
EOT	End-of-Treatment
EOS	End-of-Study
ERS	European Respiratory Society
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSFV	First Subject First Visit
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ISAC	Independent Statistical Analysis Center
ISF	Investigator site file
i.v.	Intravenous
LSLV	Last Subject Last Visit
LT	Liver test
LOCF	Last observation carried forward
MAD	Multiple-ascending dose
MCP-Mod	Multiple Comparison Procedure and Modelling
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
o.d.	Once daily
OCT	Optical coherence tomography
OSB	Ophthalmology Safety Board
PD	Pharmacodynamic
PDS	Pharmacodynamics Analysis Set
PFT	Pulmonary funtion test
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PPS	Per-protocol Set
QTcB	QT corrected for heart rate on the basis of Bazett's formula
QTcF	QT corrected for heart rate on the basis of Fridericia's formula
RBC	Red blood cells
S1P	Sphingosine-1-phosphate
$S1P_1$	Sphingosine-1-phosphate receptor 1
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SF-36v2™	36-Item Short Form Health Survey v2

SIV	Site initiation visit
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index-2000
SOC	System Organ Class
SOP	Standard operating procedure
SRBC	Sheep red blood cell
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half life
TB	Tuberculosis
TBL	Total bilirubin
ULN	Upper limit of the normal range
WBC	White blood cells
WOCBP	Women of childbearing potential

PROTOCOL SYNOPSIS AC-064A201

TITLE	A multicenter, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ACT-334441 in subjects with systemic lupus erythematosus.
OBJECTIVES	**Main objectives** • To investigate the pharmacodynamics (PD) of ACT-334441 in adult subjects with systemic lupus erythematosus (SLE). • To investigate the safety and tolerability of ACT-334441 in adult subjects with SLE. **Exploratory objectives** • To investigate the pharmacokinetics (PK) of ACT-334441 in adult subjects with SLE. • To investigate the effect of ACT-334441 treatment on disease activity in adult subjects with SLE.
DESIGN	Prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, two-part, dose-response Phase 1/2 study. This study is divided in two parts: • **Part A**: Four parallel treatment groups (including 0.5 mg, 1 mg, or 2 mg of ACT-334441 and placebo control). An interim safety review will be conducted by the Independent Data Monitoring Committee (IDMC) when all subjects enrolled into Part A have completed Visit 4, unless prematurely discontinued. The IDMC will then evaluate the safety profile of ACT-334441 in SLE patients and give a recommendation whether or not to continue the study as planned (i.e., proceed to Part B). • **Part B:** Two parallel treatment groups (including 4 mg ACT-334441 and placebo control). Note: Subjects enrolled in Part A are not eligible to participate in Part B.

PERIODS	**There will be three periods in Part A and Part B.** **Screening period**: This period starts up to 30 days before randomization and includes the **Screening visit** and the pre-randomization assessments. **Treatment period**: The treatment period will last 12 weeks. Visits during the treatment period will consist of a **Randomization visit** and visits at Weeks 2, 4, 8, and 12. The **End-of-Treatment (EOT) visit** will take place at Week 12, or earlier in case of premature discontinuation of study treatment. In all cases, the EOT visit should take place 1 day after the last dose of study treatment but no later than 7 days after the last dose of study treatment. **Follow-up period**: Subjects will undergo an **End-of-Study (EOS)** Visit 6 weeks after the last dose of study treatment. **Follow-up** assessments via telephone calls will be performed 11 weeks and 16 weeks after the last dose of study treatment to evaluate potential serious adverse events (SAEs) and to assess pregnancy status (urine test).
STUDY TREATMENT DISCONTINUATION CRITERIA AND STUDY-SPECIFIC CRITERIA FOR INTERRUPTION / CLINICAL STUDY STOP	**Study treatment discontinuation** At any time during the double-blind treatment period, subjects meeting the study-specific criteria for **permanent discontinuation** of study treatment as described in Sections 5.1.9 and 5.1.10 are to be permanently discontinued from study treatment and will perform EOT and EOS visits and will be followed up for a total of 16 weeks after last study treatment intake (follow-up telephone calls for pregnancy and SAEs). **Study-specific criteria for interruption / stopping of the clinical study or Part B** • Part A: if 12 or more subjects out of the planned 36 subjects in the combined active treatment groups (0.5, 1, or 2 mg) or 6 or more subjects out of the planned 12

	subjects in the high dose group (2 mg) have been discontinued from study treatment due to meeting any of the individual patient's stopping rules as defined per safety area of interest [see Section 9.3], the entire study will be put on hold. A detailed safety signal assessment and recommendations from IDMC and Health Authorities may allow a potential restart of the study. • Part B: if 4 or more subjects out of the planned 12 subjects in the active treatment group (4 mg) have been discontinued study treatment due to meeting any of the individual patient's stopping rules as defined per safety area of interest [see Section 9.3], all subjects included in Part B will stop study treatment. A detailed safety signal assessment and recommendations from IDMC and Health Authorities may allow a potential restart of the Part B.
PLANNED DURATION	**Part A:** Approximately 11 months from First subject-First visit (FSFV) to Last Subject-Last Visit (LSLV). **Part A and B:** Approximately 20 months from FSFV to LSLV.
SITE(S) / COUNTRY(IES)	Approximately 21 sites notably in the USA, Russia and Europe.
SUBJECTS / GROUPS	**Part A:** Approximately 48 subjects will be randomized (1:1:1:1) via an interactive response technology (IRT) system to one of four groups (i.e., 12 subjects in each group; three dose levels of 0.5 mg, 1 mg, or 2 mg ACT-334441, or placebo once daily [o.d.]). **Part B:** Approximately 16 subjects will be randomized (3:1) via an IRT system to one of two groups (i.e., 12 subjects receiving 4 mg ACT-334441 and 4 receiving placebo o.d.).
INCLUSION CRITERIA	1. Signed informed consent prior to initiation of any study-mandated procedure. 2. Men or women ≥ 18 and ≤ 65 years of age. 3. Women of childbearing potential as defined in Section 4.5.1: • must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at

	Randomization at least 3 weeks apart; • must agree to undertake a urine pregnancy test as indicated in Table 1 (bi-weekly/ monthly) during the study and up to 16 weeks after study treatment discontinuation; • must use methods of contraception, as described in Section 4.5.2, from the Screening visit until 16 weeks after study treatment discontinuation. 4. Presenting with a diagnosis of SLE made at least 6 months prior to Screening, by fulfilling at least 4 of the 11 criteria for SLE, as defined by the American College of Rheumatology (criteria are cumulative and do not need to be present concurrently) [Tan 1982; Hochberg 1997]. 5. Presenting with a Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) score of at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers) at Screening. 6. History or presence at Screening of positive anti-nuclear antibodies (ANA) or anti-double-stranded DNA (anti-dsDNA) antibodies. 7. Currently treated for at least 30 days prior to Randomization with stable doses of one or more of the following background medications: • Non-steroidal anti-inflammatory drugs (NSAIDs), • Corticosteroids (≤ 10 mg/day prednisolone or equivalent), • Anti-malarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine)[#], • Mycophenolate mofetil (≤ 2 g/day)[#], • Azathioprine (≤ 2 mg/kg/day)[#], • Methotrexate (≤ 20 mg/week)[#]. [#]Treatment with anti-malarials, mycophenolate mofetil, azathioprine, or methotrexate must have been started at least 90 days prior to Randomization and must not have been stopped within 30 days prior to Randomization.
EXCLUSION CRITERIA	**Pregnancy and breastfeeding** 1. Breastfeeding, pregnant women or women planning to

	become pregnant during the study. **SLE disease** 2. Subjects with active lupus nephritis (defined by proteinuria > 1 g/24 h, or equivalent using spot urine protein-to-creatinine ratio) within 90 days prior to randomization; subjects with central nervous system lupus (e.g., aseptic meningitis, seizures, cerebritis, polyneuropathy, cerebrovascular disease) within 90 days prior to Randomization; subjects with lupus vasculitis within 90 days prior to Randomization. 3. Subjects presenting with a SLEDAI-2K score > 12 at Screening or at Randomization. **Cardiovascular** 4. History or presence of cardiac rhythm disorders (e.g., sinoatrial heart block, second- or third-degree atrioventricular block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest). 5. Resting heart rate (HR) < 55 bpm as measured by the pre-dose 12-lead electrocardiogram (ECG) on Day 1; an increased QT corrected for HR on the basis of Fridericia's formula (QTcF) interval of > 470 ms (females), > 450 ms (males) at Screening, or on Day 1 ECG prior to study treatment initiation. 6. History or presence of ischemic heart disease. 7. History or presence of myocarditis or endocarditis. 8. Presence of valvular heart disease associated with symptoms or hemodynamic change. 9. History of syncope associated with cardiac disorders. 10. History or presence of cardiac failure. 11. Systemic arterial hypertension not controlled by medication according to investigator judgment. 12. History or presence of vascular thrombosis at any time or a history of pregnancy morbidity in the context of anti-phospholipid antibody syndrome within 5 years prior to Randomization. 13. Clinically relevant hypotension according to investigator's judgment or orthostatic hypotension (i.e., > 20 mmHg decrease in systolic blood pressure [SBP] or > 10 mmHg decrease in diastolic blood pressure [DBP] from supine to

	standing position measured between 1 and 3 minutes after standing) at Screening. 14. Known pulmonary arterial hypertension of functional class III or IV. **Pulmonary** 15. History or presence of severe respiratory disease or pulmonary fibrosis, based on medical history, lung function and chest X-ray (CXR) performed at Screening or within 3 months prior to Screening. 16. Bronchial asthma or chronic obstructive pulmonary disease. 17. Abnormal pulmonary function tests: forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted normal value; FEV_1/FVC ratio <0.7. **Treatments** 18. Treatment or planned treatment with the following medications*: a. Within 15 days or 5 half-lives of the medication, whichever is longer, prior to Randomization: ○ β-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR-lowering systemic therapy (list of drugs provided in Appendix 1). ○ QT-prolonging drugs with known risk of torsades de pointes, for any indication (list of drugs provided in Appendix 2). ○ Short- and long-acting β2-agonists (e.g., albuterol, levalbuterol, formoterol, terbutaline salmeterol). b. Within 30 days or 5 half-lives of the medication, whichever is longer, prior to Randomization: ○ Cyclophosphamide, cyclosporine, tacrolimus, sirolimus, etc., ○ Pulse methylprednisolone ○ Vaccination with live vaccines. c. Within 90 days prior to Randomization: ○ Belimumab, leflunomide, ○ Any investigational immunosuppressive or immunomodulatory agent (within 90 days or 5 half-lives of the drug prior to start of study treatment, whichever is

	longer). d. Within 12 months prior to Randomization: o B cell-depleting biological agents such as rituximab or ocrelizumab. e. Any time prior to Randomization: o Alemtuzumab, sphingosine-1-phosphate (S1P) modulators (e.g., fingolimod). *For immunosuppressants or anti-inflammatory drugs not listed among the fordidden medications, the investigator should discuss adequate wash-out time with the sponsor. **Infection and infection risk** 19. Active or latent tuberculosis (TB), as assessed by CXR performed at Screening or within 3 months prior to Screening, and interferon gamma release assay (QuantiFERON-TB-Gold®) at Screening, except if there is documentation that the subject has completed adequate and successful treatment for latent TB infection or TB disease previously. 20. Ongoing known bacterial, viral or fungal infection that is of clinical concern in the judgment of the investigator. 21. A history of any serious infection, defined as life-threatening or requiring intravenous (i.v.) antibiotics or hospitalization, within 30 days prior to Randomization. 22. Hepatitis B and C, congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at Screening. 23. Negative antibody test for varicella-zoster virus at Screening. **Malignancy** 24. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation. **Transplantation** 25. History or presence of bone marrow or solid organ transplantation. **Ophthalmology** 26. Presence of macular edema or active uveitis. **Metabolic and hepatic** 27. Type 1 or 2 diabetes that is poorly controlled according to

	investigator judgment, or diabetes complicated with organ involvement such as diabetic nephropathy or retinopathy. 28. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin (TBL), serum albumin, international normalized ratio, as well as on presence/absence and severity of ascites and hepatic encephalopaty. 29. TBL > 1.5-fold upper limit of normal (ULN; unless in the context of known Gilbert's Syndrome). 30. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2-fold ULN. **Hematology** 31. Hemoglobin < 9 g/dL. 32. White blood cell count < 2500/μL (2.5×10^9/L). 33. Lymphocyte count < 800 /μL (0.8×10^9/L). 34. Platelets < 75,000/μL (75×10^9/L). **Renal** 35. Proteinuria > 1.0 g/24 hour or equivalent using spot urine protein-to-creatinine ratio. 36. Estimated glomerular filtration rate < 60 mL/min/1.73 m^2. **Other categories** 37. History of clinically significant drug or alcohol abuse. 38. Known allergy to S1P receptor 1 modulators or any of the ACT-334441 formulation excipients. 39. Any other clinically relevant medical or surgical condition that in the opinion of the investigator would put the subject at risk if participating in the study. 40. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits or likelihood of not completing the study, including mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
STUDY TREATMENTS	**Investigational treatment** ACT-334441 0.5 mg, 1 mg, 2 mg capsules for Part A, and 4 mg capsules for Part B, administered orally o.d. in the morning. **Placebo** Placebo matching ACT-334441 capsules administered orally o.d. in the morning.

CONCOMITANT THERAPY	**Allowed concomitant therapy** • i.v. atropine in the event of symptomatic bradycardia [see study-specific criteria for permanent discontinuation of study treatment in Section 5.1.10]; • Dilating eye drops, mydriatics, including parasympathetic antagonists (e.g., tropicamide) or sympathetic agonists (e.g., phenylephrine) for topical use; • Vaccination with non-live vaccines; • Stable systemic corticosteroid therapy; corticosteroids are not to be started or stopped during the study, and the dose should be kept stable. However, the investigator may see reason to initiate or increase the dose of systemic corticosteroid to treat an SLE flare or another condition. In such cases, the dose may be increased for a period of not more than 14 days up to double the baseline dose or a maximum of 20 mg/day prednisolone or equivalent (please refer to conversion table in Appendix 8); • Topical treatment therapy including topical use of corticosteroid; • Stable antimalarial therapy (e.g., hydroxychloroquine, chloroquine, quinacrine); therapy is not to be started or stopped during the study, and dose should be kept stable; • Stable NSAID chronic therapy. Therapy is not to be started or stopped during the study; – Temporary use and/or dose change for treatment of non-SLE-related conditions (e.g., headache, menstrual cramps) is allowed; • Stable immunosuppressant therapy (i.e., methotrexate, azathioprine, or mycophenolate mofetil). Therapy is not to be started or stopped during the study, and dose should be kept stable. **Forbidden concomitant medication** • Immunosuppressives not listed in allowed concomitant medication such as cyclophosphamide, cyclosporine, leflunomide, sirolimus, tacrolimus, etc.;

	• Immunosuppressive or immunomodulatory biological agents (e.g., belimumab, i.v. immunoglobulin, rituximab, S1P modulators other than ACT-334441); • β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR-lowering therapy (as listed in Appendix 1); • QT-prolonging drugs with known risk of torsades de pointes (list of drugs provided in Appendix 2); • Short- and long-acting β_2-agonists (e.g., albuterol, levalbuterol, formoterol, terbutaline salmeterol); • Vaccination with live vaccines.
ENDPOINTS	**Pharmacodynamic endpoints** • Change in total lymphocyte count from baseline to EOT • Change in total lymphocyte count from baseline to each post-baseline assessment **Safety endpoints** The treatment-emergent period is defined as the time from first study treatment intake up to 6 weeks (inclusive) after last study treatment intake. • Treatment-emergent adverse events (AEs), SAEs, and adverse events of special interest (AESI[#]); • AEs leading to premature discontinuation of study treatment; • Changes in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for HR on the basis of Bazzett's formula [QTcB] and QT corrected for HR on the basis of Fridericia's formula [QTcF]), from pre-dose to selected post-dose assessments (1 h, 2 h, 3 h, 4 h, 5 h, 6 h) on Day 1 and on day of study drug re-initiation; • Occurrence of treatment-emergent 12-lead ECG outliers (e.g., HR, PR, QTc defined in the Statistical Analysis Plan [SAP]); • Occurrence of treatment-emergent 12-lead ECG abnormalities; • Occurrence of treatment-emergent ECG-Holter abnormalities on Day 1;

	• Change in SBP and DBP from baseline up to EOS; • Change in FEV_1 and FVC, expressed in absolute value (L) and percent value from baseline up to EOS; • Occurrence of treatment-emergent decrease of FEV_1 or FVC > 15% from baseline values; • Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline up to EOS; • Treatment-emergent laboratory abnormalities according to CTCAE 2010 v4.03 [CTCAE 2010] and Food and Drug Administration (FDA) guidelines [FDA 2009] (for ALT/AST/TBL); • Change in protein-to-creatinine ratio from baseline to EOT; • Change in body weight from baseline to EOT. [#]AESI considered for the analyses are described in Appendix 3. **Pharmacokinetic endpoints** • C_{trough} ACT-334441 plasma concentrations prior to dosing at Weeks 2, 4, 8, and 12 (EOT) or at EOT visit after premature study treatment discontinuation (if applicable); • ACT-334441 plasma concentration at EOS (i.e., 6 weeks after study treatment discontinuation). **Exploratory disease activity endpoints** • Change in SLEDAI-2K score from baseline to each post-baseline assessment; • Change in Physician's Global Assessment (PGA) score from baseline to each post-baseline assessment; • Change in SLEDAI-2K mucocutaneous and/or muscoskeletal scorings from baseline to each post-baseline assessment. **Quality of life endpoints** • Change in SF-36v2™ Health Survey domain and component scores from baseline to EOT.

	Exploratory biomarker endpoints • Change in immunoglobulin serum levels (IgG, IgM, IgA) from baseline to each post-baseline assessment; • Change in ANA and anti-dsDNA antibody titers from baseline to each post-baseline assessment; • Change in serum complement components C3 and C4, C-reactive protein, fibrinogen, B lymphocyte stimulator and C-X-C motif chemokine 10 from baseline to each post-baseline assessment; • Change in blood lymphocyte subsets from baseline to EOT and EOS.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	All statistical analyses will be conducted by Actelion or by designated Contract Research Organizations supervised by Actelion. The SAP will be finalized prior to database lock. Baseline is defined as the last assessment prior to initiation of the study treatment. **Analysis sets** Screened Analysis Set: includes all subjects who were screened and received a subject number. Safety Analysis Set: includes all randomized subjects who received at least one dose of study treatment. Unless otherwise stated, any analysis using the Safety Analysis Set will use all available safety data up to 6 weeks after discontinuation of study treatment. Subjects will be analyzed based on actual dose taken, not the randomized dose. PD Analysis Set: includes all subjects who received at least 3 weeks of study treatment and have at least one lymphocyte count measurement between the Week 4 visit and Week 12 visit. Subjects will be analyzed according to the treatment they received. Full Analysis Set (FAS): includes all randomized subjects. Subjects will be analyzed according to their randomized

	treatment. Per-Protocol Set (PPS): defined as subjects from the FAS without any major protocol deviations. Major protocol deviations are described in Section 11.2.4. PK Analysis Set: includes all randomized subjects who received at least one ACT-334441 dose and provided at least one blood sample for PK evaluation. Subjects will be analyzed based on actual dose taken, not the randomized dose. **Pharmacodynamic variable** The change in lymphocyte count from baseline to EOT is defined as: • Total lymphocyte count at EOT – total lymphocyte count at baseline Last observation carried forward (LOCF; using the Week 4 visit or later) will be used for subjects with a missing EOT assessment. **Exploratory disease activity variables** The change from baseline in the SLEDAI-2K (modified to exclude leukopenia) score at each visit is calculated as : • SLEDAI-2K score at each visit – SLEDAI-2K score at baseline. The change from baseline in PGA score and the SLEDAI-2K mucocutaneous and/or muscoskeletal score will be calculated in a similar manner. **Overall testing strategy for the pharmacodynamic endpoint** An optimized contrast test according to the Multiple Comparison Procedure (MCP)-Mod approach [Bretz 2005] for each considered dose-response model will be performed. The existence of dose-response effects will be tested using the maximum of the model-based contrast tests. Multiplicity adjusted p-values will be calculated using the Dunnett-distribution. **Pharmacodynamic endpoint analysis** Null and alternative hypotheses

	The null hypothesis is that there is no dose response in terms of lowering of lymphocyte count (p, which is a negative value for a lowering of the lymphocyte count) from baseline to EOT, and the alternative hypothesis is the existence of a dose response: $H_0: p_d \geq p_{Placebo}$ for all doses d = 0.5, 1, 2, 4 mg vs $H_1: p_d < p_{Placebo}$ for at least 1 dose d = 0.5, 1, 2, 4 mg If Part B of the trial is not performed, the hypothesis will be $H_0: p_d \geq p_{Placebo}$ for all doses d = 0.5, 1, 2 mg vs $H_1: p_d < p_{Placebo}$ for at least 1 dose d = 0.5, 1, 2 mg To meet the objective of demonstrating existence of a dose response of ACT-334441 on the lymphocyte count reduction from baseline in subjects with SLE, the null hypotheses must be rejected by the test with a one-sided significance level of 5%. <u>Main pharmacodynamic analysis</u> The MCP-Mod approach consists of a set of optimized contrast tests for establishing the existence of dose-response effects. The overall strategy is described as follows: Definition of a set of likely dose response relations (see sample size section for more details): • Maximum effect (E_{max}) with 50% of the maximum effect at dose 0.2 mg • E_{max} with 50% of the maximum effect at dose 0.4 mg • E_{max} with 50% of the maximum effect at dose 1.0 mg • Quadratic with maximum effect at dose 3.0 mg (only if the 4 mg dose is studied) • Sigmoid-E_{max} with 50% of the maximum effect at dose 0.4 mg and 95% of the maximum effect at dose 2.0 mg The existence of dose-response effects will be assessed with the optimized contrast tests. Dose-response effects are established at one sided level α=5%, if the following condition on the *p*

	value holds for at least one contrast *i*: $p_i := 1 - F_{\Sigma_{Dunnett}}(Z_i) < 0.05$, where $F_{\Sigma_{Dunnett}}$ describes the Dunnett-distribution with correlation matrix $\Sigma_{Dunnett}$. The model with the minimum p-value will be fitted to the data. As a sensitivity analysis, all remaining significant models will be fitted to the data and model-based dose estimates will be calculated. Given established dose-response effects with MCP-Mod, PD effects will be analyzed based on pairwise comparisons of reduction in lymphocyte count from baseline for each active dose levels to placebo using an analysis of covariance (ANCOVA) model adjusted for baseline lymphocyte counts. Testing will be done with a two-sided significance level of 5%. The type-1 error will be controlled via a hierarchical ordering of the tests: pairwise comparison will be conducted in decreasing dose order. The dose-response data will be summarized with point-wise and model-based estimates, standard deviation and 95% confidence intervals (CI) on the reduction in lymphocytes from baseline at the examined dose levels. A plot of the estimated dose response curve with 95% credibility interval limits will be presented along with the observed response at each dose. This analysis will be performed on the PD analysis set, and a supportive analysis will be performed on the FAS and the PPS. **Exploratory efficacy endpoint analysis** The exploratory efficacy endpoint change from baseline in SLEDAI-2K score at Week 12 will be analyzed using an ANCOVA, with treatment and baseline score as factors. Missing values at Week 12 will be imputed using LOCF. The mean treatment difference including 95% CI for each ACT-334441 dose compared to placebo will be presented. A sensitivity analysis will be performed using observed data without imputation. Other changes from baseline variables will be analyzed in a similar manner using an ANCOVA. All exploratory efficacy endpoints will be analyzed on the FAS

	and PPS populations. No multiplicity adjustments will be made on exploratory efficacy endpoints. **Safety endpoints** Safety endpoints will be mainly analyzed descriptively by treatment group on the Safety Set. **Sample size** The sample size for the study was determined based on simulations. A maximum % lymphocyte reduction compared to baseline of 70% was assumed based on results obtained in Phase 1 with ACT-334441 and with other S1P receptor modulators. A sample size of 64 subjects (12 in each ACT-334441 dose group of 0.5 mg, 1 mg, 2 mg, 4 mg, and 16 in the placebo group) would provide an average power of at least 90% to show a significant dose response relationship at a one-sided significance level of 5%, under the assumption of a % lymphocyte reduction compared to baseline of 0% (mean at Week 12 = 2.0×10^9/L) for placebo and a maximum of 70% for any ACT-334441 dose (mean at Week 12 = 0.6×10^9/L). The pooled SD is assumed to be 0.45×10^9/L. This takes into account 10% of subjects being excluded from the PD analysis set. If Part B is not conducted and the 4 mg dose is not tested, then there will be an average power of at least 80% to show a significant dose-response relationship with three dose levels at a one-sided significance level of 5%, using the same assumptions as above (based on a total sample size of 48 subjects [12, 12, 12 and 12 in placebo, 0.5 mg, 1 mg and 2 mg, respectively]). Assumptions on the placebo response rate, maximum effect sizes and candidate dose-response models are based on the observed lymphocyte count in study AC-064-101.
STUDY COMMITTEES	**Independent Data Monitoring Committee** An IDMC has the overall responsibility for safeguarding the interests of subjects by monitoring data obtained in the study in an unblinded fashion and making appropriate recommendations based on the reported data, thus ensuring that the study is being

	conducted with the highest scientific and ethical standards. The IDMC will be fully operational prior to enrolment of the first subject into the study. The IDMC will review unblinded data at regular intervals, will provide recommendation to apply study stopping rules (if indicated) and in addition will review interim safety data collected when all subjects enrolled into Part A have completed Visit 4 (Week 4), unless prematurely discontinued [see Section 11.5]. The composition and operation of the IDMC is described in the IDMC charter. **Ophthalmology Safety Board** An Ophthalmology Safety Board (OSB) composed of two independent ophthalmologists will review and evaluate in a blinded fashion any new or suspected case of macular edema. The composition and operation of the OSB is described in the OSB charter.

Table 1 Visit and assessment schedule (same for part A and part B)

Periods	Name	Pre-randomization	Treatment period					FU			Unscheduled	
	Duration	Up to 30 days	12 weeks					16 weeks			NA	
Visits	Number	1	2	3	4	5	6	7	8	9	U1, U2,...	I
	Name	Screening	Randomization (15)	W2	W4	W8	EOT	EOS	Phone call FU	Phone call FU	Unscheduled (17)	Re-initiation
	Time	Day −30 to −1	Day 1	Week 2	Week 4	Week 8	Week 12 or earlier in case of premature discontinuation (16)	Last study treatment intake + 6 weeks	Last study treatment intake + 11 weeks	Last study treatment intake + 16 weeks	Any day between Day 1 and EOS	For study treatment interruptions that started up to Day 14
	Visit window			± 3 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	NA	
Informed consent*		X										
Inclusion/exclusion criteria*		X	X									
Demographics*		X										
Medical history/smoking status*		X										
SLE history* (1)		X										
Concomitant medications/SLE therapies*		X	X	X	X	X	X	X			X	X
Physical examination* (2)		X	X	X	X	X	X	X			X	
Body weight and height* (3)		X					X					
Disease activity scales*: SLEDAI-2K, PGA		X	X		X	X	X	X			X	
Quality of life questionnaire*: SF-36 v2™			X				X					
Chest X-ray (4)		X										
SBP/DBP* (5;6)		X	X	X	X	X	X	X			X	X
12-lead ECG** (5)		X	X	X	X	X	X	X			X	X
ECG-Holter** (7)		X	X									
Echocardiography*		X					X					
Spirometry** (8)		X		X	X	X	X	X				
Ophthalmological examination*		X	.	X	X	X	X	X				
OCT		X					X					
Hematology (9)/ blood Chemistry**		X	X	X	X	X	X	X			X	
Pregnancy test */** (10)		X	X	X	X	X	X	X	X	X	X	
Viral serology / tuberculosis test**		X										

Periods	Name	Pre-randomization	Treatment period					FU			Unscheduled	
	Duration	Up to 30 days	12 weeks					16 weeks			NA	
Visits	Number	1	2	3	4	5	6	7	8	9	U1, U2,...	I
	Name	Screening	Randomization (15)	W2	W4	W8	EOT	EOS	Phone call FU	Phone call FU	Unscheduled (17)	Re-initiation
	Time	Day −30 to −1	Day 1	Week 2	Week 4	Week 8	Week 12 or earlier in case of premature discontinuation (16)	Last study treatment intake + 6 weeks	Last study treatment intake + 11 weeks	Last study treatment intake + 16 weeks	Any day between Day 1 and EOS	For study treatment interruptions that started up to Day 14
	Visit window			± 3 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	NA	
Additional serum sample for viral serology***			X									
ANA, anti-dsDNA antibodies, complement C3 and C4**		X	X		X	X	X	X			X	
Exploratory biomarkers** (10)			X		X	X	X	X				
Lymphocyte subsets*** (11)			X				X	X				
Urine protein-to-creatinine ratio**		X	X				X				X	
Urinalysis (dipstick)*		X	X	X	X	X	X	X			X	
PK sampling (pre dose)***				X	X	X	X	X				
Study treatment dispensing & accountability* (13)			X	X	X	X	X					X
AEs* (14)		X	X	X	X	X	X	X			X	X
SAEs* (14)		X	X	X	X	X	X	X	X	X	X	X

* Data collected in the eCRF
** Electronically transferred to sponsor
*** Sample collection date recorded in the eCRF (for PK samples, time will also be recorded)

Assessments in part A and B are identical.

Day 1 (date of Randomization visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

For WOCBP, the serum pregnancy test at Visit 1 must be performed at least 3 weeks before the urine pregnancy test performed at Visit 2 prior to randomization.

The intervals between Visit 4 (Week 4), Visit 5 (Week 8) and Visit 6 (EOT) should not exceed 36 days.

(1) History of positive ANA / anti-ds DNA antibodies will be included.
(2) Complete physical examination (i.e., inspection, percussion, palpation and auscultation) will be performed at Visit 1 (Screening) and Visit 6 (EOT). A symptom-driven, abbreviated physical examination will be performed at all other visits in order to capture assessments needed for the SLEDAI-2K
(3) Height only at Screening.

(4) A chest X-ray that has been performed within 3 months prior to Screening can be used (in this case, no need to repeat chest X-ray at Screening).
(5) On Day 1 and at re-initiation, SBP/DBP assessment and 12-lead ECG will be done pre-dose and hourly until 6 h post-dose; after 6 h, subjects may be discharged from the hospital if they meet the discharge criteria, otherwise SBP/DBP assessments and 12-lead ECG will be performed hourly until discharge criteria are met. If discharge criteria are not met after 12 h, the subject must be permanently discontinued. At all other visits, only pre-dose SBP/DBP assessments and 12-lead ECG will be performed.
(6) At Screening, SBP/DBP will be assessed in supine position and after 1 to 3 minutes in standing position to assess orthostatic hypotension. At all other visits, SBP/DBP will be assessed in supine position.
(7) At Screening, 24 hour ECG-Holter will start before 12:00. On Day 1, 24 hour ECG-Holter will start immediately before dosing.
(8) Two spirometry assessments will be performed at Visit 1 (Screening). The assessments should be at least 5 days apart. The last assessment will count as baseline.
(9) Hematology assessments including coagulation tests will be performed at each visit until EOS
(10) Serum pregnancy tests will be performed at Screening and EOS. Urine pregnancy tests will be performed at all other visits (including telephone calls FU, 11 weeks and 16 weeks after study treatment discontinuation).
(11) IgM, IgG, IgA, CRP, fibrinogen, and BLyS will be measured in serum. At Randomization visit only, anti-Smith, anti-cardiolipin, and anti-ribosomal P will also be measured. EDTA plasma samples will be shipped via central laboratory to Actelion for analysis of CXCL10 and other soluble biomarkers potentially related to SLE and/or $S1P_1$ modulation.
(12) Blood samples will be shipped via central laboratory to Actelion for lymphocyte subsets analysis.
(13) No study drug dispensing at V3 and re-initiation visit
(14) All AEs and SAEs that occur after signing the Informed Consent Form and up to 6 weeks (AEs) or 16 weeks (SAEs) after study treatment discontinuation must be reported.
(15) Prior to randomization, the following central laboratory results must be available to confirm eligibility: ANA, anti-dsDNA, Hepatitis B surface antigen, Hepatitis C, HIV1 and HIV2, varicella-zoster virus, urine protein-to-creatinine ratio, ALT/AST/TBIL, pregnancy test (if applicable).
(16) EOT visit should preferably take place 1 day after last study treatment dose, and no later than 7 days.
(17) Unscheduled visits may be performed at any time during the study. Recording of changes in concomitant medications and background SLE therapies since last visit needs to be performed at each unscheduled visit. Further assessments including 12-lead ECG, SBP/DBP, SLEDAI-2K, PGA, laboratory assessments for SLEDAI-2K scoring (i.e., hematology/blood biochemistry, urinalysis, anti-dsDNA, complement C3 and C4) may be performed at the discretion of the investigator.

AE = adverse event; ALT = alanine aminotransferase; ANA = anti-nuclear antibodies; anti-dsDNA = anti-double-stranded DNA; AST = aspartate aminotransferase; BLyS = B lymphocyte stimulator; CRP = C-reactive protein; CXCL10 = C-X-C motif chemokine 10; ECG = electrocardiogram; eCRF = electronic Case Report Form; EDTA= ethylenediaminetetraacetic acid; DBP = diastolic blood pressure; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; HIV = human immunodeficiency virus; NA = not applicable; OCT = optical coherence tomography; PGA = Physician's Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; $S1P_1$ = sphingosine-1-phosphate receptor 1; SBP = systolic blood pressure; SF-36 = Short-Form 36; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000; TBIL = total bilirubin; WOCBP = women of childbearing potential.

PROTOCOL

1 BACKGROUND

1.1 Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a complex and heterogeneous autoimmune disease of unknown etiology, characterized by the production of pathogenic autoantibodies, tissue deposition of immune complexes, and tissue damage across multiple organ systems. The adaptive T and B cells and the innate immune system are considered to play a major pathophysiological role in this disease.

SLE is primarily a disease of young women with a peak incidence between the ages of 15 and 40 years [Borchers 2010; Pons-Estel 2010] and an estimated male to female ratio of 1:7 to 1:10 [Govoni 2006].

The natural history of SLE is characterized by relapses or flares, alternated with periods of remission. The outcome is highly variable, ranging from prolonged remission to high morbidity with progression of organ damage and death.

Clinical manifestations of SLE include rash, arthritis, anemia, thrombocytopenia, serositis, nephritis, seizures, and psychosis among others [Rahman 2008]. Current treatment of SLE is based on the use of anti-inflammatory and immunosuppressive therapies. With improved diagnosis and treatment, the life expectancy of SLE patients has improved from an approximate 4-year survival rate of 50% in the 1950s to a 15-year survival rate of 80% [Abu-Shakra 1995].

1.1.1 Clinical manifestations and diagnosis

The clinical presentation of SLE is highly heterogeneous and includes a constellation of signs and symptoms involving various organs with an undulating course and accumulation of organ involvement over time [Boumpas 1995a; Boumpas 1995b].

The more commonly involved organ systems are mucocutaneous, musculoskeletal, renal, nervous, cardiovascular, pleura, and lungs. The mucocutaneous and musculoskeletal systems are involved in over 75% of SLE patients. While these common manifestations are debilitating and negatively impact the patients' quality of life, they are generally not fatal.

Renal involvement occurs in one-half to two-thirds of patients and is associated with a poor outcome and mortality. Neuropsychiatric manifestations occur in about two-thirds of patients with varying manifestations, such as mood disorders, anxiety, and psychosis. Central nervous system (CNS) vasculitis and transverse myelitis are less common but serious acute manifestations. Most patients with SLE also have general constitutional symptoms including fatigue, malaise, fever, anorexia, and weight loss.

The unifying laboratory abnormality of SLE is the presence of circulating autoantibodies including anti-nuclear antibodies (ANA). The American College of Rheumatology (ACR) has designated 11 classification criteria incorporating major clinical features (mucocutaneous, articular, serosal, renal, and neurologic) and laboratory findings (hematologic and immunologic), which have been recently validated for the diagnosis of SLE [Petri 2012; Tan 1982; Hochberg 1997]. The presence of four or more criteria occurring either simultaneously or in succession is strongly suggestive of the diagnosis of SLE.

1.1.2 Epidemiology

Epidemiological studies of incidence and prevalence of SLE have shown large differences in different regions of the world and within the same country. Of note, diagnostic criteria have been updated in 1997, and many of the available epidemiological studies are based on previous criteria.

Recent publications (applying the most updated diagnostic criteria) reported overall prevalence rates (per 100,000 inhabitants) ranging from 45.3 in Australia to 100 in USA [Bossingham 2003; Lerang 2012; Chiu 2010; Mok 2011; Helmick 2008; Furst 2013]. Overall incidence rates (per 100,000 person-year) range from 3 in Norway to 7.2 in USA and 8.1 in Taiwan [Lerang 2012; Chiu 2010; Furst 2013]. There are great differences in prevalence and incidence based on race: most of the studies indicate that SLE more frequently affects non-Caucasian individuals (e.g., in USA, the occurrence of SLE was three to four times higher among African-American than Caucasian women [Alarcón 2002; Danchenko 2006]).

Categorized as a fatal condition in the beginning of the last century, patients with SLE now live years if not decades after diagnosis. Since the mid-1970s, most studies in Europe, the USA, Canada, and Latin America have demonstrated 5-year survival rates among newly diagnosed patients of over 90%, and 15- to 20-year survival rates of around 80% [Mok 2011; Pons-Estel 2010]. In addition to failure of controlling renal and neurologic disease, infections and thrombosis are the leading causes of death in SLE patients [Kataoka 2004; Cervera 2009; Ward 2006].

1.1.3 Current treatments of SLE

The current standard of care for treatment of SLE includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, glucocorticoids, and immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, azathioprine, or methotrexate. Guidelines for the pharmacological treatment of SLE were developed by the ACR in 1999 [ACR 1999] and the EULAR task force in 2008 [Bertsias 2008].

The choice of therapy is highly individualized and depends on symptom manifestations, organ involvement, and disease severity. Life-threatening or organ-threatening manifestations of SLE, such as those involving the kidneys, CNS, or blood vessels are treated with high-dose corticosteroids, immunosuppressive drugs, and biologics. Prednisone, hydroxychloroquine, and belimumab are approved therapies for SLE; other therapies including immunosuppressive drugs, rituximab, and intravenous (i.v.) immunoglobulins are used off-label [Yildirim-Toruner 2011]. Management of disease refractory to standard treatments, especially nephritis, cutaneous and neuropsychiatric manifestations as well as the prevention of disease flares, remain unsatisfactory and new therapeutic options are needed.

This study will require patients to receive stable doses of at least one standard SLE therapy, which may include NSAIDs, antimalarials, glucocorticoids, methotrexate, azathioprine, or mycophenolate mofetil.

1.1.3.1 Nonsteroidal anti-inflammatory drugs

NSAIDs are commonly used to relieve SLE manifestations including arthralgia, inflammation, serositis, and fever. They can be used in combination with low doses of steroids or antimalarial agents [Gurevitz 2013].

1.1.3.2 Antimalarial drugs

Chloroquine-based antimalarial drugs such as chloroquine and hydroxychloroquine, often in combination with NSAIDs, are generally used as a first-line treatment for patients with mild SLE. Hydroxychloroquine (Plaquenil®) is approved for the treatment of SLE in the USA [FDA Plaquenil] and in some European countries including United Kingdom, France and Belgium.

Antimalarials were found to prevent lupus flares and increase long-term survival of patients with SLE [Ruiz-Irastorza 2010]. Antimalarials are most useful for constitutional symptoms (e.g., fatigue and fever), musculoskeletal, and skin manifestations. Antimalarials have also possible cardioprotective and thromboprotective effects [Jung 2010]. Common adverse effects are gastrointestinal discomfort and dermatological reactions. Rarely, retinal toxicity has been reported, and regular eye examinations are recommended.

1.1.3.3 Glucocorticoids

Glucocorticoids rapidly relieve inflammation and modulate the immune system. The dose of glucocorticoid treatment depends on the severity and organ involvement in SLE.

Low doses of oral prednisone (e.g., 0.1–0.2 mg/kg/day) can be used for the treatment of cutaneous or musculoskeletal manifestations not responding to other treatments and can help to prevent flares in clinically stable but serologically active patients [Gurevitz 2013;

Amissah-Arthur 2010]. A medium dose of oral prednisone (e.g., 0.5 mg/kg/day) can be used for moderate SLE with cardiopulmonary or hematological involvement. Finally, a high dose of oral prednisone (e.g., 1 mg/kg/day) or pulse methylprednisolone i.v. is used to treat severe disease with major organ involvement including the kidneys, CNS, or blood vessels, often in conjunction with immunosuppressive agents such as cyclophosphamide or mycophenolate mofetil [Kalunian 2009].

Long-term treatment with glucocorticoids can have several adverse effects including hyperglycaemia, osteoporosis, hypertension, glaucoma, gastrointestinal discomfort, myopathy, and accelerated atherosclerosis for which patients should be monitored. The lowest dose and shortest effective duration of treatment should be used.

1.1.3.4 Immunosuppressives

Treatment with immunosuppressives is reserved for patients with severe manifestations. These drugs usually include methotrexate, cyclophosphamide, mycophenolate mofetil, and azathioprine. Cyclosporine, tacrolimus, and leflunomide are used less frequently.

Methotrexate has anti-inflammatory effects and can be beneficial in patients with articular and cutaneous involvement, decreasing SLE activity and allowing the use of lower glucocorticoid dose [Fortin 2008; Yildirim-Toruner 2011]. Adverse effects include stomatitis, bone marrow suppression, hepatotoxicity, alopecia, and pneumonitis.

Cyclophosphamide has a cytotoxic effect on lymphocytes. In conjunction with glucocorticoids, cyclophosphamide is the standard of care for treatment of severe organ-threatening manifestations including lupus nephritis, neuropsychiatric lupus, and systemic vasculitis [Kalunian 2009]. Adverse effects include cystitis, infertility, alopecia, malignancies, and infections.

Mycophenolate (the active metabolite of mycophenolate mofetil) blocks the proliferation of lymphocytes. Mycophenolate mofetil is often used instead of cyclophosphamide in combination with glucocorticoids for the treatment of lupus nephritis. Mycophenolate mofetil can be used for maintenance of renal response in patients with lupus nephritis [Dooley 2011]. Adverse effects include nausea, abdominal pain, diarrhea, bone marrow suppression, and infections.

Azathioprine blocks lymphocyte proliferation. It is effective for treatment of articular and cutaneous manifestations and is frequently used to manage mild lupus nephritis and as a steroid-sparing agent [Yildirim-Toruner 2011]. Adverse effects include bone marrow suppression, gastrointestinal intolerance, and hepatotoxicity.

1.1.3.5 Biologics

Belimumab is a human IgG1λ monoclonal antibody that inhibits B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS).

Belimumab (Benlysta®) was approved by the FDA in 2011 for use in adult patients with active, autoantibody-positive SLE who are receiving standard therapy [FDA Benlysta] [Furie 2011; Navarra 2011]. In the EU, belimumab is approved as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti-double-stranded DNA [anti-dsDNA] and low complement) despite standard therapy [EMA Benlysta]. Adverse effects observed in the clinical studies were mainly injection reactions. Biologics have reported therapeutic effects in SLE clinical studies. Rituximab depletes CD20+ B cells including autoreactive B cells [Yildirim-Toruner 2011]. Although placebo-controlled trials in SLE failed to demonstrate clinical improvement with rituximab, a number of small studies have suggested therapeutic benefit, and the drug is often used for treatment of severe refractory SLE especially lupus nephritis. Adverse effects include lymphopenia, neutropenia, and severe infections.

Small clinical trials have reported beneficial effects of i.v. immunoglobulins, and this is sometimes used to treat refractory SLE. Other biologics with immunomodulatory activity, including abatacept (an inhibitor of T-cell activation), epratuzumab (a monoclonal antibody to CD22), blisibimod (a peptide inhibitor of BAFF), have reported potential beneficial effects, and clinical studies are ongoing to confirm preliminary findings [Ding 2013].

1.1.4 Unmet needs in SLE

Despite the significant improvements in diagnosing and managing the disease, treatment of SLE remains an area of significant unmet need. With the exception of belimumab, no new drug has received an approval for treatment of SLE in the last 50 years. Therapies for SLE consist of relatively non-specific immunosuppressive and anti-inflammatory drugs that are not effective in some patients and can be associated with significant side effects. Novel treatment options are needed for patients with severe disease, especially renal and CNS manifestations, and for patients with disease refractory to conventional therapies. Although approved for treatment of SLE, belimumab has shown modest efficacy and slow onset of effect and is not approved for treatment of lupus nephritis or CNS lupus.

There is a great need for effective and safe steroid-sparing therapies that can help reduce toxicity from long-term use of high-dose glucocorticoids. Accelerated atherosclerosis and cardiovascular disease represent significant burden for patients with SLE that may be exacerbated by chronic use of glucocorticoids. Fatigue is a very common symptom of SLE that negatively affects quality of life in the majority of SLE patients; none of the currently available treatments has shown significant effects on fatigue. Furthermore, the prevention of disease flares represents also a high medical need.

1.2 Sphingosine-1-phosphate receptors

Sphingosine 1-phosphate (S1P) plays a central role in lymphocyte trafficking [Cyster 2005, Brinkmann 2007, Brinkmann 2010, Schwab 2007, and references therein]. S1P is synthesized and secreted by many cell types, including platelets, erythrocytes, and mast cells, and elicits a variety of physiological responses [Cyster 2005, Alvarez 2007]. Among other effects, lymphocyte egress from primary and secondary lymphoid organs is dependent on the S1P receptor 1 ($S1P_1$). $S1P_1$ modulators block lymphocyte migration out of lymphoid tissue into the lymphatic and vascular circulation, thereby reducing peripheral lymphocyte count and preventing lymphocyte recruitment to sites of inflammation. Following withdrawal of an $S1P_1$ modulator, the functional lymphocytes return to the circulation from their sites of sequestration. First-line immunological protection by granulocytes and monocytes, and antigen-dependent T-cell activation and expansion are not affected by this mechanism [Pinschewer 2000].

S1P itself induces pleiotropic effects, which are mediated by a family of five G protein-coupled receptors, $S1P_1$-$S1P_5$, located on endothelial cells, vascular and cardiac smooth muscle cells, and cardiac myocytes [Alvarez 2007, Brinkmann 2007, Brinkmann 2010]. The first S1P receptor modulator, fingolimod (FTY720, Gilenya®), which has been approved by the FDA [FDA Gilenya] and the EMA [EMA Gilenya] for the treatment of multiple sclerosis, is not selective for $S1P_1$ but interacts also with $S1P_3$, $S1P_4$, and $S1P_5$ [Brinkmann 2007, Brinkmann 2010].

1.3 ACT-334441

ACT-334441 is a potent, orally active, selective $S1P_1$ modulator that blocks the egress of lymphocytes from lymphoid organs and thus reduces the availability of circulating effector T and B cells that can invade target organs. This pharmacodynamic (PD) effect is sustained with continued daily oral dosing but is reversible upon drug discontinuation.

1.3.1 Nonclinical data

The main findings in the nonclinical studies conducted on ACT-334441 were:

[redacted]

More detailed information on the data collected thus far on ACT-334441 can be found in the Investigator's Brochure (IB) [ACT-334441 IB]. The sponsor will notify the principal investigator of important nonclinical safety data (e.g., toxicology, ADME) that may become available during the study.

1.3.2 Clinical studies

The human clinical experience with ACT-334441 consists of one Phase 1 study (AC-064-101) in 84 healthy subjects (80 males and 4 females; 64 received ACT-334441 [62 males, 2 females] and 20 placebo). The study included four parts:

- Part A: single-ascending doses of 1, 3, 10, and 25 mg.
- Part B: multiple-ascending doses for 35 days of 0.5, 1, 2, and 4 mg.
- Part C: food effect after a single dose of 1 mg.
- Part D: combination of multiple doses of ACT-334441 (2 mg) and a single dose of another selective $S1P_1$ modulator, ponesimod (10 mg).

The study has recently been completed, and main findings of the study are summarized in the next sections. More detailed information can be found in the Investigator's brochure [ACT-334441 IB].

1.3.2.1 Clinical pharmacokinetics

Following administration of single doses to male healthy subjects, the PK profile of ACT-334441 was characterized by low inter-subject variability (coefficient of variation [CV] < 30% for area under the curve, maximum observed plasma concentration [C_{max}], and half life [$t_{½}$]). C_{max} was achieved within 5–6 h after dosing and $t_{½}$ was between 170 and 199 h (~ 7–9 days).

Following administration of multiple once daily (o.d.) doses, steady-state conditions were attained between 20–32 days of treatment, and the $t_{½}$ after the last administration was between 12–22 days. ACT-334441 accumulated in plasma, with 5- to 9-fold higher C_{max} and area under the curve from 0 to 24 hours (AUC_{0-24}) at steady-state when compared to the first day of treatment. C_{max} and AUC_{0-24} were shown to be dose proportional across the 0.5–4 mg dose range.

The effect of food on the PK of a single 1 mg dose was investigated in study AC-064-101. No relevant effect of food on the PK parameters of ACT-334441 was observed.

Only limited clinical data are currently available regarding the metabolism of ACT-334441. No information is available regarding the effects of disease (e.g., renal or hepatic impairment), age, or ethnicity on the PK of ACT-334441. Only limited data are available on the effects of sex on the PK of ACT-334441 (examination of the data from the 2 female subjects who received ACT-334441 suggest that the PK profile is not influenced by sex).

1.3.2.2 Pharmacodynamics in humans

Effect on lymphocyte count

Oral administration of ACT-334441 at single doses ≥ 3 mg reduced lymphocyte count in humans. The extent of lymphocyte count reduction was dose dependent. A reduction from baseline of approximately 76% was achieved after the highest single dose of 25 mg. The nadir in lymphocyte count was attained within 16 h following a given dose. After a single dose of ACT-334441, the lymphocyte count generally returned to normal range within 6 days.

Repeated o.d. dosing of ACT-334441 (0.5 mg, 1 mg, 2 mg, or 4 mg) for 35 days led to a gradual, dose-dependent reduction in absolute lymphocyte count. Compared to baseline, multiple doses of ACT-334441 induced a decrease ranging from 34% to 64% with doses from 0.5 mg to 4 mg. The time the mean lymphocyte counts returned to within normal

range (i.e., $\geq 1 \times 10^9$ cells/L) dose dependently increased and was 28 days for the 4 mg dose group.

No relevant differences in the effect on lymphocyte count reduction were seen after single-dose administration of 1 mg ACT-334441 in the fed and fasted states.

1.3.2.3 Safety and tolerability

Single doses of 1 mg, 3 mg, 10 mg, and 25 mg were evaluated in healthy subjects. The 10 mg dose was identified as the maximal tolerated single dose of ACT-334441. In the 25 mg group, a serious life-threatening event of hypotensive shock (preferred term: circulatory collapse) was reported. Per study stopping criteria, dose escalation was halted after the 25 mg dose group. One event of non-serious syncope of moderate intensity was also reported in the 10 mg treatment group.

Multiple doses of 0.5 mg, 1 mg, 2 mg, and 4 mg ACT-334441 were administered o.d. for up to 35 days. All doses were found to be well tolerated, with no serious adverse events (SAEs) and no adverse events (AEs) leading to treatment discontinuation. The most frequently reported AEs in the active treatment groups were headache (37.5%), chest pain (all combined chest pain, chest discomfort, musculoskeletal chest pain, non-cardiac chest pain; 33.3%), followed by nasopharyngitis (16.7%), and dizziness (16.7%).

Effect on heart rate

In the single-ascending dose part of the study, a transient decrease in heart rate (HR) was observed as the most frequent drug-related effect with ACT-334441, with maximal reduction reached approximately 4 h post-dose and resolved within 12 h after dosing.

In the multiple-ascending dose (MAD) part of the study, a transient decrease in HR was observed on Day 1 following treatment with ACT-334441 in all dose groups, when compared to placebo. The HR changes from baseline were not clinically significant, did not increase with dose, and were followed by a return to baseline over time (between 7 and 14 days of treatment), with repeated administration of ACT-334441.

In Part D of study AC-064-101, repeated administration of 2 mg ACT-334441 o.d. reduced the effect on HR of subsequent administration of 10 mg ponesimod, another $S1P_1$ modulator with first-dose effect on HR. This shows that chronic o.d. administration of a 2 mg ACT-334441 dose can lead to desensitization of $S1P_1$.

Effect on blood pressure

Blood pressure (BP) reduction was observed following a single high-dose administration (10 mg and 25 mg), with a maximal reduction reached approximately 6–8 h post-dose. In the MAD study, no relevant changes in BP were observed in the 0.5–4 mg dose groups following multiple o.d. dosing of ACT-334441.

Effect on liver enzyme elevations

A transient increase in alanine aminotransferase (ALT) and/or aspartate aminotransferate (AST) and/or gamma glutamyl transferase (GGT) was observed in 8 subjects on active treatment after multiple doses of ACT-334441 (Part B). These changes were transient and not accompanied by an increase in bilirubin. No relevant changes in other clinical chemistry variables were observed. None of the out-of-normal-range values in ALT and/or AST and/or GGT were considered as clinically significant, therefore none were reported as an AE.

Effect on pulmonary function test

No relevant effects on mean forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were observed.

1.4 Purpose and rationale of the study

The central role of $S1P_1$ in T and B lymphocyte trafficking and the ability of an $S1P_1$ modulator to reduce the availability of circulating lymphocytes create a promising therapeutic approach for several autoimmune diseases including SLE. S1P modulation has been proven effective for the treatment of multiple sclerosis [Kappos 2010] and has recently been shown to have therapeutic potential also in psoriasis [Vaclavkova 2014].

$S1P_1$ modulators, including fingolimod (non-selective), ponesimod and KRP203 (both selective for $S1P_1$), have shown beneficial effects in mouse models of SLE. Positive effects have been observed on kidney disease, serological abnormalities, and survival [Okazaki 2002; Ando 2010; Alperovich 2007; Wenderfer 2008]. Based on these data, it is plausible to hypothesize a therapeutic effect of ACT-334441 in patients with SLE. Patients with SLE have a number of immune system abnormalities, with the disease involving multiple organs and systems. The complexity and heterogeneity of SLE manifestations make it important to initially characterize the safety and biological activity of a potential novel treatment. For these reasons, the main purpose of this study is to investigate the dose response for lymphocyte count reduction and the safety and biological activity of ACT-334441 in SLE patients.

Data from the non-selective S1P modulator fingolimod have shown that a 70% decrease in lymphocyte count compared to baseline is associated with efficacy in multiple sclerosis. Other selective $S1P_1$ modulators such as siponimod and ponesimod have also shown that a lymphocyte count reduction of 60–70% from baseline is associated with a plateau of efficacy in multiple sclerosis, while a 20–30% reduction in lymphocyte counts is associated with minimal efficacy [Olsson 2014; Selmaj 2013].

The dose levels of 0.5 mg, 1 mg, 2 mg, and 4 mg of ACT-334441 planned for this study were well tolerated and have shown lymphocyte count reduction from baseline in the range 34–64% in healthy subjects in Phase 1. This approach is expected to allow the

characterization of the safety and biological activity for a range of potentially efficacious doses of ACT-334441 in SLE patients, and to possibly enable the selection of dose(s) for subsequent studies.

2 STUDY OBJECTIVES

2.1 Main objectives

- To investigate the PD of ACT-334441 in adult subjects with SLE.
- To investigate the safety and tolerability of ACT-334441 in adult subjects with SLE.

2.2 Exploratory Objectives

- To investigate the PK of ACT-334441 in adult subjects with SLE.
- To investigate the effect of ACT-334441 treatment on disease activity in adult subjects with SLE.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, two-part, dose-response Phase 1/2 study.

This study is divided in two parts:

Part A

Part A will consist of four parallel treatment groups (including 0.5 mg, 1 mg, or 2 mg of ACT-334441 and placebo control).

Approximately 48 subjects will be randomized (1:1:1:1) via an interactive response technology (IRT) system to one of four groups (i.e., 12 subjects in each group; three dose levels of 0.5 mg, 1 mg, or 2 mg ACT-334441, or placebo o.d.).

Interim safety review

An interim safety review will be conducted by the Independent Data Monitoring Committee (IDMC) when all subjects enrolled into Part A have completed Visit 4 (Week 4), unless prematurely discontinued. The IDMC will then evaluate the safety profile of ACT-334441 in SLE patients and give a recommendation whether or not to continue the study as planned (i.e., proceed to Part B) [see Section 11.5].

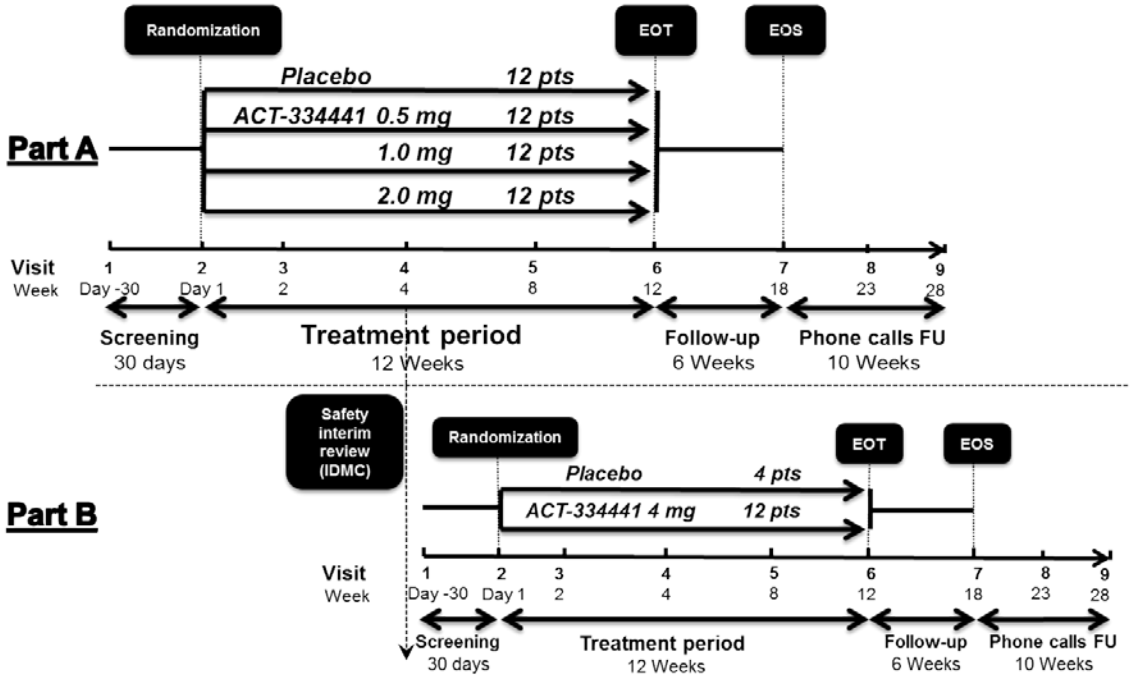
Part B

Part B will consist of two parallel treatment groups (including 4 mg ACT-334441 and placebo control).

Approximately 16 subjects will be randomized (3:1) via an IRT system to one of two groups (i.e., 12 subjects receiving 4 mg ACT-334441 and 4 receiving placebo o.d.). Subjects enrolled in Part A are not eligible for Part B.

The overall study design is shown in Figure 1.

Figure 1 AC-064A201 study design



EOT = End-of-Treatment; EOS = End-of-Study; FU = follow-up; IDMC= Independent Data Monitoring Committee.

3.1.1 Study periods

There will be three periods in Part A and Part B:

3.1.1.1 Screening period

This period starts up to 30 days before Randomization at the time of the Informed Consent Form (ICF) signing and ends with subject randomization. It includes the Screening visit and the pre-randomization assessments.

3.1.1.2 Treatment period

The treatment period will last 12 weeks. Visits during the treatment period will include the post-randomization assessments of the Randomization visit and visits at Weeks 2, 4, 8, 12.

The End-of-Treatment (EOT) visit will take place at Week 12 or earlier in case of premature permanent discontinuation of study treatment. In all cases, the EOT visit should take place 1 day after the last dose of study treatment intake but no later than 7 days after the last dose of study treatment intake.

3.1.1.3 Follow-up period

This period starts immediately after the last dose of study treatment intake and ends approximately 16 weeks after the last dose of study treatment intake. The End-of-Study (EOS) visit will take place 6 weeks after the last dose of study treatment intake.

After EOS, the subject will be followed up for an additional 10 weeks and will be contacted by telephone for follow-up 11 weeks and 16 weeks after last dose of study drug intake for SAEs and pregnancy status assessments.

3.1.2 Study duration

The planned study duration for Part A is approximately 11 months from First subject-First Visit (FSFV) to Last Subject-Last Visit (LSLV) and approximately 20 months until LSLV from Part B.

3.2 Study design rationale

This Phase 1/2 study is the first ACT-334441 study in SLE patients and the first study of an $S1P_1$ modulator in SLE. The study has been designed to investigate the dose response for lymphocyte count reduction, and the safety, tolerability, PK, and biological activity of ACT-334441 in subjects with SLE who have at least one mucocutaneous and/or musculoskeletal manifestation despite receiving standard therapy. Because side effects of ACT-334441 may overlap with major organ involvement in SLE, patients with renal, cardiac, CNS, lung, and liver involvement are excluded. Patients with high disease activity (SLEDAI-2K > 12) will not be allowed to enter the study. (For the rationale of the study population, see Section 4.2.)

A randomized, placebo-controlled, double-blind approach is used to eliminate bias in reporting safety and biological activity data. During the study, several decisions and assessments will have to be performed. In order to limit the risk of bias, specific measures are implemented to reduce the risk of unblinding. These measures include preventing access to results of white blood cell (WBC) and lymphocyte counts to the study site personnel and sponsor's team, and preventing access of first-dose HR data

(12-lead electrocardiogram [ECG] on Day 1 and day of re-initiation and 24-hour Holter ECG on Day 1) to the the investigator, unless deemed necessary for patient safety.

The use of ACT-334441 as adjunctive therapy to the standard of care is a suitable approach that enables evaluation of ACT-334441 in the context of commonly used SLE medications. Background standard therapy for SLE is allowed to ensure feasibility and representativeness of the real-life setting, but the type and dose of background therapies are limited and required to be stable to avoid confounding the evaluation of safety and biological activity of ACT-334441.

A 12-week treatment duration is considered adequate for the initial evaluation of potential risks associated with ACT-334441 treatment. Twelve weeks is a sufficient time for ACT-334441 to reach steady-state concentration and is expected to allow an evaluation of biological activity (e.g., lymphocyte count reduction), an assessment of acute effects on HR and atrioventricular (AV) conduction, as well as of potential effects on pulmonary function. A 6-week follow-up period is considered adequate based on results from the Phase 1 study in healthy volunteers, in which the lymphocyte count normalized within 28 days for the 4 mg dose group. Additional 11-week and 16-week follow-up telephone calls are implemented to further increase patients' safety.

The dose levels of 0.5 mg, 1 mg, 2 mg, and 4 mg of ACT-334441 planned for this study have shown a dose response for lymphocyte count reduction, with a decrease in the range from −34 to −64% from baseline in healthy subjects in Phase 1, and are expected to be efficacious doses of ACT-334441 in SLE patients.

The study will be performed in two parts. The first part (Part A) consists of a parallel-group treatment period, in which approximately 48 patients are randomized in a 1:1:1:1 ratio to receive 0.5, 1, 2 mg ACT-334441 or placebo for 12 weeks. The second part (Part B) consists of a parallel-group treatment period, in which approximately 16 patients are randomized in a 3:1 ratio to receive 4 mg ACT-334441 or placebo for 12 weeks. For safety reasons, the second part testing the highest dose of 4 mg will commence only after an interim safety review of data from Part A is completed by the IDMC. This interim safety review will take place once all patients randomized in Part A have completed the Week 4 visit, unless prematurely discontinued. Four weeks of treatment are selected for this interim review as, based on observations in healthy subjects, this is a sufficient time to approach a plateau in the reduction of lymphocyte counts and to detect the main adverse effects of ACT-334441 treatment, including acute effects on HR and AV conduction.

Study-specific stopping rules will be applied separately for the first part (Part A) and the second part (Part B). For Part A, if 12 or more subjects out of the planned 36 subjects in the combined active dose groups (0.5, 1, or 2 mg), or 6 or more subjects out of the

planned 12 subjects in the 2 mg dose group, have been discontinued study treatment due to meeting any of the individual patient's stopping rules as defined per safety area of interest [see Section 9.3], the entire study will be put on hold. A detailed safety signal assessment and recommendations from IDMC and Health Authorities may allow a potential restart of the study.

For Part B, if 4 or more subjects out of the planned 12 subjects in the active dose group (4 mg), have been discontinued study treatment due to meeting any of the individual patient's stopping rules as defined per safety area of interest [see Section 9.3], all subjects included in Part B will stop study treatment. A detailed safety signal assessment and recommendations from IDMC and Health Authorities may allow a potential restart of the Part B.

This study has been designed in accordance with the FDA guidance [FDA 2010], draft EMA guidelines [EMA 2013] and EULAR recommendations [Bertsias 2008] for clinical investigations in SLE.

3.3 Site personnel and their roles

In order to maintain the blind throughout the study [see Section 5.1.5] and to facilitate the performance of assessments required by the protocol, it is essential that:

- the site personnel have the appropriate medical expertise to perform these assessments;
- the roles are defined clearly upfront.

It is recommended that the designated personnel remain unchanged throughout the entire course of the study and that an adequately trained back-up is designated in case of absence of any of the staff listed below.

At each site, the study staff will consist of:

- A principal investigator;
- A treating physician (the principal investigator may be acting as treating physician);
- A cardiac safety assessor (CSA) responsible for close cardiac monitoring of the subject on Day 1 after dosing and at study treatment re-initiation visits, as well as at other visits as needed (for a given subject, the roles of treating physician and CSA are irreconcilable and must be assumed by two distinct physicians);
- An echocardiography specialist responsible for echocardiographies;
- A clinical coordinator/study nurse (if required);
- An ophthalmologist responsible for the ophthalmological assessments (incl. optical coherence tomography [OCT]);

- A pulmonary function laboratory technician or expert responsible for spirometry.

3.3.1 Principal investigator

The principal investigator is responsible for the overall conduct of the study at the clinical site. It is her/his responsibility to assign appropriate personnel to the protocol-requested assessments (including safety and efficacy) and to define their roles. The principal investigator oversees the accrual of appropriate subjects, the conduct of the study according to the trial protocol, and the collection of the required data.

3.3.2 Treating physician

The treating physician can be a rheumatologist or a physician with specific training and experience in the management of patients with SLE. The principal investigator may act as the treating physician.

It is the responsibility of the treating physician to explain the study in all its aspects to the subject and to obtain her/his informed consent.

The treating physician will be responsible for subject clinical care and management, e.g., eligibility evaluation, supervision of study drug administration, reporting of disease activity, safety monitoring (including recording and treating of AEs, SAEs, physical examination, and routine laboratory results), and concomitant medications monitoring and reporting.

The treating physician will be responsible for completing the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) and the Physician's Global Assessment (PGA). She/he must be trained to use the the SLEDAI-2K.

The treating physician can consult the CSA and/or a cardiologist for interpretation of 12-lead ECG and 24-hour ECG assessments made at Visit 1 (Screening) and Visits 3 to 7.

The same physician must maintain the role of the treating physician for a given subject throughout the study. A back-up treating physician may conduct a subject study visit only if the primary treating physician is not available.

3.3.3 Cardiac safety assessor

The CSA must be a physician adequately trained and experienced in cardiology or a physician who is experienced in making health care decisions based on ECG interpretation reports that may be provided by another cardiologically experienced person. She/he can support the principal investigator / treating physician in making a decision on eligibility of the subject prior to randomization, and in providing adequate treatment in case of cardiac events.

The CSA will be responsible to perform all BP, 12-lead ECGs and 24-hour Holter ECG assessments at Visit 2 (Day 1) or at study treatment re-initiation as requested by the protocol [see Sections 7.2.2, 7.2.3, and 7.2.4]. This includes the hourly 12-lead ECGs and systolic BP (SBP) / diastolic BP (DBP) assessments during the first 6 hours and up to 12 hours following the first study treatment intake. She/he will independently assess the subject's eligibility for discharge [see Appendix 4] or study drug discontinuation [see Sections 5.1.9 and 5.1.10].

While the exams themselves may be performed by a delegate (e.g., study nurse), the review and/or interpretation of 12-lead ECGs and Holter ECG reports must be performed by the CSA only. The reporting of BP and dates and time of ECG assessments will be performed by a delegate (e.g., main study nurse or clinical coordinator) in the electronic Case Report Form (eCRF).

Reports and alerts from 12-lead ECGs performed at Visit 2 (Day 1) or at study treatment re-initiation and from 24-hour Holter ECG performed at Visit 2 (Day 1) will be sent only to the CSA and must not be shared with the treating physician.

At Visit 2 (Day 1) or at study treatment re-initiation, significant findings (e.g., new ECG abnormalities, bradycardia), which in the view of the CSA meet the definition of an AE, must be reported to the primary investigator / treating physician and recorded on an AE page of the eCRF. Any treatment administered by the CSA (if applicable) will be reported to the primary investigator / treating physician and recorded as concomitant medication in the eCRF.

3.3.4 Echocardiography specialist

The physician conducting and interpreting Standard 2D/Doppler echocardiography must have qualifications equivalent at least to those defined for Level 2 training by the American College of Cardiology Board / American Heart Association clinical competence statement on echocardiography [see Appendix 5; Quiñones 2003]. In case a sonographer conducts the examination, the physician must review and interpret the results.

3.3.5 Clinical coordinator / study nurse

Depending on the organization of the investigational site, a clinical coordinator / study nurse may be required to assist the principal investigator / treating physician in all aspects of subject management. She/he will be responsible for scheduling visits and assessments as planned in the study protocol, recording concomitant medications, maintaining source documentation, and transcription of data into the eCRF. She/he will instruct the subjects on study drug administration, and collect, process, and send all blood and urine samples to the central laboratory. Additionally, she/he may be responsible for coordinating the pulmonary function tests (PFTs), ophthalmological and cardiac examinations, and the

36-Item Short Form Health Survey v2 (SF-36v2™) questionnaire. In the absence of a clinical coordinator / study nurse, the above tasks will be performed by the principal investigator.

Important note: A person supporting the principal investigator / treating physician in performing or reporting study assessments cannot be delegated by the CSA to conduct 12-lead ECG and Holter ECG at Day 1 or study re-initiation with unblinding potential.

3.3.6 Ophthalmologist

The ophthalmologist will review and interpret the ophthalmological examinations including OCT assessments as scheduled in the study protocol [see Sections 7.2.7 and 7.2.8]. In the event of findings observed at any visit during the study, the ophthalmologist will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis, and the treating physician will be notified for reporting any AEs or SAEs.

3.3.7 Pulmonary function laboratory technician or expert

Spirometry testing will be performed by a PFT technician, respiratory therapist or expert, or by a person with qualifications equivalent to those defined for a Registered Pulmonary Function Technologist and/or Registered Respiratory Therapist by the American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines [Miller 2005a]. Minimum requirements include sufficient education and training to assure that the technician understands the fundamentals of the tests, the common signs of pulmonary diseases and the management of the acquired pulmonary function data [Miller 2005a] .

To the extent logistically feasible, attempts should be made to have the same tester throughout the study for a subject. Back-up testers (PFT technician, respiratory therapist or expert, or an equally experienced person according to the ATS/ERS guidelines [Miller 2005a] may conduct spirometry if the primary tester is not available. All PFT technicians or other experienced persons participating in the study will be trained before study start on the specific study requirements and if compliance issues are identified.

3.4 Study Committees

3.4.1 Independent Data Monitoring Committee

An IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety data obtained in the study in an unblinded fashion and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with the highest scientific and ethical standards. The IDMC will be fully operational prior to enrolment of the first subject into the study. The IDMC will review unblinded safety data at regular intervals, including frequency of AEs, adverse events of special interest (AESIs), SAEs, AEs leading to treatment discontinuation (by dose and safety area of interest dependent manner). The IDMC will provide recommendation to

apply study stopping rules (if indicated [see Section 9.3]). In addition, the IDMC will review interim data from Part A when all subjects enrolled into Part A have completed Visit 4 (Week 4), (unless prematurely discontinued) [see Section 11.5] and will recommend whether or not to continue the study as planned (i.e., proceed to Part B).

The composition and operation of the IDMC is described in the IDMC charter.

3.4.2 Ophthalmology Safety Board

An Ophthalmology Safety Board (OSB) composed of two independent ophthalmologists will review and evaluate in a blinded fashion any new or suspected case of macular edema. The composition and operation of the OSB is described in the OSB charter.

4 SUBJECT POPULATION

4.1 Subject population description

This Phase 1/2 study will enroll adult patients with a confirmed diagnosis of SLE ≥ 6 months, as defined by the 1997 update of the 1982 ACR revised criteria for classification of SLE [Hochberg 1997; Tan 1982]. Per the classification, patients will have fulfilled ≥ 4 of the 11 ACR diagnostic criteria, either serially or simultaneously.

Presence of at least one mucocutaneous or musculoskeletal manifestation including myositis, arthritis, rash, alopecia, mucosal ulcers will be required at Screening [see Appendix 6]. A positive serum antibody test (ANA or anti-dsDNA) at Screening or a documented history of positive test will also be needed to ensure correct SLE diagnosis.

Background therapies for SLE are allowed and at least one background therapy is required, with ACT-334441 used as adjunctive treatment. This defines a target population with remaining active disease and an unmet need for additional treatment despite standard therapy. Concomitant background therapy for SLE is permitted if treatment has been stable for 30 days prior to randomization and will have to include at least one of the following: NSAIDs, glucocorticoids, anti-malarials (hydroxychloroquine, chloroquine, quinacrine), mycophenolate mofetil, azathioprine, or methotrexate. The dose of these medications will be required not to exceed certain thresholds [see Section 4.3] and will be kept stable during the study.

Patients with underlying pulmonary, cardiac or liver disease as well as patients with severe lupus (SLEDAI-2K score > 12 points) will be excluded. Subjects with active lupus nephritis, as proteinuria > 1.0 g/24 h, or equivalent using spot urine protein-to-creatinine ratio or subjects with CNS lupus (e.g., aseptic meningitis, seizures, cerebritis, polyneuropathy, cerebrovascular disease) within 90 days prior to Randomization will be excluded from the study.

Please refer to Sections 4.3 and 4.4 for a complete listing of the inclusion/exclusion criteria for the study.

4.2 Rationale for the selection of the study population

Clinical manifestations of SLE are highly heterogeneous, ranging from fatigue, arthralgia, oral ulcerations, skin rash to life-threatening renal, hematological, and neurological disease. Current treatments remain inadequate, with many patients having an incompletely controlled disease and suffering from debilitating side effects of therapies. Patients with active disease receiving standard therapies represent a significant unmet need for new therapeutic options.

Involvement of skin and/or joints is present in over 75% of SLE patients [see Section 1.1.1]. Inclusion of patients with musculoskeletal or mucocutaneous manifestations at Screening ensures the inclusion of subjects representative of the major SLE population.

Subjects with severe SLE, active lupus nephritis and CNS lupus are excluded due to potential increased risk for end-organ damage. In addition, subjects presenting organ manifestations (i.e., pulmonary, cardiac or liver disease) that could overlap with potential toxicities of ACT-334441 will be excluded. This approach is intended to minimize the risk of adverse effects and to limit the type and dose of glucocorticoids and immunosuppressive therapies that can confound the evaluation of safety, tolerability, and biological activity of ACT-334441.

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permissible to waive any of the criteria for any subject:

1. Signed informed consent prior to initiation of any study-mandated procedure.
2. Men or women ≥ 18 and ≤ 65 years of age.
3. Women of childbearing potential (WOCBP) as defined in Section 4.5.1:
    - must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization at least 3 weeks apart;
    - must agree to undertake a urine pregnancy test as indicated in Table 1 (bi-weekly/ monthly) during the study and up to 16 weeks after study treatment discontinuation;
    - must use methods of contraception as described in Section 4.5.2 from the Screening visit until 16 weeks after study treatment discontinuation.
4. Presenting with a diagnosis of SLE made at least 6 months prior to Screening, by fulfilling at least 4 of the 11 criteria for SLE as defined by the ACR (criteria are cumulative and do not need to be present concurrently) [Tan 1982; Hochberg 1997].

5. Presenting with a SLEDAI-2K score of at least 2 points for musculoskeletal or mucocutaneous manifestations (i.e., myositis, arthritis, rash, alopecia, mucosal ulcers) at Screening.
6. History or presence at Screening of positive ANA or anti-dsDNA antibodies.
7. Currently treated for at least 30 days prior to Randomization with stable doses of one or more of the following background medications:
    - NSAIDs;
    - Corticosteroids (≤ 10 mg/day prednisolone or equivalent),
    - Anti-malarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine)[#],
    - Mycophenolate mofetil (≤ 2 g/day)[#],
    - Azathioprine (≤ 2 mg/kg/day)[#],
    - Methotrexate (≤ 20 mg/week)[#].

#Treatment with anti-malarials, mycophenolate mofetil, azathioprine, or methotrexate must have been started at least 90 days prior to Randomization and must not have been stopped within 30 days prior to Randomization.

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permissible to waive any of the criteria for any subject:

Pregnancy and Breastfeeding

1. Breastfeeding, pregnant women or women planning to become pregnant during the study.

SLE disease

2. Subjects with active lupus nephritis (defined by proteinuria > 1 g/24 h, or equivalent using spot urine protein-to-creatinine ratio) within 90 days prior to Randomization; subjects with CNS lupus (e.g., aseptic meningitis, seizures, cerebritis, polyneuropathy, cerebrovascular disease) within 90 days prior to Randomization; subjects with lupus vasculitis within 90 days prior to Randomization.
3. Subjects presenting with a SLEDAI-2K score > 12 at Screening or at Randomization.

Cardiovascular

4. History or presence of cardiac rhythm disorders (e.g., sinoatrial heart block, second or third degree AV block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest).
5. Resting HR < 55 bpm as measured by the pre-dose 12-lead ECG on Day 1; an increased QT corrected for heart rate on the basis of Fridericia's formula (QTcF) interval of > 470 ms (females), > 450 ms (males) at Screening, or on Day 1 ECG prior to study treatment initiation.

6. History or presence of ischemic heart disease.
7. History or presence of myocarditis or endocarditis.
8. Presence of valvular heart disease associated with symptoms or hemodynamic change.
9. History of syncope associated with cardiac disorders.
10. History or presence of cardiac failure.
11. Systemic arterial hypertension not controlled by medication according to investigator judgment.
12. History or presence of vascular thrombosis at any time or a history of pregnancy morbidity in the context of anti-phospholipid antibody syndrome within 5 years prior to Randomization.
13. Clinically relevant hypotension according to investigator's judgment or orthostatic hypotension (i.e., > 20 mmHg decrease in SBP or > 10 mmHg decrease in DBP from supine to standing position measured between 1 and 3 minutes after standing) at Screening.
14. Known pulmonary arterial hypertension of functional class III or IV.

Pulmonary

15. History or presence of severe respiratory disease or pulmonary fibrosis, based on medical history, lung function and chest X-ray (CXR) performed at Screening or within 3 months prior to Screening.
16. Bronchial asthma or chronic obstructive pulmonary disease.
17. Abnormal PFTs: FEV_1 or FVC < 70% of predicted normal value; FEV_1/FVC ratio < 0.7.

Treatments

18. Treatment or planned treatment with the following medications*:
    a. Within 15 days or 5 half-lives of the medication, whichever is longer, prior to Randomization:
        - β-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR-lowering systemic therapy (list of drugs provided in Appendix 1).
        - QT-prolonging drugs with known risk of torsades de pointes, for any indication (list of drugs provided in Appendix 2).
        - Short- and long-acting β2-agonists (e.g., albuterol, levalbuterol, formoterol, terbutaline salmeterol).
    b. Within 30 days or 5 half-lives of the medication, whichever is longer, prior to Randomization:
        - Cyclophosphamide, cyclosporine, tacrolimus, sirolimus, etc.,
        - Pulse methylprednisolone,
        - Vaccination with live vaccines.
    c. Within 90 days prior to Randomization:

- Belimumab, leflunomide
- Any investigational immunosuppressive or immunomodulatory agent (within 90 days or 5 half-lives of the drug prior to start of study treatment, whichever is longer).

d. Within 12 months prior to Randomization:

- B cell-depleting biological agents such as rituximab or ocrelizumab.

e. Any time prior to Randomization:

- Alemtuzumab, S1P modulators (e.g., fingolimod).

*For immunosuppressants or anti-inflammatory drugs not listed among the fordidden medications, the investigator should discuss adequate wash-out time with the sponsor.

Infection and infection Risk

19. Active or latent tuberculosis (TB), as assessed by CXR performed at Screening or within 3 months prior to Screening, and interferon gamma release assay (QuantiFERON-TB-Gold®) at Screening, except if there is documentation that the subject has completed adequate and successful treatment for latent TB infection or TB disease previously.
20. Ongoing known bacterial, viral or fungal infection that is of clinical concern in the judgment of the investigator.
21. A history of any serious infection, defined as life-threatening or requiring i.v. antibiotics or hospitalization, within 30 days prior to Randomization.
22. Hepatistis B, C, congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at Screening.
23. Negative antibody test for varicella-zoster virus at Screening.

Malignancy

24. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation.

Transplantation

25. History or presence of bone marrow or solid organ transplantation.

Ophthalmology

26. Presence of macular edema or active uveitis.

Metabolic and hepatic

27. Type 1 or 2 diabetes that is poorly controlled according to investigator judgment, or diabetes complicated with organ involvement such as diabetic nephropathy or retinopathy.
28. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin (TBL), serum albumin, international normalized ratio (INR), as well as on presence/absence and severity of ascites and hepatic encephalopaty.

29. TBL > 1.5-fold upper limit of normal (ULN; unless in the context of known Gilbert's Syndrome).
30. ALT or AST > 2-fold ULN.

Hematology

31. Hemoglobin (Hb) < 9 g/dL.
32. WBC count < 2500/μL (2.5×10^9/L).
33. Lymphocyte count < 800 /μL (0.8×10^9/L).
34. Platelets < 75,000/μL (75×10^9/L).

Renal

35. Proteinuria > 1.0 g/24 hour or equivalent using spot urine protein-to-creatinine ratio.
36. Estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Other categories

37. History of clinically significant drug or alcohol abuse.
38. Known allergy to $S1P_1$ modulators or any of the ACT-334441 formulation excipients [see Section 5.1.1].
39. Any other clinically relevant medical or surgical condition that in the opinion of the investigator would put the subject at risk if participating in the study.
40. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits or likelihood of not completing the study including mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Premature ovarian failure confirmed by a specialist.
- XY genotype, Turner syndrome, uterine agenesis.
- Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

4.5.2 Acceptable methods of contraception

WOCBP [see Section 4.5.1] must use one of the following methods of contraception from Visit 1 (Screening) up to at least 16 weeks after study treatment discontinuation:

i. Two methods of contraception, one from Group 1 and one from Group 2, defined as follows:

- Group 1: Oral, implantable, transdermal, or injectable hormonal contraceptives or intrauterine devices. If a hormonal contraceptive is chosen from this group, it must be taken for at least 1 month prior to Randomization.
- Group 2: Female or male condoms, diaphragm or cervical cap.

OR

ii. Sterilization of the male partner with documented post-vasectomy confirmation of the absence of sperm in the ejaculate.

OR

iii. Permanent female sterilization (tubal occlusion/ligation at least 6 weeks prior to Screening).

OR

iv. True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject.

Rhythm methods or the use of a condom by a male partner alone are not considered acceptable methods of contraception for this study.

The methods of contraception used (including non-pharmacological methods) must be recorded in the eCRF.

4.6 Medical history

4.6.1 General medical history

Relevant medical history, as defined below, must be recorded in the eCRF:

- Chronic medical conditions including cardiac, cardiovascular, pulmonary, CNS, liver function, renal function, eye disorder, and skin conditions at any time in the past
- New acute medically relevant conditions including any serious infection, defined as life-threatening or requiring i.v.antibiotics or hospitalization in the past 6 months
- Exposure to healthcare settings in the past 3 months (e.g., hospitalization, emergency care admissions, visit to emergency medical services facility)
- Pregnancy morbidity (e.g., fetus loss, spontaneous abortion, premature birth)
- Previous and concomitant baseline therapy [see Section 5.2]
- History of chemotherapy, radiotherapy, operations, immunosuppression or any other relevant medical treatment

4.6.2 SLE-relevant disease history

SLE disease characteristics as defined below, evidenced by documentation in the subject charts, will be recorded on the SLE history page of the eCRF:

- Date of first SLE symptoms
- Date of SLE diagnosis
- SLE symptoms according to ACR criteria [ACR 1997]

1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed OR 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR 2. Psychosis--in the absence of offending drugs or or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis OR 2. Leukopenia--< 4,000/mm3 on ≥ 2 occasions

	OR 3. Lymphopenia--< 1,500/ mm3 on ≥ 2 occasions OR 4. Thrombocytopenia--<100,000/ mm3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. OR 3. Positive finding of antiphospholipid antibodies on: 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

In the eCRF, the date of first documented appearance and duration of the above ACR criteria will be recorded (when applicable).

- History of detectable ANA or anti-dsDNA testing.
    - ANA
        - Date of testing
        - Titer value
        - Reference range
        - Test kit (e.g., Hep-2 titer, ELISA)
        - Testing laboratory
    - Anti-dsDNA
        - Date of testing
        - Titer value
        - Reference range
        - Test kit (e.g., Far assay, ELISA)
        - Testing laboratory

Important notes:
If, at the Screening visit, ANA and anti-dsDNA results are negative per central laboratory testing, a positive historical test must be recorded to assess patient eligibility [see Section 4.3, inclusion criterion 6]. A historical testing is considered positive if ANA and/or anti-dsDNA antibodies was/were measured above the detection limit of the specific test kit used. The elevated ANA and/or anti-dsDNA should unequivocally be due to SLE in the opinion of the investigator.

5 TREATMENTS

5.1 Study treatment

Study treatments include ACT-334441 and matching placebo, which are administered during a 12-week double-blind treatment period.

5.1.1 Investigational treatment: description and rationale

ACT-334441 is supplied as capsules at the doses of 0.5 mg, 1 mg, 2 mg, or 4 mg. The matching placebo is supplied as identical capsules formulated with the same excipients but without the active ingredient, ACT-334441.

The four treatment doses of 0.5 mg, 1 mg, 2 mg, or 4 mg were selected based on PK, PD, safety, and tolerability results from the Phase 1 study, where such doses were administered o.d. up to 35 days in healthy subjects [see Section 1.3.2].

Inactive ingredients of ACT-334441 formulation are: methycellulose, sodium lauryl sulfate, mannitol, colloidal silicon dioxide and dipalmitoylphosphatidylcholine; the capsule shell contains hydroxypropylmethylcellulose and titanium dioxide.

5.1.2 Study treatment administration

One capsule of ACT-334441 or placebo will be taken orally irrespective of food intake. The capsule will be swallowed as a whole. It is preferable that the capsule be taken each day at approximately the same time (preferably each morning).

On the day of the study visits, study drug must be taken only after the completion of the pre-dose safety assessments (SBP, DBP, ECGs, PFTs, laboratory tests) and PK sampling.

5.1.3 Treatment assignment

In Part A, a total of 48 eligible subjects will be randomized in a 1:1:1:1 ratio to ACT-334441 0.5 mg, 1 mg, and 2 mg or placebo. In Part B, a total of 16 eligible subjects will be randomized in a 3:1 ratio to ACT-334441 4 mg or placebo.

Each of the clinical study sites will be assigned a unique site number. At Visit 1 (Screening), all screened subjects will be assigned a study-specific subject number by the IRT system, which identifies the subject throughout the study. After having confirmed

the eligibility of the subject and prior to the start of study treatment, the investigator/delegate contacts the IRT system at Visit 2 to randomize the subject. The IRT system assigns a randomization number to the subject and assigns the bottle number that matches the treatment arm assigned by the randomization list to the randomization number.

The randomization list is generated by the independent IRT provider and is kept strictly confidential.

5.1.4 Blinding

5.1.4.1 Study drug material related blinding

This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the clinical research associates (CRAs), all Clinical Trial Team (CTT) members at Actelion and Contract Research Organizations (CROs) involved in the conduct of the study will remain blinded to the treatment allocation until study closure. Actelion staff responsible for clinical trial supply will need to be unblinded to ensure adequate distribution of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file, and they will not take part in any CTT meetings after the study set-up has been completed.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential and accessible only to authorized persons who are not involved in the conduct and analysis of the study [see Section 5.1.5]. A sealed randomization code is kept by Actelion Global Quality Management in a safe cabinet. A second set will be provided to the statistician of the Independent Statistical Analysis Center (ISAC) for the production of unblinded IDMC statistical outputs.

The investigational treatment and its matching placebo are indistinguishable, and all bottles will be packaged in the same way.

5.1.4.2 Functional blinding

First-dose effects on HR and AV conduction and lymphocyte counts reduction have been identified as potentially unblinding information. Access to this information by the site's staff and sponsor's study team will be restricted.

The following measures will be taken to ensure that the main site staff and the Actelion study team will remain blinded to lymphocyte counts and that the medical review of cardiac safety assessments with unblinding potential will be performed without introducing bias:

- Results of the total WBC count and total lymphocyte count will not be communicated to the sites, sponsor, and CRO unless a total lymphocyte count

< 200 cells/µL at any study visits until EOT or < 800 cells/ µL at EOS, is recorded by the central laboratory. In these events an alert will be sent to the principal investigator and to the sponsor including lymphocyte count results. Follow-up monitoring must be provided as described in Section 5.1.10.2.

- Blood samples for lymphocyte subset exploratory analysis will be analyzed by the sponsor within 6 days after sampling. In order to avoid potential unblinding, the blood samples will be shipped to Actelion via the central laboratory with scrambled identification numbers. The Actelion team performing the analysis will be separated from the Actelion study team and will not have access to the subject number, date and time of the sampling (i.e., baseline or EOT) prior to database lock.

- At the site level:

    - A CSA will perform and evaluate the cardiac safety assessments on Day 1 (Randomization) and on days of study treatment re-initiation.

    - The subject will be instructed not to discuss any results related to the first-dose administration (i.e., ECG results) with the principal investigator / treating physician or any other blinded site personnel.

    - The central reading reports on 12-lead ECG and 24-hour Holter ECG performed after first dosing will be sent to the CSA only and must not be shared with the principal investigator / treating physician.

    - The principal investigator / treating physician and the CSA must not discuss any issues related to subject care and management on Day 1 or first day of study drug re-initiation, unless mandated for subject safety reasons. The principal investigator should not access the blinded ECG results, unless medically mandated to ensure subject's safety.

- At the sponsor level:

    - The medical review of all first-dose data assessed on Day 1 (Randomization) or on days of study treatment re-initiation (including hourly post-dose 12-lead ECGs and 24-hour Holter ECG data with unblinding potential, as well as other relevant data) will be performed by a first-dose monitor. He/she will only discuss the first-dose data with the CSA, the site CRA and/or IDMC members. Further details on the role of the first-dose monitor are described in the first-dose monitor charter.

    - Other sponsor team members involved in the medical review of other study data will not have access to first-dose data.

5.1.5 Unblinding

5.1.5.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure in accordance with Actelion standard operating procedures (SOPs).

5.1.5.2 Unblinding for interim analyses

An ISAC, not otherwise involved in the design, conduct and analysis of the study, will have access to the randomization code in order to prepare the interim analysis reports and unblinded periodic reports for review by the IDMC during the course of the trial. The randomization code will be made available to the ISAC in accordance with the sponsor's SOPs.

5.1.5.3 Unblinding before final analyses

The randomization code will be made available to the PK bioanalytic laboratory in accordance with the sponsor's SOPs.

5.1.5.4 Unblinding for suspected unexpected serious adverse reactions

When a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment. The randomization code will not be communicated to the site staff or to the Actelion study team; unblinded SUSAR information will be anonymized and provided to Actelion Global Drug Safety, respective health authorities and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs), and the IDMC. SUSARs will be reported to investigators in a blinded fashion.

5.1.5.5 Emergency procedure for unblinding

The investigator, study staff and sponsor staff must remain blinded to the subject's treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded randomization code for study treatment allocation through the IRT system. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator should discuss the intended code break with the sponsor.

The occurrence of any code break during the study must be clearly justified and explained by the investigator. The investigator must not disclose the unblinded treatment in the eCRF or to the sponsor or its delegates. In all cases, the sponsor must be informed as soon as possible before or after the code break.

The circumstances leading to the code break must be documented in the site study file and eCRF.

Refer to the IRT system guidelines for complete information regarding the IRT system procedures for randomization, study drug assignment, and unblinding.

5.1.6 Study treatment supply

Manufacture, labeling, packaging and supply of study treatments will be conducted according to Good Manufacturing Practice, Good Clinical Practice (GCP) and any local or national regulatory requirements.

All treatment supplies are to be used only in accordance with this protocol and not for any other purpose.

5.1.6.1 Study treatment packaging and labeling

5.1.6.1.1 Study treatment packaging and preparation

Study treatment (ACT-334441 or placebo) is provided as capsules and is supplied in childproof bottles.

5.1.6.1.2 Study treatment labeling

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

The batch number and the retest date (or expiry date) will be given on the study treatment labels.

5.1.6.2 Study treatment distribution and storage

Treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the medication labels.

5.1.6.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used, partially used and unused study treatment bottles at each visit. The protocol-mandated study drug dispensing/return procedures may not be altered without prior written approval from the sponsor. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.6.4 Study treatment return and destruction

On an ongoing basis and/or upon termination of the study, the CRA will collect used and unused subject kits, which will be sent to the warehouse, where the sponsor or a representative will check treatment reconciliation. In certain circumstances, used and

unused treatment bottles may be destroyed at the site once treatment accountability is finalized and checked by the sponsor or a representative, and written permission for the destruction has been obtained from the sponsor

If the CRA is not able to reconcile the treatment due to lost or prematurely destroyed bottles prior to destruction, the site is to provide detailed documentation that describes the loss or premature destruction to justify treatment accountability.

5.1.7 Study treatment accountability and compliance with study treatment

5.1.7.1 Study treatment accountability

The inventory of study treatment dispensed and returned (i.e., study treatment accountability) must be performed by the study staff on the day of the subject visit and before providing further study treatment. It is recorded on the investigational medicinal product dispensing and accountability log and in the eCRF and checked by the CRA during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment bottle dispensed to the subject:

- Dispensed bottle number
- Date dispensed / number of capsules dispensed (pre-populated in eCRF)
- Date returned / number of capsules returned

All study treatment supplies, including partially used or empty bottles, must be retained at the site for review by the CRA.

If the subject forgets to bring the remaining study treatment to a study visit, he/she must be instructed to not take any tablet/capsules from the remaining study treatment and to bring it to the next visit.

5.1.7.2 Study treatment compliance

Treatment compliance will be assessed based on study treatment accountability:

Accountability based compliance =

[(number of capsules dispensed at Visit n − number of capsules returned at Visit n+1) / number of capsules that should have been taken during the period*] × 100

*The period is defined as the number of days elapsed between the respective visits.

During the study, study treatment compliance based on accountability is expected to be above 80%. If below 80%, without a medical justification (e.g., adverse event), this will be considered as a protocol deviation. The investigator must check with the subject the

reasons for this non-compliance and discuss actions to be taken to avoid re-occurrence at the next visit. If the subject forgets to bring the remaining study treatment to a study visit, he/she will be asked to bring it to the next visit.

At Visit 3 and re-initiation visits, a compliance review based on study drug accountability, will be performed by the investigator (or delegate) and recorded in the eCRF.

5.1.8 Study treatment interruptions

Study treatment should not be interrupted. If study treatment intake is interrupted by the subject for a day or more for any reason, she/he must immediately inform the principal investigator / treating physician. If a subject forgets to take study treatment in the morning, she/he should take it on the same day and resume regular dosing the next morning.

The following guidance is provided for re-initiation of study treatment after study treatment interruptions.

Note that under no circumstances should a subject take more than one capsule per day.

5.1.8.1 Between Day 1 and Day 14

- If the subject misses to take the dose for 1 day or more, he/she must interrupt the treatment and immediately inform the principal investigator / treating physician. A re-initiation visit should take place within 7 days after the first dose was missed. Re-initiation of study treatment must be monitored on site following the cardiac assessment schedule and applying the discharge criteria as on Day 1.

- If the study treatment cannot be re-initiated within 7 days after the treatment interruption, the subject should be permanently discontinued. (Note that re-initiation visits may be performed after Day 14 if initial missed dosing occurred between Day 7–14)

- If, at any visits (scheduled or unscheduled), the subject reports to the investigator having missed to take the dose for one or more days during the initial 2 weeks of treatment (Day 1 to Day 14) but has then resumed study treatment without reporting promptly the interruption to the investigator, information on any event potentially related to the interruption should be collected and the subject should be counselled on the risks of non-compliance. Based on the information available, the investigator may decide to permanently discontinue the subject or to continue study treatment as planned. No re-initiation should be performed in such a case.

Note that a subject can be re-initiated only once during the study duration.

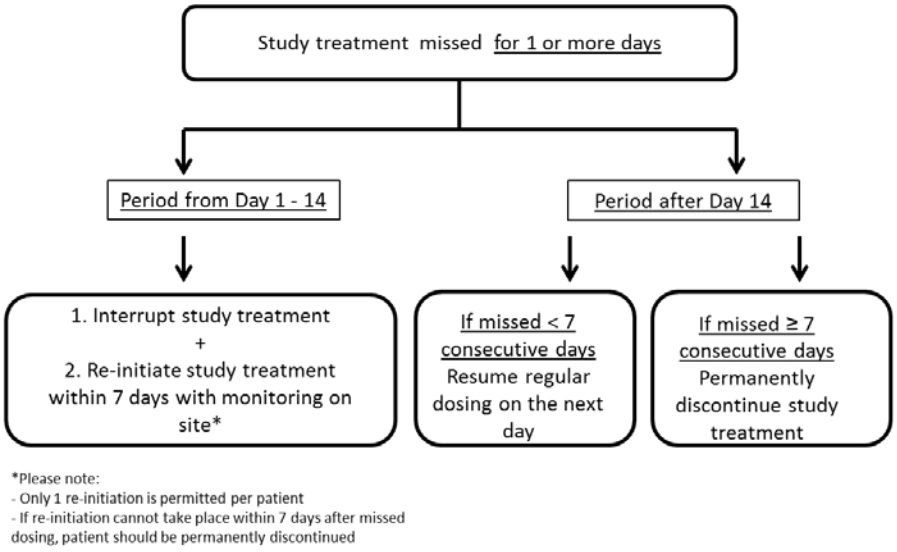
5.1.8.2 After Day 14

- If the subject missed doses for less than 7 consecutive days:
  - Regular dosing should be continued with the morning dose on the following day.
  - Subjects must be instructed to contact the investigator immediately if they experience any symptoms of bradycardia (e.g., dizziness, vertigo, syncope).

- If the subject missed doses for more than 7 consecutive days:
  - The subject should be permanently discontinued.

A schematic overview is provided in Figure 2.

Figure 2 Algorithm for management of study treatment interruptions



5.1.9 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Actelion. The main reason and whether discontinuation of study treatment is the decision of the subject, the investigator, or Actelion must be documented in the eCRF.

A subject has the right to prematurely discontinue study treatment at any time by withdrawal from study treatment only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study [see Section 9.2]).

The investigator should discontinue study treatment for a given subject if, on balance, she/he believes that continued administration would be contrary to the best interests of the subject. Study treatment may be discontinued in response to an AE, lack of efficacy (including disease progression, treatment failure, worsening of subject condition), a protocol deviation (including not meeting eligibility criteria, non-compliance with study requirements, such as non-compliance with study treatment intake or visit attendance), or if the subject is lost to follow-up. Study-specific criteria for discontinuation of study treatment are described in Section 5.1.10.

Premature discontinuation of study treatment may also result from a decision by Actelion, e.g., in case of premature termination or suspension of the study [see Section 9.3]. A subject who prematurely discontinues study treatment is not considered as withdrawn from the study, provided that the subject's consent for this limited participation in the study has not been withdrawn. Subjects who prematurely discontinue study treatment will be asked to return for an EOT visit within 7 days of last study treatment intake, to attend an EOS Visit 6 weeks after the last dose of study treatment and will be followed-up for a total of 16 weeks after last study treatment intake (telephone call follow-up for pregnanacy and SAEs).

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 9.2 and 9.4, respectively.

5.1.10 Management of clinical events and study-specific criteria for interruption / premature discontinuation of study treatment

5.1.10.1 Cardiovascular

Subjects must be permanently discontinued from study treatment if any of the following occurs:

- HR < 40 bpm at two consecutive hourly 12-lead ECG post-dose on Day 1 (or on days of re-initiation following study treatment interruptions), or
- SBP < 90 mmHg at two consecutive hourly BP measurements post-dose on Day 1 (or on days of re-initiation following study treatment interruptions), or
- The subject does not meet the criteria for discharge from the hospital on Day 1 (or on days of re-initiation following study treatment interruptions) after 12-hour post-dose monitoring [see Appendix 4], or

- QTcF > 500 ms is observed at any time throughout the study, as documented by 12-lead ECG.

In addition, the investigator should consider permanent discontinuation of study treatment if a subject reports at any time symptomatic bradycardia or hypotension (e.g., syncope).

Follow-up monitoring will have to be provided until the event resolves, the condition is stable, or the change is regarded as no longer clinically relevant.

Continuous ECG monitoring is recommended for subjects who meet study treatment discontinuation criteria related to bradycardia or other arrhythmia. Subjects who are permanently discontinued should not be discharged from the monitored setting before vital signs return to near baseline values and until there is no persisting ECG abnormality (e.g., QT prolongation, AV block second degree or higher) or ongoing AE requiring (continued) hospitalization, or until medically indicated. Any clinically relevant findings meeting the definition of an AE will be recorded accordingly in the eCRF.

In case of any signs and symptoms of bradycardia or other arrhythmia (e.g., syncope, palpitations, dizziness) at any time during the study treatment, the CSA should be consulted. In case a cardiac origin of any event is suspected, permanent discontinuation of study treatment should be considered.

In case subjects develop new or worsening of pre-existing hypertension during the course of the treatment with the study treatment that in the opinion of the investigator cannot be adequately controlled by medications, study treatment should be permanently discontinued.

5.1.10.2 Immune system

Subjects must be permanently discontinued from study treatment at any time throughout the study in the event of:

- Confirmed total lymphocyte count < 200 cells/μL

Confirmation will be done as follows:

Whenever a total lymphocyte count < 200 cells/μL, is recorded by the central laboratory, an alert will be sent to the principal investigator and the sponsor. The primary investigator will immediately contact the subject and ask her/him to return to the site within 48 hours at the latest to repeat the test at trough level (pre-dose) by the central laboratory (unless the clinical situation mandates an immediate local testing). If the repeat test confirms a total lymphocyte count < 200 cells/μL, the study treatment must be discontinued, and lymphocyte counts must be monitored on a regular basis (e.g., every

2 weeks) at least until the EOS visit (6 weeks after study drug discontinuation). If lymphocyte count is still < 800 cells/µl at the EOS visit, monitoring should continue on a regular basis (e.g., every 2 weeks) by the local laboratory until the lymphocyte count has returned to ≥ 800 cells/µL or until medically indicated.

In the event that clinically relevant, persistent blood cell count abnormalities (e.g., a marked abnormal low value for neutrophils, RBC or platelets flagged "LLL"; see Appendix 7) are observed, the investigator should consider permanent discontinuation of study treatment and/or discontinuation of concomitant immunosuppressive medications.

5.1.10.3 Respiratory system

In case of abnormal spirometry results or persistent respiratory symptoms (e.g., dyspnea), the subject will be closely observed, spirometry assessments will be repeated, and study treatment must be permanently discontinued, according to the guidance provided in Table 2 and below.

Table 2 Guidelines for FEV_1 and/or FVC decrease

Item	Parameter	Guideline
1	If FEV_1 and/or FVC > 15% decrease from the study baseline.	Repeat spirometry assessments preferably within 1 week See item 1a, 1b.
1a	If at repeat spirometry assessment: FEV_1 and/or FVC > 15% decrease from the study baseline.	Permanently discontinue study treatment and perform FU spirometry assessments.
1b	If at repeat spirometry assessment: FEV_1 and/or FVC ≤ 15% decrease from the study baseline.	Resume regular spirometry assessment schedule. If at any other scheduled assessment FEV_1 and/or FVC > 15% decrease from the study baseline: permanently discontinue study treatment and perform FU spirometry assessment.

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; FU = follow-up.

If clinically significant, persistent respiratory AEs (e.g., dyspnea) are reported, PFTs must be performed and study treatment must be permanently discontinued. Further diagnostic work-up and consultation with a pulmonologist or other specialist should be considered according to local practice and the clinical situation.

In all cases of permanent study treatment discontinuation, follow-up monitoring must be provided until respiratory AEs are resolved and changes in pulmonary function are no longer clinically relevant or until medically indicated.

5.1.10.4 Pregnancy

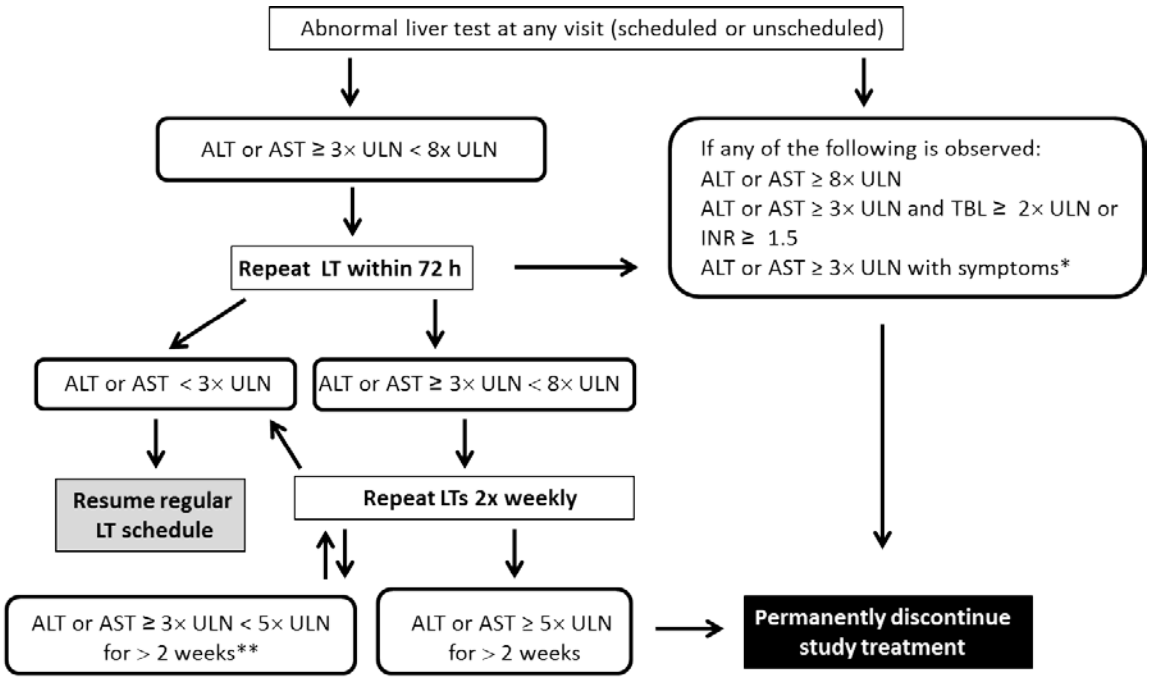
If a subject becomes pregnant while on study treatment, study treatment must be permanently discontinued.

If a subject has a positive urine pregnancy test, study treatment must be interrupted immediately. A serum pregnancy test must be performed as soon as possible. If the pregnancy is confirmed, study treatment must be permanently discontinued (apart from study drug, also some co-medications may have to be considered for discontinuation). If the result of the serum pregnancy test is negative, study drug may be re-initiated as indicated in study treatment interruptions section [see Section 5.1.8].

5.1.10.5 Liver abnormalities

In case of abnormal liver tests (LTs) or signs and symptoms suggestive of drug-induced liver injury (DILI), the subject will be closely observed, LTs will be repeated, and study treatment must be permanently discontinued, according to the guidance provided in Figure 3.

Figure 3 Guidance for monitoring liver test abnormalities



* Symptoms include unusual lethargy or fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, anorexia, dark urine, fever, rash, itching and/or eosinophilia (>5 %); ** Investigator may consider permanent discontinuation
AST = aspartate aminotransferase, ALT= alanine aminotransferase, INR = international normalized ratio, LT = Liver test, TBL = total bilirubin, ULN = upper limit of normal.

When marked abnormalities levels for AST, ALT, TBL or INR are reached as indicated in Figure 3, an alert will be sent by the central laboratory, to the principal investigator and the sponsor, as defined in Appendix 7. The sponsor will contact the principal investigator to ensure that she/he will immediately contact the subject to enquire about symptoms and ask her/him to return to the site within 72 hours at the latest to repeat the test by the central laboratory (unless the clinical situation mandates immediate local testing). In the case of repeated abnormal LFTs within 72 hours, the subject will be closely observed and liver enzyme and bilirubin tests will be repeated by the central laboratory or locally according to the scheme illustrated in Figure 3. Further diagnostic work-up and consultation with a hepatologist or other specialist should be considered according to local practice and the clinical situation.

In all cases of permanent study treatment discontinuation, follow-up monitoring must be provided until signs and symptoms have resolved and changes in liver function abnormalities are no longer clinically relevant or until medically indicated.

5.1.10.6 Ocular abnormalities

Subjects with suspected macular edema or retinal vasculitis should be confirmed by diagnostic work-up as recommended by local guidelines (e.g., OCT, fluorescence angiography). The OSB will receive all information related to suspected cases of macular edema and will perform a review of OCT results and the subject's data. In case of confirmed macular edema, study treatment must be permanently discontinued and the subject must be followed up until resolution or until medically indicated.

5.1.10.7 Infections

Infections are a leading cause for morbidity and mortality in subjects with SLE [Danza 2013]. Bacterial infections are most frequent, followed by viral and fungal infections. Disease activity, disease duration, leukopenia, use of glucocorticoids and immunosuppressives have been linked to increased risk of infections in SLE patients, in particular in the respiratory system and urinary tract as well as in the skin and soft tissues.

Diagnosis of infections may be delayed because they may mimic an SLE flare, therefore the investigator needs to maintain a high level of vigilance [Mosca 2010].

TB infection in SLE is mainly localized to the lung with upper lobe infiltrates, miliary lung disease, and pleural effusions, and may be confused with pulmonary lupus manifestations. Opportunistic infections caused by the reactivation of human herpes viruses (herpes simplex viruses, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus) may be associated with cutaneous and neurological symptoms. The neurotropic herpes viruses (herpes simplex and varicella-zoster) are frequent human pathogens, and their reactivation can cause serious infections of the CNS, such as encephalitis and meningitis [Steiner 2007]. The most frequent characteristics of these

infections are of acute onset, associated with fever, headache, confusion, personality changes, and disorientation. These symptoms may be difficult to distinguish from CNS lupus manifestations, therefore heightened vigilance is required. Particular vigilance is required for rare and unusual neurological symptoms, as their recognition is crucial for the early diagnosis of neurotropic herpes viruses infections and progressive multifocal leucoencephalopathy, caused by reactivation of John Cunningham virus [Nived 2008].

The physical examination and blood tests on the routine visits should be focused on any potential sign of skin, mucosal surfaces, lung, gastrointestinal tract, liver, CNS, hematological abnormality and organ dysfunction suggesting a potential opportunistic infection.

Subjects should be advised to be pro-active and alert in reporting any unusual neurological symptoms and any signs and symptoms indicative of systemic infections, such as fever, malaise and fatigue.

In the event of a suspected clinically relevant infection (e.g., serious infection, opportunistic infection), the subject should be treated as clinically indicated and study treatment must be permanently discontinued. Concomitant immunomodulatory medications may also be discontinued at the discretion of the investigator. The decision to permanently discontinue study treatment will be made after evaluation of all available information concerning all potential causes of infection and the clinical status of the subject. Further diagnostic work-up and consultation with an infectious disease specialist or other specialist should be considered according to local practice and the clinical situation.

In the event of permanent discontinuation from study treatment due to infection, adequate treatment needs to be provided, and the subject must be monitored until complete resolution of the infection. Furthermore, in the event of permanent discontinuation from study treatment due to any reason, subjects should not receive any of the prohibited systemic immunosuppressive treatment during the follow-up period of 16 weeks after last study drug intake, unless clinically indicated and justifiable in the opinion of the investigator.

5.1.10.8 Premature treatment discontinuation after study treatment interruption, background therapy changes, administration of forbidden therapies, or study drug mis-dispensing

A subject must be permanently discontinued from study treatment if study treatment has been interrupted between Day 1 and Day 14 and not re-initiated within 7 days after treatment interruption [see Section 5.1.8.1] or the subject missed doses for more than 7 consecutive days after Day 14 [see Section 5.1.8.2].

In case of disease progression, treatment failure, worsening of subject condition requiring changes in the dose of background therapy outside of protocol-specified levels [see Section 5.2.4], the subject may be permanently discontinued from the study treatment at the discretion of the investigator and after discussion with the sponsor. In case of need to administer forbidden concomitant therapies, the subject must be permanently discontinued from the study treatment [see Section 5.2.5].

In case of study drug mis-dispensing (incorrect kit dispensed) and incorrect study drug intake, the subject must be permanently discontinued.

Furthermore, in the event of permanent discontinuation from study treatment due to any reason, subjects should not receive any of the prohibited systemic immunosuppressive treatment or other forbidden therapies during the follow-up period of 16 weeks after last study drug intake, unless clinically indicated and justifiable in the opinion of the investigator. Also, the allowed concomitant therapies should stay within the protocol-defined ranges during the follow-up period of 16 weeks after last study drug intake, and may only be changed if clinically indicated and justifiable by the investigator.

5.2 Previous and concomitant therapy

5.2.1 Background SLE therapy

5.2.1.1 Definition of background SLE therapy

In order to be eligible for the study, subjects must currently receive at least one of the below background treatments for SLE.

- NSAIDs
  - Aspirin (acetylsalicylic acid)
  - Ibuprofen
  - Naproxen
  - Celecoxib
  - Others
- Corticosteroids (≤ 10 mg/day prednisolone or equivalent; see Appendix 8)
  - Prednisolone
  - Prednisone
  - Methylprednisolone
  - Dexamethasone
  - Betamethasone
  - Hydrocortisone
  - Triamcinolone
  - Cortisone
  - Others
- Anti-malarials

  - Hydroxychloroquine (≤ 400 mg/day)
  - Chloroquine (≤ 500 mg/day)
  - Quinacrine (≤ 100 mg/day)
- Mycophenolate mofetil (≤ 2 g/day)
- Azathioprine (≤ 2 mg/kg/day)
- Methotrexate (≤ 20 mg/week)

Note:
All background SLE therapies must have been started at least 30 days prior to randomization with stable doses. Treatment with anti-malarials, mycophenolate mofetil, azathioprine, or methotrexate must have been started at least 90 days prior to randomization and must not have been stopped within 30 days prior to randomization.

5.2.1.2 Reporting of background SLE therapy in eCRF

All background SLE therapies ongoing at baseline or started during the study will be reported in the background SLE therapies pages of the eCRF.

The generic name, start/end dates of administration, route, dose and change in dose, frequency of administration, and reason for discontinuation will be recorded in the eCRF.

5.2.2 Previous SLE therapies

5.2.2.1 Definition of previous SLE therapies

A previous SLE therapy is any treatment administered for SLE and/or SLE manifestations for which the end date is prior to the start of the study (i.e., signing of ICF).

5.2.2.2 Reporting of previous SLE therapies in eCRF

All previous SLE therapies administered within 24 months prior to Screening will be reported in the previous SLE therapies pages of the eCRF.

The generic name, start/end dates of administration, route, dose, frequency, and reason for discontinuation will be recorded in the eCRF.

5.2.3 Study-concomitant therapy

5.2.3.1 Definition of study-concomitant therapy

A study-concomitant therapy is any treatment (including methods of contraception and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) given for any reason except SLE that is either ongoing at the start of study treatment or is initiated during the study treatment period, or during the follow-up period up to Visit 7 (EOS).

5.2.3.2 Reporting of study-concomitant therapy in eCRF

All study-concomitant therapies administered for non-SLE reasons will be reported in the concomitant medications pages of the eCRF.

The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, frequency, and indication will be recorded in the eCRF.

5.2.4 Allowed concomitant therapy

- i.v. atropine in the event of symptomatic bradycardia (see study-specific criteria for permanent discontinuation of study treatment in Section 5.1.10);
- Dilating eye drops, mydriatics, including parasympathetic antagonists (e.g., tropicamide) or sympathetic agonists (e.g., phenylephrine) for topical use;
- Vaccination with non-live vaccines (Note: although nonclinical data indicate no significant impairment of antibody response to immunization, no clinical data is currently available on vaccination efficacy under ACT-334441 treatment, therefore it is suggested that all planned/indicated vaccinations are completed more than 30 days before the start of treatment and, in case of vaccination during the study, titer control is recommended.);
- Stable systemic corticosteroid therapy; corticosteroids are not to be started or stopped during the study and the dose should be kept stable. However, the investigator may see reason to initiate or increase the dose of systemic corticosteroid to treat an SLE flare or another condition. In such cases, the dose may be increased for a period of not more than 14 days up to double the baseline dose or a maximum of 20 mg/day prednisolone or equivalent (please refer to conversion table in Appendix 8);
- Topical treatment therapy including topical use of corticosteroid is allowed.
- Stable antimalarial therapy (e.g., hydroxychloroquine, chloroquine, quinacrine); therapy is not to be started or stopped during the study, and dose should be kept stable;
- Stable NSAID chronic therapy. Therapy is not to be started or stopped during the study;
    - Temporary use and/or dose change for treatment of non-SLE related conditions (e.g., headache, menstrual cramps) is allowed;
- Stable immunosuppressant therapy (i.e., methotrexate, azathioprine, or mycophenolate mofetil). Therapy is not to be started or stopped during the study, and dose should be kept stable;

Background medications must be kept stable until the end of the follow-up period (16 weeks after the last study treatment intake) unless clinically indicated and justifiable in the opinion of the investigator. In case of changes in the dose of background medications outside protocol-specified levels, discontinuation of study treatment may be considered on a case-by-case basis and after discussion with the sponsor.

5.2.5 Forbidden concomitant therapy

- Immunosuppressives not listed in Section 5.2.4 such as cyclophosphamide, cyclosporine, leflunomide, sirolimus, tacrolimus, etc.;
- Immunosuppressive or immunomodulatory biological agents (e.g., belimumab, i.v. immunoglobulin, rituximab, S1P modulators other than ACT-334441);
- β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR-lowering therapy (as listed in Appendix 1);
- QT-prolonging drugs with known risk of torsades de pointes (list of drugs and specific rules provided in Appendix 2);
- Short- and long-acting β2-agonists (e.g., albuterol, levalbuterol, formoterol, terbutaline, salmeterol);
- Vaccination with live vaccines.

The forbidden concomitant therapies are not allowed during the study until the end of the follow-up period (16 weeks after the last study treatment intake) unless clinically indicated and justifiable in the opinion of the investigator.

In case of significant SLE worsening or significant disease flare requiring the administration of prohibited immunosuppressives or immunomodulatory biological agents, study treatment should be permanently discontinued. For guidance on the use of allowed concomitant medications following EOS, see Section 5.2.4.

If patients require treatment with any of the forbidden concomitant therapies or need to receive a live vaccine, study treatment should be permanently discontinued and patients should be followed up as clinically indicated.

6 STUDY ENDPOINTS

6.1 Pharmacodynamic endpoints

- Change in total lymphocyte count from baseline to EOT;
- Change in total lymphocyte count from baseline to each post-baseline assessment.

6.2 Safety endpoints

Treatment-emergent period is defined as the time from first study treatment intake up to 6 weeks (inclusive) after last study treatment intake.

- Treatment-emergent AEs, SAEs, and AESIs[#];
- AEs leading to premature discontinuation of study treatment;
- Changes in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for heart rate on the basis of Bazzett's formula [QTcB] and QT corrected for heart rate on the basis of Fridericia's formula [QTcF]), from pre-dose to selected post-dose assessments (1 h, 2 h, 3 h, 4 h, 5 h, 6 h) on Day 1 and on day of study drug re-initiation;
- Occurrence of treatment-emergent 12-lead ECG outliers (e.g., HR, PR, QTc defined in the Statistical Analysis Plan [SAP]);
- Occurrence of treatment-emergent 12-lead ECG abnormalities;
- Occurrence of treatment-emergent ECG-Holter abnormalities on Day 1;
- Change in SBP and DBP from baseline up to EOS;
- Change in FEV_1 and FVC, expressed in absolute value (L) and percent value from baseline up to EOS;
- Occurrence of treatment-emergent decrease of FEV_1 or FVC > 15% from baseline values;
- Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline up to EOS;
- Treatment-emergent laboratory abnormalities according to CTCAE 2010 v4.03 [CTCAE 2010] and FDA guidelines [FDA 2009] (for ALT/AST/TBL);
- Change in protein-to-creatinine ratio from baseline to EOT;
- Change in body weight from baseline to EOT.

[#]AESI considered for the analyses are described in Appendix 3.

6.3 Pharmacokinetic endpoints

- C_{trough} ACT-334441 plasma concentrations prior to dosing at Weeks 2, 4, 8, and 12 (EOT) or at EOT visit after premature study treatment discontinuation (if applicable).
- ACT-334441 plasma concentration at EOS (i.e., 6 weeks after study treatment discontinuation).

6.4 Exploratory disease activity endpoints

- Change in SLEDAI-2K score (modified to exclude leukopenia) from baseline to each post-baseline assessment;
- Change in PGA score from baseline to each post-baseline assessment;
- Change in SLEDAI-2K mucocutaneous and/or muscoskeletal scorings from baseline to each post-baseline assessment.

6.5 Quality of life endpoints

- Change in SF-36v2™ Health Survey domain and component scores from baseline to EOT.

6.6 Exploratory biomarker endpoints

The following exploratory biomarkers will analyzed, but the analysis is not limited to these markers:

- Change in immunoglobulin serum levels (IgG, IgM, IgA) from baseline to each post-baseline assessment;
- Change in ANA and anti-dsDNA antibody titers from baseline to each post-baseline assessment;
- Change in serum complement components C3 and C4, C-reactive protein (CRP), fibrinogen, BLyS and C-X-C motif chemokine 10 (CXCL10) from baseline to each post-baseline assessment.
- Change in blood lymphocyte subsets from baseline to EOT and EOS.

7 STUDY ASSESSMENTS

All study assessments are performed by an experienced study staff member: medical, nursing, or specialist technical staff, and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF.

If the principal investigator delegates any study procedure/assessment for a subject, e.g., ECG, OCT, blood sampling etc., to an external facility, he/she should inform the sponsor to whom these tasks are delegated. The set-up and oversight will be agreed upon with the sponsor. The supervision of any external facilities remains under the responsibility of the principal investigator.

Calibration certificates for the following devices used to perform study assessments must be available at the clinical site prior to the randomization of the first subject:

- Temperature measurement devices for study medication storage area and freezer.

- Spirometer; in addition, a copy of the calibrations check (syringe check) of the day of measurement must be stored and a log of calibration check results must be maintained at the site [see Section 7.2.6].
- 12-lead ECGs and 24-hour Holter ECG.
- BP monitoring device.

Calibration certificates for echocardiography and OCT devices should be available as indicated in Sections 7.2.5 and 7.2.8.

7.1 Screening/baseline assessments

7.1.1 Informed consent (Screening visit)

Prior to performing any study-specific procedure or assessment, the subject must provide written informed consent to participate in the study. If the signing of informed consent and performance of the first study-specific procedures or assessments take place on the same day, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed (i.e., time of procedures documented). If a study-specific procedure or assessment has been performed as part of routine assessments and the results are available prior to the subject's signing of informed consent (e.g., SLE-relevant disease history, CXR; see Sections 4.6.2 and 7.2.9), such procedure or assessment may be used to assess eligibility and does not have to be repeated. In such cases, it must be clear from the source document when and for which reason the assessment was done prior to the signing of the informed consent. It is the responsibility of the principal investigator / treating physician to explain the study in all its aspects to the subject and obtain her/his informed consent. The informed consent process will be documented in the investigator site file. The language used in the oral and written information about the trial, and including the informed consent form, will be provided in a language that is fully understandable to the subject.

7.1.2 Baseline demographics and disease characteristics

At Visit 1 (Screening), the below data are to be recorded in the eCRF.

- Baseline demographics (sex, age, race/ethnicity, body weight and height).
- Complete, clinically relevant medical history and current conditions, as well as smoking status.
- SLE-relevant disease history, ACR criteria [see Section 4.6.2] and SLE assessments (i.e., SLEDAI-2K and PGA) [see Section 7.4].

7.1.3 Previous and concomitant therapies

All background/previous SLE therapies, as well as all study-concomitant therapies [see Section 5.2], will be reported in the corresponding eCRF pages [see Section 5.2].

7.2 Safety assessments

The definitions, reporting and follow-up of AEs and SAEs are described in Section 10.

7.2.1 Laboratory assessments

7.2.1.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be automatically transferred from the central laboratory database to the sponsor's clinical database. Analysis of lymphocyte subsets will be performed by the sponsor [see Section 7.6].

In exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency, or missing central laboratory values), local laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated eCRF pages. Testing of WBC and total lymphocyte counts at a local laboratory should not performed unless deemed absolutely necessary by the investigator to ensure subject's safety. In this particular case, the local results of WBC and total lymphocyte counts will be recorded in the eCRF.

In case a central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time window and these test results are available.

Central laboratory reports will be sent to the investigator. In case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert the sponsor and the concerned clinical site. Values that will trigger such alert notification are displayed in Appendix 7.

All laboratory reports must be signed and dated by the primary investigator or delegate within 3 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are present at the time of signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant laboratory abnormalities detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10] and must be followed until the value returns to within the normal range or is

stable, or until the change is no longer clinically relevant. Further laboratory analyses should be performed as indicated and according to the judgment of the investigator.

Details about the collection, sampling, storage, shipment procedures, reporting of results and abnormal findings can be found in the laboratory manual.

7.2.1.2 Laboratory tests

Blood samples will be drawn at all scheduled visits. At unscheduled visits, blood samples will be collected at the investigator's discretion. Sample collection dates will be recorded in the eCRF.

Hematology

- Hb
- Hematocrit, MCH, MCV, and MCHC
- Erythrocyte count (reticulocyte count)
- Leukocyte count with differential counts*
- Platelet count

*For the purpose of functional blinding [see Section 5.1.4.2], the WBC and the lymphocyte counts will not be available to sites and the sponsor during the study. This data will be available only after database lock. Non-lymphocyte differential counts will be available during the course of the study as specified in the laboratory manual. If a lymphocyte count < 200 cells/µl is recorded by the central laboratory, an alert including lymphocyte count results will be sent to the investigators and to the sponsor at any study visits until EOT. If lymphocyte count < 800 cells/µl at EOS visit, an alert including lymphocyte count results will be sent to the investigator and to the sponsor's team, and lymphocyte count should be monitored on a regular basis (e.g., every 2 weeks) by the local laboratory until the lymphocyte count has returned to ≥ 800 cells/µL or until medically indicated.

Clinical chemistry

- Aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase
- Creatinine
- Blood urea nitrogen
- Uric acid
- Glucose
- Cholesterol, triglycerides
- Sodium, potassium, chloride, calcium

- Protein, albumin

Test for tuberculosis

- An interferon gamma release assay will be performed at Visit 1 (Screening) to screen for active or latent TB [see Section 7.2.10].

Coagulation tests

- Prothrombin time and INR
- Activated partial thromboplastin time

Pregnancy test

A serum pregnancy test for WOCBP will be performed at Visit 1 (Screening) and Visit 7 (EOS), and if pregnancy is suspected during the study. Urine pregnancy tests will be performed at all other visits.

In order to be randomized in the study, WOCBP must have a confirmed negative serum pregnancy test at Visit 1 (Screening) and a second confirmed negative urine pregnancy test prior to Randomization. **The two tests must be performed a minimum of 3 weeks apart.**

At Visit 7 (EOS), two urine pregnancy test kits will be dispensed to WOCBP to perform the test at their home 1–2 days before the planned follow-up telephone calls (11 weeks and 16 weeks after study drug discontinuation). The result of the tests (positive/negative) will be communicated to the treating physician during the follow-up telephone calls.

Serum pregnancy test results data will be automatically transferred from the central laboratory database to the sponsor's clinical database. Urine pregnancy testing results will be recorded in the eCRF (except for the follow-up telephone calls). In case of pregnancy up to the follow-up telephone calls, a Pregnancy Form must be completed [see Section 10.3.2].

Virus serology

- Hepatitis B surface antigen, Hepatitis C antibodies, HIV1 and HIV2 antibodies, varicella-zoster virus IgG antibodies will be assessed in serum at Visit 1 (Screening) (a confirmatory test might be required in case of positive testing results [e.g., positive Hepatitis C antibodies]).

Additional analyses in the event of infections

- A serum sample will be taken at Visit 2 (Randomization) and stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections (e.g., suspected opportunistic infection) during the study.

Urinalysis

Including but not limited to:

- pH
- Glucose
- Proteins
- Blood
- Leukocytes

A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments. Urine dipsticks provided by the central laboratory will be used to perform the urinalysis at all visits. The test will be performed and analyzed at the site, and the results will be recorded in the eCRF.

If the dipstick results are positive for protein, leukocytes, or blood, the urine sample will be subject to further analysis as clinically indicated (i.e., microscopic analysis of WBC, red blood cells [RBC], casts, and protein quantification). The results of any further analysis must be documented in the source documents / subject charts and can be used for assessment of the SLEDAI-2K score.

Urine protein-to-creatinine ratio

At Visit 1 (Screening), Visit 2 (Randomization) and Visit 6 (EOT), urine samples will be collected and sent to the central laboratory for protein and creatinine measures, and determination of the protein-to-creatinine ratio.

7.2.2 12-lead ECG

Digital 12-lead ECG devices will be provided to each site by the central ECG laboratory for the duration of the study.

Digital ECG recording will be performed for all subjects at all scheduled study visits with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement. Pre-dose ECGs also need to be performed at unscheduled visits (U1, U2, etc.) to the study protocol schedule. During the treatment period, 12-lead ECGs must be performed prior to dosing. The data records (i.e., flashcards) will be sent to the evaluation center for central reading.

Details will be provided in the 12-lead ECG laboratory manual.

The following parameters will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. QTc (ms) will be calculated according to Bazett's and Fridericia's formula ($QTcB = QT/(RR)^{0.5}$ and $QTcF = QT/(RR)^{0.33}$, respectively).

ECG printout tracings must be reviewed, signed and dated by the physician responsible for the performance (i.e., principal investigator / treating physician or CSA) as soon as possible after the examinations; a copy of the tracing should be made and both original and copy will be kept in the subject file. The tracings signed by the CSA will be kept in a separate file and will not be made accessible to the principal investigator / treating physician.

All ECG reports (received from central reader) must be signed and dated by the primary investigator / treating physician or CSA within 3 calendar days of receipt and filed with the source documentation. The investigator / treating physician or CSA must indicate on the ECG report whether abnormal values are considered clinically relevant or not. Clinically relevant ECG findings that are present at the time of signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant ECG abnormalities detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10] and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

At all visits, except at Visit 2 (Randomization) and study treatment re-initiation visits (see below), the 12-lead ECGs will be performed under the responsibility of the treating physician who may consult the CSA.

At Visit 2 (Randomization / Day 1) and at study treatment re-initiation visits where post-dose monitoring is required, the pre- and post-dose 12-lead ECG assessments will be performed under the responsibility of the CSA who will interpret the results.

The pre-dose 12-lead ECG interpretation (before Randomization) provided by the CSA will support the subject's final eligibility decision made by the principal investigator / treating physician according to the inclusion/exclusion criteria.

The post-dosing 12-lead ECGs will be performed together with BP assessments hourly until 6 hours post-dose. At this time, subjects may be discharged from the hospital if they meet the discharge criteria [see Appendix 4], otherwise 12-lead ECG and BP will be assessed hourly until discharge criteria are met. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the subject will be permanently discontinued from the study treatment and will be kept in the hospital for observation.

The CSA must ensure that the main study team at site including the principal investigator / treating physician, clinical coordinator / study nurse, and other personnel involved in subjects' clinical care and management do not access first-dose ECG data with unblinding potential, including hourly post-dose 12-lead ECGs and 24-hour Holter ECG data of Day 1 or at re-initiation (e.g., central reading reports, tracings).

7.2.3 ECG Holter

ECG Holter monitoring will be performed for 24 hours at Visit 1 (Screening) and Visit 2 (Randomization). Testing at Visit 1 (Screening) can be performed at any time during the Screening period.

Digital ECG Holter devices will be provided to the sites for the duration of the study. The data records will be sent to the ECG Holter core laboratory for central reading.

At Visit 1 (Screening), the 24-hour ECG Holter will be performed under the responsibility of the principal investigator / treating physician. The performance of the assessment may be delegated to the CSA. The recording must be initiated before 12 pm (noon) and must be obtained for 24 hours.

At Visit 2 (Randomization / Day 1), the 24-hour ECG Holter will be performed under the responsibility of the CSA. The recording must be initiated immediately before first dosing. The subject will be allowed to leave the clinic with the Holter and to perform her/his usual daily activities. The recording will be stopped 24 hours post-dose. It is essential to have uninterrupted recording during the 24 hours (including sleep hours).

The central reading results (including alert notifications in case of specific findings) of the ECG Holter performed at Visit 1 (Screening) will be sent to the principal investigator / treating physician and to the CSA. The central reading results (including alert notifications in case of specific findings) of the Holter performed at Visit 2 (Randomization) will be sent only to the CSA.

The ECG Holter reports must be signed and dated by the primary investigator / treating physician (Visit 1) or the CSA (Visit 2) within 3 calendar days of receipt and filed with the source documentation. The ECG Holter reports signed by the CSA will be kept in a separate file. The physician signing the ECG Holter report must indicate on the report whether abnormal values are considered clinically relevant or not. Clinically relevant ECG Holter findings that are present at the time of signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant ECG Holter abnormalities detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10] and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

7.2.4 Blood pressure

BP measurements include SBP and DBP. BP will be assessed at all scheduled visits.

BP assessment will be performed using the same type of device throughout the study on the same arm with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement. At each pre-dose assessment, SBP and DBP will be measured twice. The two obtained measurements (i.e., two SBP measurements and two DBP measurements) and the position and arm used are to be recorded in the eCRF. The means of the two obtained measurements will be calculated by the eCRF. Any clinically relevant BP abnormalities detected after informed consent signature must be reported as an AE or SAE as appropriate [see Section 10].

At all visits, except at Visit 2 (Randomization) and study treatment re-initiation visits (see below), the SBP/DBP assessments will be performed under the responsibility of the treating physician, who may consult the CSA.

At Visit 1 (Screening), SBP and DBP will be measured sequentially once in supine and once in standing position to determine the presence of orthostatic hypotension (i.e., > 20 mmHg decrease in SBP or > 10 mmHg decrease in DBP from supine to standing position, measured between 1 and 3 minutes after standing; see exclusion criteria 13.)

At Visit 2 (Randomization / Day 1) and visits for re-initiation of study treatment when post-dose monitoring will be required, the SBP/DBP assessments will be performed under the responsibility of the CSA who will interpret the results.

The pre- and post-dose SBP/DBP assessments will be performed in parallel to 12-lead ECGs until subject discharge.

The hourly post-dose assessments will only be measured once at each hourly timepoint. Single SBP measurements will be used for determining discharge criteria.

7.2.5 Echocardiography

Echocardiography will be performed at Visit 1 (Screening) and Visit 6 (EOT) using the equipment present at the clinical site.

Standard 2D/Doppler echocardiography should assess regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction. The echocardiography equipment needs to be maintained and calibrated according to the manufacturer's recommendations. A copy of the calibration certificates done before the day of assessment must be stored as source documents at the site.

The physician conducting and interpreting standard 2D/Doppler echocardiography must have a level of experience equivalent to at least a Level 2 training, as defined in the American College of Cardiology Board / American Heart Association clinical competence statement on echocardiography [Quiñones 2003]. In case an expert sonographer is conducting the examination, the physician must review and interpret the echocardiography results.

In the eCRF, the date of the echocardiography performance will be recorded. Echocardiography results will be documented in the patient charts but will not be reported in the eCRF. The presence/absence (i.e., Yes/No) of any abnormality will be entered in the eCRF. Clinically relevant echocardiography findings that are present at the time of signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant echocardiography abnormalities detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10] and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

7.2.6 Spirometry

Spirometry will be performed at all scheduled visits except Visit 2 (Randomization). Spirometry at Visit 1 (Screening) will consist of two assessments performed at least 5 days apart during the Screening period. Spirometry at Visit 3 (Week 2) can be performed up to 3 days prior to or after the visit date. Spirometry from Visit 4 (Week 4) to Visit 7 (EOS) can be performed up to 5 days prior to or after the visit date. All spirometry assessments should preferably be performed in the morning at approximately the same time to avoid diurnal variation, and prior to study drug intake.

Spirometry testing will assess FVC and FEV_1.

A central reader will provide equipment and a PFT manual with detailed instructions for the procedures, calibration and validation of spirometers. All recorded spirometry values will be transmitted to the centralized provider, and will be reviewed by independent central readers. Quality of the assessments will be evaluated for compliance with ATS/ERS criteria [Miller 2005a, Miller 2005b], and queries may be sent to the sites for clarification. If quality issues are identified, additional training will be provided. The selection of the highest (largest) FEV_1 and FVC values to be used for the main endpoint derivations will be validated by the independent central readers prior to being electronically transferred to the sponsor. No data will be reported in the eCRF.

PFT values that trigger study drug discontinuation will be flagged and sent to the sites and the sponsor. Any clinically relevant PFT abnormality detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10] and

must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

The predicted normal values for FEV_1 and FVC used to determine the exclusion and discontinuation criteria [see Section 5.1.10.3] will be those as defined by the European Community for Coal and Steel including ethnic group adjustments [Quanjer 1993].

7.2.7 Ophthalmological examination

An ophthalmological examination will be performed by an ophthalmologist at any time during the Screening period. Examination at Visit 3 can be performed up to 3 days prior to or after the visit date. Examinations from Visit 4 (Week 4) to Visit 7 (EOS) can be performed up to 5 days prior to or after the visit date.

The ophthalmological examination should include previous eye history and ophthalmic condition, any new or current ophthalmological symptoms, assessment of best corrected visual acuity (Early Treatment Diabetic Retinopathy Study charts), measurement of Goldmann applanation tonometry (recommended, if not available other applanation tonometer allowed), slitlamp examination of the anterior segment, and dilated indirect funduscopy. While the visual acuity and measurement of applanation tonometry exams may be performed by a delegate (e.g., experienced technician, optometrician), the review and interpretation must be performed by the ophthalmologist. Conduct, review, and interpretation of all other ophthalmological exams must be performed by the ophthalmologist.

The purpose of the assessment prior to randomization is to exclude subjects with macular edema or active uveitis from the study and to document a baseline assessment. Assessments at each visit will ensure that any new ophthalmological abnormality is detected and treated at an early stage.

In the eCRF, the date of the ophthalmological examination will be recorded. The results will be documented in the patient charts but will not be reported in the eCRF. The presence/absence of any abnormality (i.e., Yes/No) will be recorded in the eCRF. Clinically relevant findings that are present at the time of signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant ophthalmological abnormalities (including OCT findings [see Section 7.2.8]) detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10] and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

7.2.8 Optical coherence tomography

OCT will be assessed at Visit 1 (Screening) and Visit 6 (EOT). Testing at Visit 1 can be performed at any time during the Screening period. At Visit 6 (EOT), testing may be

performed up to 7 days prior to the visit date but no later than 7 days after the discontinuation of study drug. In addition, unscheduled OCT examination will have to be assessed in the event of visual symptoms or findings suggestive of macular edema according to the ophthalmologist's decision or in case of active uveitis diagnosed during the study. While the OCT exam may be performed by a delegate (e.g., experienced technician, optometrician), the review and interpretation must be performed by the ophthalmologist.

The purpose of the assessment prior to randomization is to exclude subjects with macular edema or active uveitis from the study, and to document a baseline assessment. The site will use the OCT device available locally and must ensure it is working properly. A copy of the calibration certificates done before the day of assessment must be stored as source documents at the site. To the extent that is logistically feasible, the same OCT machine is to be used for each individual subject throughout the study.

In the eCRF, the date of the OCT assessment will be recorded. The results will be documented in the patient charts but will not be reported in the eCRF. The presence/absence of any abnormality (i.e., Yes/No) will be recorded in the eCRF. Any clinically relevant abnormalities detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 10].

The OSB will receive all information related to suspected cases of macular edema and will perform a central, blinded review of OCT images and subject's data of suspected cases of macular edema.

7.2.9 Chest X-ray

A CXR will be performed at Visit 1 (Screening) and assessed by the local radiologist in order to exclude any subject with findings suggestive of active or latent TB. Any CXR that had been performed within 3 months prior to Screening can be used; if available, there is no need to repeat CXR at Screening. The report of the CXR must be recorded in the patient file.

7.2.10 Test for tuberculosis

An interferon gamma release assay (QuantiFERON-TB-Gold®) will be performed at Visit 1 (Screening) to screen for active or latent TB. The test will be analyzed and interpreted at the central laboratory and electronically transferred to the eCRF database.

Only subjects with a negative test at Screening and without CXR findings [see Section 7.2.9] at Screening or within the previous 3 months suggestive of active or latent TB can be included in the study. If the test result is positive, subjects must not be included in the study, except if there is documentation that the subject has completed adequate and successful treatment for TB previously. If the test result is inconclusive

(invalid, indeterminate, or borderline), the test may be repeated one time and a negative result must be obtained prior to randomization in order to include the subject. If the result of the repeated test is inconclusive, subjects must not be included in the study.

Details on the performance of the test for TB will be provided in the specific central laboratory manual.

7.2.11 Weight and height

Height will be measured at Visit 1 (Screening). Body weight (in underwear) will be measured at Visit 1 (Screening) and at Visit 6 (EOT).

7.2.12 Physical examination

Complete physical examination (i.e., inspection, percussion, palpation and auscultation) will be performed at Visit 1 (Screening) and Visit 6 (EOT). A symptom-driven, abbreviated physical examination will be performed at all other visits in order to capture assessments needed for the SLEDAI-2K scoring (note: SLEDAI-2K not assessed Visit 3).

The observations should be reported according to body system in the eCRF as either normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page, describing the signs related to the abnormality (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency). Clinically relevant findings that are present at study start (i.e., before signing of informed consent) must be recorded on the Medical History or SLE-relevant disease history eCRF page. Physical examination findings made after study start that meet the definition of an AE/SAE [see Sections 10.1.1 and 10.1.2] must be recorded by the principal investigator / treating physician on an AE page of the eCRF and must be reported to Actelion Global Drug Safety department (SAEs only).

7.3 Pharmacodynamic and pharmacokinetic assessments

7.3.1 Pharmacodynamic assessments

The PD marker is total lymphocyte counts, which will be measured as part of the hematology tests [see Section 7.2.1.2].

7.3.2 Pharmacokinetic assessments

PK samples will be collected pre-dose (except EOT and EOS) at all visits from Visit 3 (Week 2) to Visit 7 (EOS).

The date and the time of blood sample collection will be entered in the eCRF. The date and time of the last study treatment dosing before blood draw will be entered in the eCRF.

The site staff will ship the plasma samples to the central laboratory. The central laboratory will ship the samples to the CRO in charge of the PK analysis (see page 3 for contact details).

7.4 Disease activity assessments

7.4.1 Systemic Lupus Erythematosus Activity Index-2000

The SLEDAI-2K will be assessed by the treating physician at all visits except Visit 3 (Week 2) [see Appendix 6].

The original SLEDAI is a validated tool for global measure of disease activity introduced in 1985 [Bombardier 1992]. The SLEDAI-2K is an updated version of the original SLEDAI. It has been validated as a measure of global disease activity and is suitable for use in clinical trials [Gladman 2002].

The treating physician will perform physical examinations as required [see Section 7.2.12], question the subject on her/his current state and about any potential SLE symptoms and/or manifestation that may have occurred during the past 10 days, and collect all laboratory parameters relevant to the scoring (e.g., protein-to-creatinine ratio, anti-dsDNA titer, dipstick urinalysis). If the dipstick results are positive, urine sample will be further analyzed as clinically indicated (i.e., microscopic analysis of WBC, RBC, casts, and protein quantification).

All relevant data will be entered in the SLEDAI-2K form of the eCRF [see Appendix 6]. In case of musculoskeletal symptoms, the number of affected joints will be assessed.

Important note:

Reduction in WBC count (lymphocytes) is the main PD effect of $S1P_1$ modulators including ACT-334441. Therefore, leukopenia is not assessable in the present study and will be excluded from the SLEDAI-2K scoring.

7.4.2 Physician's Global Assessment of disease

The PGA will be assessed by the treating physician at all visits except Visit 3 (Week 2).

The PGA is a visual 100 mm analog scale for assessment of disease activity by the physician ranging from 0 to 3 [see Appendix 9]. The scale is anchored at 0="None", 1="mild", 2="moderate", 3="severe" [Petri 2005].

Paper sheets will be provided to clinical sites. The treating physician will rate the overall state of the subject and make a vertical mark on the scale. Only original sheets should be used (i.e., no photocopies). A metric ruler will be used to measure the length between 0 and the vertical mark. The length will be entered into the eCRF.

7.5 Quality of Life assessments: 36-Item Short Form Health Survey v2

The SF-36v2™ questionnaire (SF-36v2™ Health Survey© 1996, 2000 by Medical Outcomes Trust and Quality Metric Incorporated) [see Appendix 10] is used to assess the subject's quality of life. The SF-36v2™ will be completed by the subject at Visit 2 (Randomization) and Visit 6 (EOT). Preferably, the SF-36v2™ questionnaire will be completed by the subject in the morning prior to any other protocol assessment and prior to any other discussion with the investigator or treating physician.

In the SF-36v2™ questionnaire, subjects are instructed to rate their health and capacity to perform daily living activities in eight domains including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health during the last 4 weeks. Raw domain scores are determined and transformed to a 0–100 scale as described in the SF-36v2™ manual, and individual domain scores are used to determine the physical and mental component summary scores as described in the SF-36v2™ manual [Maruish 2011].

The standard SF-36v2™ considering the past 4-week period will be used. A sample of the SF-36v2™ (in English) is provided in Appendix 10. The subject will complete the questionnaire in local language on a validated paper form that will be collected and transcribed in the eCRF.

Actelion has been granted a license agreement for the use of the SF-36v2™ questionnaire.

7.6 Biomarker assessments

Serum and ethylenediaminetetraacetic acid (EDTA) plasma samples will be drawn at indicated visits and will be tested by the central laboratory (except lymphocyte subsets, which will be analyzed by the sponsor). Sample collection date will be recorded in the eCRF.

Details of the collection, labeling and shipment of the samples can be found in the laboratory manual provided to the investigator. The tubes and labels for the samples will be provided to the investigator and/or staff by the sponsor or the central laboratory.

ANA, anti-dsDNA, complement factors and exploratory biomarkers

ANA and anti-dsDNA are a hallmark of SLE, and titers of these autoantibodies have been found to correlate with clinical disease activity and the response to therapy [Ravirajan 2001]. Low C3 and C4 complement have also been found to correlate with clinical disease activity [Swaak 1986]. Immunoglobulins may be elevated in SLE patients, and cytokines and other soluble factors have been found to be elevated in serum of SLE patients.

The following biomarkers as indicated below (but not limited to) will be measured at baseline and during the course of study treatment in order to support the SLE diagnosis of involved subjects, to explore their predictive value for treatment response and to explore changes in response to ACT-334441 treatment.

- ANA, anti-dsDNA, complement C3 and C4 (all visits except Visit 3)
- IgM, IgG, IgA, CRP, fibrinogen, and BLyS (Visit 2 and Visits 4 to 7)
- anti-Smith, anti-cardiolipin (IgA, IgG, IgM) , anti-ribosomal P, (Visit 2 only).
- CXCL10 (EDTA-plasma; Visit 2 and Visits 4 to 7)

At Visit 1 (Screening), ANA and/or anti-dsDNA antibody testing should be positive in order to fulfill inclusion criterion 6 [see Section 4.3] unless a documented historical positive testing is available to confirm the subject's eligibility [see Section 4.6.2].

Aliquots of the EDTA plasma samples will be transferred to the sponsor for exploratory analysis of new soluble biomarkers potentially related to SLE and/or $S1P_1$ modulation. Frozen samples will be kept for a maximum duration of 15 years and will be destroyed thereafter.

Blood lymphocyte subsets

$S1P_1$ modulators such as ACT-334441 reduce total lymphocyte counts (T and B lymphocytes) in healthy subjects. T and B cells consist of different subsets with potential distinct functions in SLE disease manifestation and progression. Specific subsets of B and T cells such as recently activated short-lived plasma cells are increased in the circulation of SLE patients [Grammer 2003a; Grammer 2003b; Klinman 1991]. Analysis of specific blood lymphocyte subsets may provide a better understanding of the immunomodulatory effect of ACT-334441 in SLE patients.

Blood samples for lymphocyte subset analysis will be taken at Visit 2 (Randomization) , Visit 6 (EOT) and Visist 7 (EOS).

The site staff will ship the blood samples to the central laboratory. The central laboratory will then ship the samples to the sponsor for analysis. B and T cell subsets will be analyzed using a combination of cell surface markers (e.g., CD3, CD4, CD 19, CD 20).

7.7 Total blood volume

The expected total blood volume to be drawn per subject during the entire course of the study is described in Table 3.

Table 3 Expected total blood volume to be drawn per patient

Test	Number of tests	Volume per test	Total volume per scheduled study visits
Viral serology at screening (including test confirmation)	1	9 mL	9 mL
Interferon gamma release assay for tuberculosis at screening	1	3 x 1 mL	3 mL
Serum sample at randomization[1]	1	5 mL	5 mL
Hematology (including coagulation)	7	6 mL	42 mL
Blood chemistry[2]	7	7.5 mL	52.5 mL
ACT-334441 PK	5	3 mL	15 mL
Complement C3/C4, ANA, anti-ds DNA	6	7.5 mL	45 mL
Exploratory biomarkers (serum)	5	5.5 mL	27.5 mL
Exploratory biomarkers (plasma)	5	5 mL	25 mL
Lymphocyte subsets	3	5 mL	15 mL
Total blood volume drawn at scheduled study visits: 239 mL[3]			

1. To be stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections.
2. Includes serum pregnancy.
3. Total blood volume may vary depending on re-test and unscheduled samples
ANA = anti-nuclear antibodies; anti-ds DNA = anti-double-stranded DNA; PK = pharmacokinetic.

8 SCHEDULE OF VISITS

To ensure compliance, at each visit, the study personnel must remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

A tabulated summary of all visits and assessments described in the following sections is provided in Table 1. The schedule of visit dates should be established at the time of Screening. It is recommended that subjects adhere to the established visit schedule.

The timepoint for every visit is defined taking as a reference Day 1 (Visit 2), which is the day of randomization.

When scheduling the different assessments for a subject visit, the following should be taken into account:

- The subject must come to the clinic in a fasted condition for all visits, and, when applicable, before administration of study drug.
- The intervals between all visits following Visit 4 (Week 4) and up to EOT (Week 12) visit should not exceed 36 days.
- At Visit 2 (Randomization; Day 1) and on the days of re-initiation of study drug (if applicable), the assessments during the visits will be divided into two parts: before (pre-dose) and after (post-dose) the administration of the study drug, which will be taken at the site.

- At other visits, ECGs, SBP/DBP, spirometry, blood drawings for hematology and biochemistry, along with all other assessments, are to be performed at pre-dose.
- All PK sampling should be done at pre-dose (except EOT and EOS).
- Resting time:
    - When the subject is to go to another department within the hospital for a specific test, sufficient time should be allowed for the subject to rest prior to the examination.
    - Sufficient time between blood drawing and cardiac assessments (i.e., ECGs and/or BP measurement) is to be allowed.

Re-screening

It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication, etc.), provided that documented authorization has been received from Actelion. Subjects who were not eligible due to a negative test for varicella zoster antibodies may also be re-screened once after having been vaccinated. All pre-randomization assessments should then be repeated at the time of re-screening (with the exception of CXR evaluation).

A subject who failed the screening for Part A may be re-screened for Part A or screened for Part B.

8.1 Screening period

The Screening period must take place within 30 days prior to Randomization and include the Visit 1 (Screening) and the pre-dose assessments of Visit 2 (Day 1).

The start of the Screening period is defined as the day of the first Screening assessment (i.e., signature of informed consent).

8.1.1 Visit 1 (Screening)

Visit 1 will be performed up to 30 days prior to Randomization. Visit 1 date is defined as the date of the first assessment performed for the study (i.e., informed consent signature).

During this visit, subject informed consent will be obtained, and the assessments required for subject eligibility will be performed. These assessments may generally be performed on separate days within the Screening period.

Visit 1 includes:

- After discussing the study with the investigator and after agreeing to participate, the subject must sign the ICF. It is the responsibility of the investigator to obtain written

informed consent prior to any screening assessment. Subjects will be assigned a subject number by the IRT provider, for identification throughout the study. In case of re-screening, the subject number assigned during the first screening procedure will be retained.

- Recording of demographics, medical history, smoking status, and disease history (including documented history of ANA, anti-dsDNA antibodies)
- Review of SLE diagnosis and ACR criteria
- Recording of previous SLE therapies, concomitant medications and background SLE therapies
- Complete physical examination
- Body weight, and height
- SLEDAI-2K and PGA
- CXR (any CXR performed within 90 days prior to Screening can be used). In case of re-screening, CXR does not need to be repeated.
- SBP/DBP (including supine and standing position to assess orthostatic hypotension; see excluion criterion 13)
- 12-lead ECG
- 24-hour ECG-Holter (starting before 12:00)
- Echocardiography (under the responsibility of the echocardiography specialist)
- Spirometry (under the responsibility of the pulmonary function laboratory technician or expert)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)
- Hematology (including coagulation tests), blood chemistry, and serum pregnancy test for WOCBP
- Viral serology
- TB test
- ANA, anti-dsDNA antibodies, complement C3 and C4
- Urine protein-to-creatinine ratio
- Urinalysis (dipstick)
- Recording of AEs/SAEs: all AEs/SAEs occurring after signing of the ICF are to be reported in the eCRF and on an SAE form, if applicable.

The principal investigator / treating physician must check inclusion/exclusion criteria. The next visit (Visit 2) will only be scheduled if the subject meets all the eligibility criteria. Date of screen failure will be collected in the IRT system and in the eCRF; additionally, the reasons for screen failure are documented in the eCRF (screening information is collected for all screen failure subjects).

8.2 Treatment period

The treatment period consists of Visits 2 to 6 (Randomization – Day 1, Weeks 2, 4, 8, and 12 (EOT).

8.2.1 Visit 2 – Randomization Day 1

Visit 2 corresponds to the start of the treatment period (Day 1 of the study). The ECGs (pre- and post-dose), BP (pre- and post-dose), and first-dose administration must be performed on the same day and define the date of the visit. This date should preferably correspond to the date of randomization in the IRT system. The assessments during this visit will be *divided* into two parts: before (pre-dose) and after study drug administration (post-dose).

Important note: For WOCBP, the serum pregnancy test at Visit 1 (Screening) must be performed at least 3 weeks before the urine pregnancy test performed at Visit 2 prior to Randomization.

8.2.1.1 Visit 2 – Day 1 – pre-dose assessment

The principal investigator / treating physician must check all inclusion/exclusion criteria. Pre-dose assessments include:

- SF-36v2™ questionnaire (to be completed prior to any other assessment)
- Recording of change in concomitant medications and background SLE therapies since Visit 1
- Recording of methods of contraception (for WOCBP)
- Abbreviated physical examination
- SLEDAI-2K and PGA
- Pre-dose SBP/DBP (under the responsibility of the CSA)
- Pre-dose 12-lead ECG (under the responsibility of the CSA)
- 24-hour ECG-Holter starting immediately before first dosing (under the responsibility of the CSA)
- Hematology (including coagulation tests), blood chemistry
- Urine pregnancy test (for WOCBP)
- Additional serum sample for viral serology
- ANA, anti-dsDNA antibodies, complement C3 and C4
- Exploratory biomarkers
- Lymphocyte subsets
- Urine protein-to-creatinine ratio
- Urinalysis (dipstick)
- Recording of AEs/SAEs: all AEs/SAEs occurring after signing of the ICF are to be reported in the eCRF and on an SAE form, if applicable.

8.2.1.2 Visit 2 – Day 1 – Randomization and post-dose assessment

After confirmation of eligibility (i.e., verification of all entry criteria) by the investigator, randomization should occur via IRT to obtain randomization and study treatment kit numbers. Study treatment should then be dispensed and the subject should take the first dose of study treatment.

Visit 2 post-dose assessments include:

- Hourly 12-lead ECG and SBP/DBP assessments for 6 hours or until the patient meets the discharge criteria (under the responsibility of the CSA [see Appendix 4]). If discharge criteria are not met after 12 hours, the subject should be permanently discontinued.
- Recording of AEs and SAEs.

The subject will be instructed to contact the site if she/he has any questions or problems. WOCBP will be reminded to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

An appointment for next visit will be scheduled and the subject will be instructed to:

  - bring back the remaining study medication for drug accountability
  - come fasted to the site
  - not take study treatment on the day of study visit prior to coming to the site
  - contact the principal investigator / treating physician immediately in the event of the appearance of any symptoms (e.g., suggestive of an SLE flare) or any AEs or SAEs or if a study treatment dose is missed.

8.2.2 Visit 3 – Week 2

The time window for this visit is ± 3 days. The date of the visit will be registered by the investigator or study staff in the eCRF only (no IRT visit registration as no study drug dispensing at Visit 3). All assessments may be performed up to 3 days prior to or after this visit date. The visit includes:

- Recording of change in concomitant medications and background SLE therapies since Visit 2
- Recording of methods of contraception (for WOCBP)
- Abbreviated physical examination
- SBP/DBP
- 12-lead ECG
- Spirometry (under the responsibility of the pulmonary function laboratory technician or expert)
- Ophthalmological examination (under the responsibility of the ophthalmologist)

- Hematology (including coagulation tests), blood chemistry
- Urine pregnancy test (for WOCBP)
- Urinalysis
- PK sampling
- Study drug accountability for compliance review
- Recording of AEs and SAEs
- Remind WOCBP to use the methods of contraception defined for this study
- Schedule an appointment for the next visit and instruct the subject to:
    - bring back any remaining study medication for drug accountability
    - come fasted to the site
    - not take study treatment on the day of study visit prior to coming to the site (study drug will be taken at the clinical site)
    - contact the principal investigator / treating physician immediately in the event of the appearance of any symptoms (e.g., suggestive of an SLE flare) or any AEs or SAEs or if a study treatment dose is missed.

8.2.3 Visit 4 – Week 4 and Visit 5 – Week 8

The visit window for these visits is ± 5 days. The date of study treatment dispensing, preferably corresponding to the date of registration of the visit in the IRT system defines the date of the visit. All other assessments may be performed up to 5 days prior to or after this visit date. The visit includes:

- Recording of changes in concomitant medications and background SLE therapies since previous visit
- Recording of methods of contraception (for WOCBP)
- Abbreviated physical examination
- SLEDAI-2K and PGA
- SBP/DBP
- 12-lead ECG
- Spirometry (under the responsibility of the pulmonary function laboratory technician or expert)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology (including coagulation tests) and blood chemistry
- Urine pregnancy test (for WOCBP)
- ANA, anti-dsDNA antibodies, complement C3 and C4
- Exploratory biomarkers
- Urinalysis
- PK sampling
- Study drug dispensing and accountability

- Recording of AEs/SAEs
- Remind WOCBP to use the methods of contraception defined for this study
- Schedule an appointment for the next visit and instruct the subject to:
    - bring back any remaining study medication for drug accountability
    - come fasted to the site
    - not take study treatment on the day of study visit prior to coming to the site (study drug will be taken at the clinical site)
    - contact the principal investigator / treating physician immediately in the event of the appearance of any symptoms (e.g., suggestive of an SLE flare) or any AEs or SAEs or if a study treatment dose is missed.

8.2.4 Visit 6 – EOT

The EOT visit will take place at Week 12 (± 5 days) or earlier in case of premature discontinuation of study treatment. In all cases, the EOT visit must preferably take place 1 day after the last dose of study treatment intake but no later than 7 days after the last dose of study treatment intake. The visit includes:

- SF-36v2™ questionnaire (to be completed prior to any other assessment)
- Recording of changes in concomitant medications and background SLE therapies since Visit 5
- Recording of methods of contraception (for WOCBP)
- Complete physical examination
- Body weight
- SLEDAI-2K and PGA
- SBP/DBP
- 12-lead ECG
- Echocardiography (under the responsibility of the echocardiography specialist)
- Spirometry (under the responsibility of the pulmonary function laboratory technician or expert)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)
- Hematology (including coagulation tests) and blood chemistry
- Urine pregnancy test (for WOCBP)
- ANA, anti-dsDNA antibodies, complement C3 and C4
- Exploratory biomarkers
- Lymphocyte subsets
- Urine protein-to-creatinine ratio
- Urinalysis
- PK sampling

- Study drug accountability
- Recording of AEs/SAEs
- Remind WOCBP to use the methods of contraception defined for this study
- Schedule an appointment for the next visit and instruct the subject to:
    - come fasted to the site
    - contact the principal investigator / treating physician immediately in the event of the appearance of any symptoms (e.g., suggestive of an SLE flare) or any AEs or SAEs or if a study treatment dose is missed.

8.3 Follow-up period

8.3.1 Visit 7 – EOS

The EOS visit will take place 6 weeks (± 5 days) after last study treatment dose. The visit includes:

- Recording of changes in concomitant medications and background SLE therapies since Visit 6
- Recording of methods of contraception (for WOCBP)
- Abbreviated physical examination
- SLEDAI-2K and PGA
- SBP/DBP
- 12-lead ECG
- Spirometry (under the responsibility of the pulmonary function laboratory technician or expert)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology (including coagulation tests) and blood chemistry
- Serum pregnancy test (for WOCBP)
- ANA, anti-dsDNA antibodies, complement C3 and C4
- Exploratory biomarkers
- Lymphocyte subsets
- Urinalysis
- PK sampling
- Recording of AEs/SAEs

A urine pregnancy test will be dispensed to WOCBP.

8.3.2 Visit 8 and Visit 9– follow-up (telephone contact visits)

Eleven weeks ± 5 days and 16 weeks ± 5 days, after the last dose of study drug has been taken, telephone calls will be made and include:

- Recording of SAEs
- Urine pregnancy test for WOCBP (performed at home prior to telephone contacts with test kits dispensed at Visit 7 – EOS)

Note that the data reported at these visits will not be entered in the eCRF. Results of the urine pregnancy tests must be reported in the source data. SAEs will be reported to Global Drug Safety and will be presented separately in the Clinical Study Report.

8.4 Unscheduled visits (U1, U2…)

Unscheduled visits may be performed at any time during the study. These visits include (but are not limited to) those performed due to safety (e.g., occurrence of an AE, laboratory abnormalities), and/or SLE disease exacerbations (e.g., renal flare).

The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF.

During an unscheduled visit, the following assessments must be performed:

- Recording of changes in concomitant medications and background SLE therapies since last visit
- Recording of AEs/SAEs

Additional assessments may be performed at the discretion of the investigator including but not limited to:

- Abbreviated physical examination
- SLEDAI-2K and PGA
- SBP/DBP
- 12-lead ECG
- Hematology (including coagulation tests) and blood chemistry
- Urine pregnancy test (for WOCBP)
- ANA, anti-dsDNA antibodies, complement C3 and C4
- Urine protein-to-creatinine ratio
- Urinalysis

Depending on the reason for the unscheduled visit (e.g., AE), additional assessments will be performed based on the judgment of the investigator, and the results will be recorded in the eCRF. For the additional assessments performed during unscheduled visit which are not part of the standard study assessments, results are not to be reported in the eCRF. However, any clinically relevant abnormalities detected must be reported as an AE or SAE as appropriate in the corresponding Adverse Event form of the eCRF. After an

unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

8.5 Additional visits for re-initiation of study treatment

Subjects may need to be monitored at the study site when re-initiating study drug following a study drug treatment interruption. Re-initiation visits should be conducted for study treatment interruptions which started prior to Day 14 [see Section 5.1.8].

Note that a subject can be re-initiated only once during the study duration

The same post-dosing procedure as described in Section 8.2.1.2 (Visit 2 – Day 1 – Randomization and post-dose assessment) must be followed:

- Hourly 12-lead ECG and SBP/DBP assessments for 6 hours or until the patient meets the discharge criteria (under the responsibility of the CSA [see Appendix 4]). If discharge criteria are not met after 12 hours, the subject should be permanently discontinued.
- Recording of AEs and SAEs (please refer to Sections 7.2.2, 7.2.4 and 10.1.5 for reporting of AEs with onset on Day 1).
- Recording of changes in concomitant medications and background SLE therapies since previous visit.
- Study drug accountability for compliance review.

These visits for post-dose monitoring of the subjects when re-initiating study treatment are additional unscheduled visits. The regular scheduled study visits must be resumed according to the original visit and assessment schedule. If the visit occurs at the same time as a regular visit, all assessments of the regular visit have to be perfomed in addition.

9 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

9.1 Study completion

For an individual subject, study completion is reached when EOT visit and EOS visit have been completed.

Ten weeks after the EOS visit, subjects will be contacted by telephone to collect follow-up information on any SAE and/or pregnancy (follow-up).

EOS on a study level occurs at the time all subjects have completed their EOS visits, as described above.

9.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, they believe that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

If premature withdrawal occurs for any reason, the reason for premature withdrawal from the study, along with who made the decision to withdraw (subject, investigator or Actelion) must be recorded in the eCRF.

If for whatever reason (except death or loss-to-follow-up) a subject was withdrawn from the study, the investigator should make efforts to conduct a last visit/contact to assess the safety and well-being of the subject, collect unused study drug and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the subject's medical records but will not be collected in the eCRF. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study or must refer them for appropriate ongoing care, as described in Section 9.4.

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual fail. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, e-mail address, person to be contacted in case the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number, and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., site staff visit to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, she/he will be considered tob e lost to follow-up.

9.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

Study-specific stopping rules will be applied separately for Part A and Part B:

- Part A: the entire study will be put on hold (all subjects will stop study treatment) if in Part A, 12 or more subjects out of the planned 36 subjects in the combined active dose groups of Part A (0.5, 1, or 2 mg), or 6 or more subjects out of the planned 12 subjects in the 2 mg dose group of Part A, have been discontinued due to meeting any of the individual patient's stopping rules as defined per safety area of interest [Table 4].
- Part B: if 4 or more subjects in the active dose group of Part B (4 mg), have been discontinued due to meeting any of the individual patient's stopping rules as defined per safety area of interest [Table 4], all subjects included in Part B will stop study treatment.

The entire study or Part B will be suspended and a detailed safety signal assessment will be conducted. An un-blinded data assessment reflecting the total study safety experience will be performed by the IDMC in a dose level specific way (as certain AEs are likely to be dose dependent and might occur in higher frequency with higher dose). Recommendations from IDMC and Health Authorities may allow a potential restart of the study or of the Part B.

If the study is prematurely suspended or terminated, Actelion will promptly inform the investigators, the IRBs/IECs and health authorities, as appropriate, and provide the reasons for the suspension or termination. A potential restart of the study will be allowed only in agreement with Health Authorities and IRBs/IECs.

The safety areas of interest have been defined by the clinical experience obtained for this class of compounds and are described in Section 5.1.10. Table 4 provides a summary of these events in these safety areas of interest that will trigger subject's discontinuation or may results in the hold of the clinical study if a certain number of patients were to be discontinued from study treatment, as indicated above.

Table 4 Safety areas of interest

Safety area of interest [See Section 5.1.10]	Specific study stopping criteria being applied to stop subject / study
Cardiovascular	• HR < 40 bpm at two consecutive hourly 12-lead ECG post-dose (Day 1 or re-initiation) • SBP < 90 mmHg at two consecutive hourly BP measurements post-dose (Day 1 or re-initiation) • Subject not meeting criteria for discharge from the hospital (Day 1 or re-initiation) • QTcF > 500 ms at any time as documented by 12-lead ECG • Symptomatic bradycardia or hypotension (e.g., syncope)
Immune system and Infections	• Confirmed total lymphocyte count < 200 cells/µL • Clinically relevant infection (e.g., serious infection, opportunistic infection)
Respiratory system	• FEV1 and/or FVC > 15% decrease from the study baseline values which has been confirmed at repeat testing • Persistent respiratory AEs (e.g., dyspnea)
Liver	• Abnormal LTs or signs and symptoms suggestive of DILI as explained in the study protocol [Section 5.1.10.5]
Ocular	• Macular edema confirmed by Ophthalmology Safety Board

AE = adverse event; BP = blood pressure; DILI = drug-induced liver injury; ECG = electrocardiogram; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = heart rate; LT = liver test; SBP = systolic blood pressure.

If the study is suspended or prematurely terminated for any reason, the investigator in agreement with Actelion must promptly inform all enrolled subjects, and ensure their appropriate treatment and follow-up, as described in Section 9.2 for subjects prematurely withdrawn from the study. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates the study without prior agreement from Actelion, the investigator must promptly inform Actelion and the IRB/IEC, and provide both with a detailed written explanation of the termination or suspension.

If the IRB/IEC suspends or terminates its approval / favorable opinion of a study, the investigator must promptly notify Actelion and provide a detailed written explanation of the termination or suspension.

9.4 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations.

In case of premature discontinuation from the study, WOCBP should be instructed to continue the use of contraception methods for at least 16 weeks after the last dose of study drug.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definitions of adverse events

An AE is any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease that occurs in a subject during the course of the study (i.e., after signing the informed consent), whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 6 weeks after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study, even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Overdose, misuse and abuse of the study treatment should be reported as an AE and, in addition, study treatment errors must be documented in the study drug log of the eCRF.

10.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the eCRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If the intensity of an AE with an onset date between informed consent signature and start of study treatment and which is ongoing at the start of treatment worsens after the start of study treatment, a new AE page must be completed. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not influence daily activities and usually does not require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 10.2]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

10.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study drug caused the AE will be provided by an investigator who is a qualified physician.

10.1.4 Adverse events associated to study design or protocol-mandated procedures

An AE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease.

10.1.5 Reporting of adverse events

All AEs occurring after study start (i.e., signing of informed consent) and up to 6 weeks after study treatment discontinuation must be recorded on specific AE pages of the eCRF.

10.1.6 Follow-up of adverse events

AEs still ongoing more than 6 weeks after study treatment discontinuation must be followed up until they are no longer considered clinically relevant.

10.1.7 Adverse events of special interest

A list of AESIs is provided in Appendix 3.

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

10.2.1.1 Serious adverse events

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs 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 the definitions above.

The following reasons for hospitalization are exempt from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.

- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

10.2.1.2 Serious adverse events associated with the study design or protocol-mandated procedures

An SAE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease or a complication of an invasive procedure that is specifically required by the protocol.

10.2.2 Reporting of serious adverse events

All SAEs occurring after study start (i.e., signing of informed consent) up to 16 weeks after study treatment discontinuation must be reported to the Actelion drug safety department within 24 hours of the investigator's knowledge of the event on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

All SAEs occurring after study start (i.e., signing of informed consent) up to 6 weeks after study treatment discontinuation must also be reported using AE pages in the eCRF.

10.2.3 Follow-up of serious adverse events

SAEs still ongoing at the end of the 16-week follow-up period must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

10.2.4 After the 16-week follow-up period

New SAEs occurring after the 16-week follow-up period must be reported to the Actelion drug safety department within 24 hours of the investigator's knowledge of the event, **only** if considered causally related to previous exposure to the study treatment by the investigator.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be faxed to the Actelion drug safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to health authorities, IRBs/IECs and investigators is the reference safety information section of the IB [ACT-334441 IB].

SLE exacerbations or SLE flares and associated symptoms are anticipated SAEs in this study as commonly seen with the underlying disease and therefore expected to occur in this subject population. These SAEs will be treated as "disease-related" and expected (unless fatal) and will therefore not require systematic unblinding or expedited reporting to health authorities, IRBs/IECs, and investigators. However, these events will be monitored during the study by the sponsor and by the IDMC [see Section 10.4]. These SAEs are treated as waived SAEs for this study.

10.3 Pregnancy

10.3.1 Teratogenicity

In embryo-fetal studies in rats and rabbits, ACT-334441 shows teratogenic potential. Therefore, appropriate precautions must be taken by WOCBP. Women must not become pregnant during the study and up to 16 weeks after study drug discontinuation. The investigator must explain and stress the importance of using methods of contraception [see Section 4.5.2].

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

10.3.2 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during the study including during the 16 weeks following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form up to 16 weeks following study treatment discontinuation, which is faxed to the Actelion drug safety department (see contact details provided on the Actelion Pregnancy form), and on an AE page in the eCRF up to 6 weeks following study treatment discontinuation (EOS).

Male contraception

Based on nonclinical data and human distribution models [see Section 1.3], it is considered very unlikely that a significant dose of ACT-334441 would be delivered to the female by seminal transfer. Furthermore, the potential risk of harm to a human fetus by ACT-334441 is considered to be very low, based on the high safety margins [ACT-334441 IB]. Therefore, there is no specific recommendation for male contraception regarding ACT-334441. *(Note: For allowed concomitant therapies during this trial that require contraception, the respective method of contraception must be applied.)*

10.3.3 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion, and its outcome must be reported to the Actelion drug safety department.

Any AE associated with the pregnancy occurring during the follow-up period after study drug discontinuation must be reported on separate AE pages in the eCRF up to 6 weeks following study treatment discontinuation (EOS). Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 10.2.5.

10.4 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and project-specific labs/examinations as required) is monitored and reviewed on a continuous basis by the Actelion Clinical team (in charge of ensuring subjects' safety as well as data quality) by periodically monitoring clinical studies' activities from protocol conception to database closure. In addition, an IDMC is monitoring safety data [see Section 3.4.1].

11 STATISTICAL METHODS

11.1 General considerations

All statistical analyses will be conducted by Actelion or by designated CROs supervised by Actelion.

The SAP for final analysis will be approved prior to database lock. The SAP for the interim safety review will be finalized prior to unblinding the study by the independent ISAC. The SAPs provide the full details of all analyses, data displays, and algorithms to be used for data derivations.

All data will be listed, and endpoints will be summarized by appropriate descriptive statistics (tables or figures), typically including:

- number of non-missing observations, number of missing observations, mean, standard deviation, median, Q1 (first quartile), Q3 (third quartile), minimum and maximum for continuous endpoints;
- number of non-missing observations, number of missing observations and frequency with percentage per category (percentages based on the number of non-missing observations) for categorical endpoints;
- number of subjects at risk, cumulative number of events, cumulative number of censored observations and Kaplan-Meier estimates of the survival function for time-to-event endpoints.

Baseline is defined as the last assessment prior to initiation of the study treatment.

Absolute changes from baseline are defined as: post-baseline value minus baseline value, i.e., a positive sign indicates an increase as compared to baseline.

A percentage (relative) change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value does not equal 0) multiplied by 100.

11.2 Analysis Sets

11.2.1 Screened Analysis Set

This analysis set includes all subjects who were screened and received a subject number.

11.2.2 PD Analysis Set

The Pharmacodynamics Analysis Set (PDS) includes all subjects who received at least 3 weeks of study treatment and have at least one lymphocyte count measurement between the Week 4 visit and Week 12 visit. Subjects will be analyzed according to the treatment they received.

11.2.3 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects. In order to adhere to the intention-to-treat principle as much as possible:

- Subjects will be evaluated according to the dose they have been randomized to (which may be different to the dose they have received)
- Unless otherwise stated, all available efficacy data up to the EOS date will be included, irrespective of whether a subject has stopped study treatment earlier or has received any SLE treatment other than that to which the subject was randomized to.

11.2.4 Per-Protocol Set

The Per-Protocol Set (PPS) comprises data from all subjects included in the FAS without selected major protocol deviations including but not limited to :

- Subjects not adhering to the treatment regimen for mandatory concomitant medication;
- Subjects with < 80% compliance to study treatment;
- Start of any prohibited systemic SLE therapies during the course of the trial.

A complete list will be provided in the SAP.

11.2.5 Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who received at least one dose of study treatment. Unless otherwise stated, any analysis using the Safety Analysis Set will use all available safety data up to 6 weeks after discontinuation of study treatment. Subjects will be analyzed based on actual dose taken, not the randomized dose.

11.2.6 PK Analysis Set

The PK Analysis Set will include all randomized subjects who received at least one ACT-334441 dose and provided at least one blood sample for PK evaluation. Subjects will be analyzed based on actual dose taken, not the randomized dose.

11.2.7 Other analysis sets

Other analysis datasets are defined in the corresponding SAPs, e.g., Biomarker analysis sets.

11.2.8 Usage of the analysis sets

The primary analysis and supportive analysis of PD endpoints will be carried out on the PDS.

All exploratory efficacy analyses will be performed using the FAS. Sensitivity analyses of PD endpoints will also be performed on the FAS.

Supplementary analysis to test the robustness of the results for selected PD endpoints and for all exploratory efficacy endpoints will be performed based on the PPS.

All safety data will be analyzed using the Safety Analysis Set.

All PK analysis be analyzed using the PK Analysis Set.

11.3 Variables

11.3.1 Main pharmacodynamic variable

The main variable is the change in lymphocyte count from baseline to EOT, defined as:

- Total lymphocyte count at EOT – total lymphocyte count at baseline

Last observation carried forward (LOCF; using data from the Week 4 visit or later) will be used for subjects with a missing EOT assessment.

11.3.2 Other pharmacodynamic variables

Other PD variables comprise:

- Absolute values of total lymphocyte count at each timepoint;
- Change in total lymphocyte count from baseline to each post-baseline assessment (expressed as absolute change from baseline and percent change from baseline).

Absolute change and percentage changes are calculated as defined in Section 11.1.

11.3.3 Safety variables

The treatment-emergent period is defined as the time from first study treatment intake up to 6 weeks (inclusive) after last study treatment intake.

- Treatment-emergent AEs, SAEs, and AESIs [described in Appendix 3];
- AEs leading to premature discontinuation of study tretment;
- Change in 12-lead ECG variables (heart rate, PR, QRS, QT, QTcB and QTcF), from pre-dose to selected post-doses assessments (1 h, 2 h, 3 h, 4 h, 5 h, 6 h) on Day 1 and on day of study drug re-initiation;
- Occurrence of treatment-emergent 12-lead ECG outliers. Full details of all outlier definitions will be provided in the SAP;
- Occurrence of treatment-emergent 12-lead ECG abnormalities at each scheduled assessment timepoint;
- Occurrence of treatment-emergent ECG-Holter abnormalities on Day 1;
- Change in SBP and DBP from baseline up to EOS;
- Change in FEV_1 and FVC, expressed in absolute value (L) and percent value from baseline up to EOS;
- Occurrence of treatment-emergent decrease of FEV_1 or FVC > 15% from baseline values;
- Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline up to EOS;
- Change in protein-to-creatinine ratio from baseline to EOT;
- Treatment-emergent laboratory abnormalities according to CTCAE 2010 v4.03 [CTCAE 2010] and FDA guidelines [FDA 2009] (for ALT/AST/TBL);
- Change in body weight from baseline to EOT.

11.3.4 Pharmacokinetic variables

PK variables comprise

- C_{trough} ACT-334441 plasma concentrations prior to dosing at Weeks 2, 4, 8, and 12 (EOT);
- ACT-334441 plasma concentration at EOS (i.e., 6 weeks after study treatment discontinuation).

11.3.5 Exploratory disease activity variables

Exploratory disease activity variables comprise the following markers, including but not limited to:

- Change from baseline in the SLEDAI-2K (modified to exclude leukopenia) score at each scheduled post-baseline assessment; the SLEDAI-2K score at each visit is calculated as the sum of all individual item score/weight;
- Change from baseline in PGA score at each scheduled post-baseline assessment;
- Change from baseline in SLEDAI-2K mucocutaneous and/or muscoskeletal score at each scheduled post-baseline assessment. The SLEDAI-2K mucocutaneous and/or muscoskeletal score is calculated as the sum of each individual mucocutaneous (mucosal ulcers, rash, alopecia) and/or muscoskeletal (arthritis and myositis) score/weight.

All exploratory disease activity variables are calculated as the score at each visit minus the score at baseline.

11.3.6 Quality of life variables

Exploratory disease activity variables comprise:

- Change from baseline to EOT in SF-36v2™ Health Survey domain and component scores, calculated as the score at EOT minus the score at baseline. Calculation of the domain and component scores will be detailed in the SAP.

11.3.7 Exploratory biomarker variables

Exploratory biomarker variables comprise but not limited to:

- Change in immunoglobulin serum levels (IgG, IgM, IgA) from baseline to each post-baseline assessment;
- Change in ANA and anti-dsDNA antibody titers from baseline to each post-baseline assessment;
- Change in serum complement components C3 and C4, CRP, fibrinogen, BLyS and CXCL10 from baseline to each post-baseline assessment;
- Change in blood lymphocyte subsets from baseline to EOT and EOS (expressed

as absolute change from baseline and percent change from baseline);

Change from baseline is calculated as the measurement reported at each visit minus the measurement reported at baseline.

11.4 Description of statistical analyses

11.4.1 Overall testing strategy

An optimized contrast test according to the Multiple Comparison Procedure and Modelling (MCP-Mod) approach [Bretz 2005] for each considered dose-response model will be performed. The existence of dose-response effects will be tested using the maximum of the model-based contrast tests. Multiplicity adjusted p-values will be calculated using the Dunnett-distribution.

11.4.2 Analysis of the main pharmacodynamic variable(s)

11.4.2.1 Hypotheses and statistical model

The null hypothesis is that there is no dose response in terms of lowering of lymphocyte counts (p, which is a negative value for a lowering of the lymphocyte count) from baseline to EOT, and the alternative hypothesis is the existence of a dose response:

$H_0: p_d \geq p_{Placebo}$ for all doses d = 0.5, 1, 2, 4 mg

vs

$H_1: p_d < p_{Placebo}$ for at least 1 dose d =0.5, 1, 2, 4 mg

If Part B of the trial is not performed, the hypothesis will be

$H_0: p_d \geq p_{Placebo}$ for all doses d = 0.5, 1, 2 mg

vs

$H_1: p_d < p_{Placebo}$ for at least 1 dose d =0.5, 1, 2 mg

To meet the objective of demonstrating existence of a dose response of ACT-334441 on the lymphocyte count reduction from baseline in subjects with SLE, the null hypotheses must be rejected by the test with a one-sided significance level of 5%.

11.4.2.2 Handling of missing data

In the primary analysis, missing lymphocyte count at EOT visit will be imputed utilizing LOCF techniques (using data from the Week 4 visit or later). Patients with missing baseline lymphocyte count and/or no lymphocyte count at or after Visit 4 will be excluded from the primary analysis.

11.4.2.3 Main analysis

The MCP-Mod approach consists of a set of optimized contrast tests for establishing the existence of dose-response effects. The overall strategy is described as follows:

Definition of a set of likely dose-response relations [see Section 11.6 for more details] (the method allows for characteristics of the curve, such as maximum effect, to be defined at doses not studied):

- Maximum effect (E_{max}) with 50% of the maximum effect at dose 0.2 mg
- E_{max} with 50% of the maximum effect at dose 0.4 mg
- E_{max} with 50% of the maximum effect at dose 1.0 mg
- Quadratic with maximum effect at dose 3.0 mg (only if the 4 gm dose is studied)
- Sigmoid-E_{max} with 50% of the maximum effect at dose 0.4 mg and 95% of the maximum effect at dose 2.0 mg.

The existence of dose-response effects will be assessed with the optimized contrast tests. Dose-response effects are established at one-sided level α=5%, if the following condition on the p value holds for at least one contrast i: $p_i := 1 - F_{\Sigma_{Dunnett}}(Z_i) < 0.05$, where $F_{\Sigma_{Dunnett}}$ describes the Dunnett-distribution with correlation matrix $\Sigma_{Dunnett}$.

The model with the minimum p-value will be fitted to the data. As a sensitivity analysis, all remaining significant models will be fitted to the data, and model-based dose estimates will be calculated.

Given established dose-response effects with MCP-Mod, PD effects will be analyzed based on pairwise comparisons of reduction in lymphocyte count from baseline for each active dose levels to placebo using an analysis of covariance (ANCOVA) model, adjusted for baseline lymphocyte counts. Testing will be done with two-sided significance level 5%. The type-1 error will be controlled via a hierarchical ordering of the tests: pairwise comparison will be conducted in decreasing dose order.

The dose-response data will be summarized with point-wise and model-based estimates, standard deviation and 95% confidence-intervals (CI) on the reduction in lymphocytes from baseline at the examined dose levels. A plot of the estimated dose-response curve with 95% credibility interval limits will be presented along with the observed response at each dose.

This analysis will be performed on the PDS.

11.4.2.4 Supportive/sensitivity analyses

A supportive analysis will be performed on the FAS and PPS. The analysis described in Section 11.4.2.3 will also be repeated on observed data with no missing data imputation. Further analysis will be described in the SAP.

11.4.2.5 Subgroup analyses

Any subgroup analysis will be described in the SAP.

11.4.2.6 Other pharmacodynamic variables

Absolute values, absolute change from baseline and percent change from baseline of total lymphocyte counts and blood lymphocyte subsets at each timepoint will be summarized descriptively. An ANCOVA model adjusted for baseline counts will be used to compare each dose to placebo at the EOT visit only.

11.4.3 Analysis of the safety variable(s)

The Safety Analysis Set will be used to perform all safety analyses.

If not otherwise stated, only treatment-emergent safety data (observations with onset or assessment dates at/after first intake of study drug up to 6 weeks after study drug discontinuation) will be considered in tables and figures. All safety data will be included in listings, with flags for safety data not considered to be treatment-emergent.

Specific safety events (AEs, laboratory tests, ECG findings, etc.) will be considered. In general, they consist of one or more well-defined safety events that are similar in nature and for which there is a specific clinical interest in connection with ACT-334441.

For specific AESIs, the number and percentage of subjects with at least one event will be reported. Point estimates and 95% CIs for safety-event incidences and the relative risk ratio relative to placebo will be provided without adjustment for multiplicity.

Exploratory analysis of time to first onset of safety events of interest may be displayed by Kaplan-Meier estimates. Subjects not experiencing the safety event will be censored at the minimum of the EOS date and 6 weeks after last dose of study drug. Where applicable, study treatment doses will be compared with placebo by hazard ratios and corresponding 95% CIs from Cox's regression model.

11.4.3.1 Adverse events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the time of database closure.

11.4.3.1.1 Treatment-emergent AEs and SAEs

Treatment-emergent AEs, SAEs and AEs leading to premature discontinuation of study drug will be tabulated by study dose, System Organ Class (SOC) and preferred terms within each SOC: the number and percentage of subjects who experienced at least one (S)AE, at least one (S)AE within each SOC and at least one S(AE) within each preferred term will be displayed. (S)AEs will also be summarized by decreasing frequency of preferred term. (S)AEs will also be tabulated by maximum intensity and relationship to each ACT-334441 dose or placebo.

11.4.3.1.2 AEs and SAEs for screening failure patients

AEs and SAEs during screening will be listed for patients who are screening failures and do not enter the study treatment period.

11.4.3.1.3 AESIs

The number and percentage of subjects who experienced at least one AESI, at least one AESI within each category and at least one AESI within each preferred term will be summarized by dose. The relative risk of having an AESI in each dose group compared to placebo will be summarized using forest plots.

11.4.3.1.4 Post-treatment AEs and SAEs

Post-treatment (S)AEs occurring over 6 weeks after treatment discontinuation will be summarized in a similar manner as described in Section 11.4.3.1.1.

11.4.3.1.5 Deaths

Fatal SAEs occurring any time after the start of treatment will be summarized in a similar manner as described in Section 11.4.3.1.1.

11.4.3.2 Cardiac safety

11.4.3.2.1 12-lead ECG assessments

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute changes from pre-dose in numeric 12-lead ECG values (HR, PR, QRS, QT, QTcB, QTcF). Data will be summarized from pre-dose to each post-dose assessments on Day 1 and also at the re-initiation of study drug.

Notable abnormalities for selected 12-lead ECG parameters (HR, PR, QT, QTcF) will be summarized for all data on Day 1, Week 12 and also at the re-initiation of study drug.

In addition treatment-emergent morphological ECG abnormalities will be summarized descriptively (using data from the ECG provider).

11.4.3.2.2 Cardiac safety events

Cardiac safety events will include:

- treatment-emergent QTc > 450 ms (male), > 470 ms (female), > 500 ms (male), and > 520 ms (female)
- treatment-emergent QTc increase from baseline > 30 ms, > 60 ms
- other treatment-emergent abnormalities observed by 12-lead ECG
- treatment-emergent (serious) cardiac AESIs.

Cardiac safety events will be summarized descriptively.

11.4.3.2.3 24-hour Holter ECG

Treatment-emergent abnormalities as assessed by 24-hour Holter ECG monitoring will be summarized by dose group and presented similarly to AEs. Hourly mean HRs will be summarized descriptively.

11.4.3.3 Pulmonary safety

11.4.3.3.1 Pulmonary function testing

Descriptive summary statistics by visit and study dose will be provided for observed treatment-emergent values and changes from baseline by visit in FEV_1, FVC and FEV_1/FVC ratio (all expressed in absolute change, % change and % of predicted value).

The number and proportion of treatment-emergent decrease of percent-predicted FEV_1 or FVC > 15 percentage points from baseline at any time up to the last treatment will be summarized by dose.

11.4.3.3.2 Pulmonary safety events

Pulmonary safety events will include:

- treatment-emergent decrease of FEV_1 or FVC to < 85% of baseline values
- (serious) pulmonary AESIs
- withdrawal due to pulmonary reasons / AE

Pulmonary safety events will be summarized descriptively.

11.4.3.4 Vital signs

Descriptive summary statistics by visit and study dose will be provided for observed treatment-emergent values and absolute changes from baseline in HR, BP and body weight.

Treatment-emergent notable BP abnormalities will also be summarized. The definition for notable abnormalities is provided in Appendix 7.

11.4.3.5 Laboratory endpoints

11.4.3.5.1 Laboratory tests

Descriptive summary statistics by visit and study dose will be provided for observed treatment-emergent values and absolute changes from baseline for laboratory tests (hematology, blood chemistry, urinalysis). Data will be displayed in Standard International units whenever possible, and graphical approaches will be applied.

11.4.3.5.2 Laboratory safety events

Laboratory safety events will include:

- treatment-emergent laboratory test abnormalities based on normal ranges of the central laboratory and according to CTCAE 2010 v4.03 [CTCAE 2010]
- treatment-emergent laboratory test abnormalities based on FDA guidance for DILI [FDA 2009] (for ALT/AST/TBL)
- lymphocyte count reversibility after EOT, expressed in absolute change and percent change from baseline

The definitions for marked abnormalities is provided in Appendix 7. Laboratory safety events will be summarized descriptively.

11.4.3.6 Ocular safety

Ocular safety events will include:

- treatment-emergent ocular AESIs

11.4.4 Analysis of the exploratory efficacy variables

The analysis of the exploratory efficacy endpoint change from baseline in SLEDAI-2K score at Week 12 will be performed using an ANCOVA with treatment and baseline score as factors. Missing values at Week 12 will be imputed using LOCF. The mean treatment difference including 95% CI for each ACT-334441 dose compared to placebo will be presented. A sensitivity analysis will be performed using observed data without imputation.

Other changes from baseline variables will be analyzed in a similar manner using an ANCOVA.

All exploratory efficacy endpoints will be analyzed on the FAS and PPS.

No multiplicity adjustments will be made on exploratory efficacy endpoints. Other analyses will be described in the SAP.

11.4.5 Analysis of other variable(s)

11.4.5.1 Pharmacokinetic endpoints

Concentrations will be summarized by descriptive statistics.

11.4.5.2 Exploratory biomarkers

Descriptive statistics of mean, median, CV, standard error of the mean, 95% CI for each time point and variable will be summarized.

Statistical analysis of means (time-point and variable) for each ACT-334441 dose group against placebo will be conducted.

Statistical analysis on the exploratory disease activity endpoint SLEDAI-2K will be performed on the difference between subjects with an exploratory biomarker value ≤ the

25th percentile compared to subjects with a value ≥ the 75th percentile. Depending on the shape of the dose-response curve observed for the main PD endpoint, dose groups may be combined to increase the power to observe differences.

Modeling of exploratory biomarkers together with PK, PD or efficacy variables might be conducted and will be described in the SAP.

The list of statistical analysis on exploratory biomarkers data is not exclusive.

11.4.5.3 Exploratory analyses

Exploratory, data-driven analyses may be performed and will be described in the SAP.

The relationship between ACT-334441 concentrations and any safety or tolerability, disease activity, biomarker, or PD data might be investigated on an exploratory basis. Whenever possible, a model will be established to describe these relationships.

11.5 Interim safety review

Prior to enrolling any subject into study Part B, the ISAC will perform an interim analysis of Part A data, which will be reviewed by the IDMC.

The IDMC will operate according to an IDMC charter jointly agreed between the IDMC members and Actelion.

11.5.1 Objectives

The objective of the interim safety review is to evaluate the safety profile of ACT-334441 in SLE patients and to determine if the study should continue as planned with initiation of Part B or if the study should be amended with protocol changes or if the study should be discontinued to ensure subject safety.

11.5.2 Timing

The interim safety review will be conducted when all subjects enrolled into Part A have completed Visit 4 (Week 4), unless prematurely discontinued.

11.5.3 Unblinded IDMC review

After blinded data review by blinded Actelion staff, an ISAC (a CRO or an Academic Research Organization not otherwise involved with study conduct or statistical analysis) will generate an unblinded interim analysis report exclusively for review by the IDMC.

No interim database lock will occur. Actelion staff will remain blinded to study treatment after the interim safety review is performed.

Based on the interim safety review with cut-off at Visit 4 and an IDMC recommendation, the study will continue as planned with Part B initiation or be amended (protocol changes or study discontinued to ensure subject safety).

11.5.4 Variables

The interim data will include the following variables:

- Demographics and disease characteristics
- Patient disposition
- Background and concomitant medications
- SAEs, AEs (including AESI), and AEs leading to study treatment discontinuation
- 12-lead ECGs and 24-hour ECG Holter data
- Spirometry data
- Hematology data including total lymphocyte counts, neutrophils and platelet counts
- Blood clinical chemistry data including liver function parameters and immunoglobulin levels (IgM, IgG, IgA)
- ACT-334441 plasma concentration data.

Data will be displayed using summary tables, listings, figures and patient profiles.

11.6 Sample size

11.6.1 Sample size justification

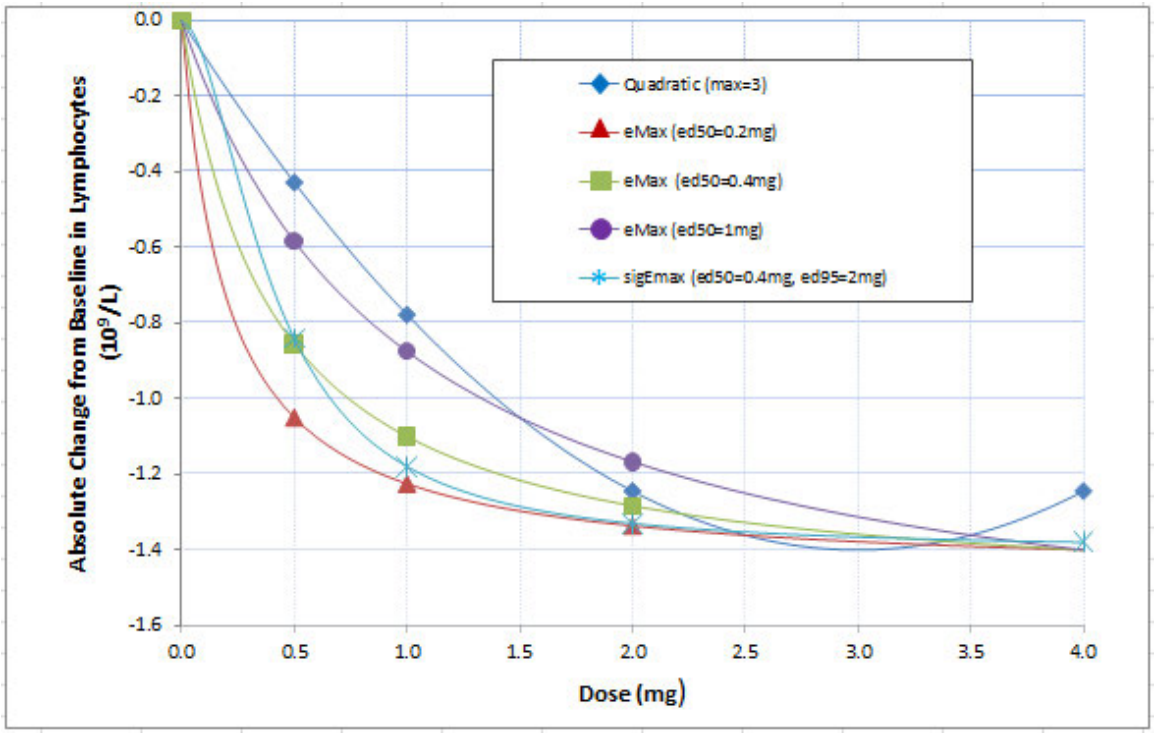
The sample size for the study was determined based on simulations. A sample size of 64 subjects (12 in each ACT-334441 dose group of 0.5 mg, 1 mg, 2 mg, 4 mg and 16 in the placebo group) would provide an average power of at least 90% to show a significant dose-response relationship at a one-sided alpha significance level of 5%, under the assumption of a lymphocyte % reduction compared to baseline of 0% (mean at Week 12 = 2.0×10^9/L) for placebo and a maximum of 70% for any ACT-334441 dose (mean at Week 12 = 0.6×10^9/L). A maximum lymphocyte % reduction compared to baseline of 70% was assumed based on results obtained in Phase 1 with ACT-334441 and with other S1P modulators. The pooled standard deviation is assumed to be 0.45×10^9/L. This takes into account 10% of subjects being excluded from the PDS.

If Part B is not conducted and the 4 mg dose is not tested then there will be an average power of at least 80% to show a significant dose-response relationship with three doses at a one-sided significance level of 5%, using the same assumptions as above (based on a total sample size of 48 subjects [12, 12, 12 and 12 in placebo, 0.5 mg, 1 mg and 2 mg, respectively]).

Assuming a % reduction in lymphocyte counts of between 25% to 70% (and pooled standard deviation = 0.45 × 10^9/L) compared to placebo, any single pairwise dose comparison will have between 77% and 100% power to detect a difference at a 2-sided significance level of 5%.

Assumptions on the placebo response rate, maximum effect sizes and candidate dose-response models are based on the observed lymphocyte counts in study AC-064-101.

Figure 4 Reduction in total lymphocyte count dose-response shapes



12 DATA HANDLING

12.1 Data collection

The investigator/delegate is responsible to ensure the accuracy, completeness, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

eCRF data will be captured via electronic data capture using the Rave system provided by Medidata Solutions, Inc., a web-based tool. The investigator and site staff will be trained

to enter and edit the data via a secure network, with secure access features (username, password and identification – an electronic password system). A complete electronic audit trail will be maintained.

Physician-reported entries recorded in the PGA are considered source data.

Subject Screening and Enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents submitted to Actelion, subjects must be identified only by number, and never by name or initials, hospital numbers or any other identifier. The investigator/delegate must keep a subject identification code list at the site, showing the randomization number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

12.3 Database management and quality control

eCRFs will be used for all subjects. The investigator will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any timepoint during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion on an ongoing basis to look for unexpected patterns in data and study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples, 12-lead ECG, 24-hour Holter ECG, and spirometry will be processed through a central reader, and the results will be sent electronically to Actelion.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate SOP. After database closure, the investigator will receive the eCRF of the subjects of her/his site (including all data changes made) on electronic media or as a paper copy.

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted.

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an IRB or IEC. Approval from the committee must be obtained before starting the study and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol after receipt of the approval must also be submitted as amendments by the investigator to the IRB/IEC in accordance with local procedures and regulations [see Section 13.6].

A list of members participating in the IRB/IEC meetings must be provided, including the names, qualifications and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation. If a study staff member was present during a meeting, it must be clear that this person did not vote.

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

The ICF will be provided in the country local language(s).

Site staff authorized to participate to the consent process and/or to obtain consent from the subject and/or legal representative will be listed on an Actelion Delegation of Authority form. A study physician must always be involved in the consent process.

The subject and/or legal representative must sign, personally date and time (if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated and timed (if the first study-mandated procedure was performed on the same day informed consent was obtained) by the authorized site staff listed on the Actelion Delegation of Authority form.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation.

The informed consent process must be fully documented in the subject's medical records, including study reference, subject number, date/time (if applicable) when the subject was first introduced to the Actelion clinical study, date/time (if applicable) of consent, who participated in the consent discussion, who consented the subject and any additional person present during the consent process (e.g., subject family member), copy of the signed ICF given to the subject / legal representative.

In the case that the site would like to recruit a subject who would be considered as vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure subject rights are respected and the consent obtained is legally valid. Actelion, the regulatory authorities (if applicable) and the IRB/IEC must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IRB/IEC, according to procedures and before subjects are recruited.

13.4 Compensation to subjects and investigators

Actelion provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative in a timely manner. The investigator/delegate must document and explain

any deviation from the approved protocol. IRB/IEC and regulatory authorities must be informed, according to their requirements, but no later than 15 calendar days after the event.

13.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. A protocol amendment must be submitted to the IRB/IEC and regulatory authorities, according to their requirements.

13.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring and available when needed.

These records are to be classified into two different categories of documents: investigator's file and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (e.g., as specified in the clinical study agreement) and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the CRA. The printouts will be considered as the official clinical study records and must be filed either with the subject medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject, regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Actelion's instructions. If it were not possible for the monitor to observe this process, it would not be possible to rely on the site's certified copies, therefore the site cannot be selected for the clinical study. The printouts should be filed either with the subject medical records or with the subject's eCRF.

13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The principal investigator must ensure that all site personnel involved in the study will be present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the initiation visit.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the principal investigator and filed in the investigator site file (ISF).

During the study, the CRA will contact and visit the investigational site regularly and, on request, must be permitted to have access to trial facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered in the eCRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

The principal investigator must ensure that the eCRF is completed after a subject's visit to the site and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in

a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site and when there are no more active subjects and after all study data have been accepted by medical review and all follow-up issues have been resolved. In case a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of Actelion.

13.9 Investigator site file

Each site will be provided with an ISF prior to the initiation visit. It will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of contents listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP as well as instructions from Actelion. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the principal investigator must inform Actelion immediately.

If the principal investigator changes, or if the site relocates, the CRA must be notified as soon as possible.

13.10 Audit

Actelion's Global Quality Management representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to Actelion's requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

The investigator and staff must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

13.11 Inspections

Health authorities and/or IRB/IEC may also wish to conduct an inspection of Actelion's clinical study (during the study or after its completion).

Should an inspection be requested by a health authority and/or IRB/IEC, the investigator must inform Actelion immediately (usually via the CRA) that such a request has been made.

The investigator and staff must cooperate with the inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

13.12 Reporting of study results and publication

Study results will be documented in a Clinical Study Report that will be signed by Actelion representatives and the coordinating investigator (or principal investigator for single-center studies).

The coordinating investigator, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion prior to publication.

Actelion will post results from its clinical studies on Actelion's Clinical Trial Register and on external/national registries, as required by law.

Actelion's Policy on Disclosure of Clinical Research Information can be found at:
http://www.actelion.com/documents/corporate/policies_charters/policy_clinical-research-information.pdf

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria and be based on:

- substantial contributions to: the conception or design of the study, or the acquisition, analysis or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of Actelion and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Actelion for review at least 30 days prior to submission for publication or presentation. Upon review, Actelion may provide comments and may also request alterations and/or

deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

Actelion's policy on scientific publications can be found at:
http://www.actelion.com/documents/corporate/policies-charters/policy-scientific-publications.pdf

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Appendix 1 Prohibited anti-arrhythmic or heart rate lowering medications

The use of the following drugs at any time during the study is prohibited [see Section 5.2.5]:

- Adenosine
- Acetobulol
- Ajmaline
- Amiodarone
- Aprinidine
- Atenolol
- Azimilide
- Bepridil
- Bisiprolol
- Betaxolol
- Bretylium
- Bunaftine
- Cibenzoline
- Diltiazem
- Digoxin
- Disopyramide
- Dofetilide
- Dronedarone
- Encainide
- Esmolol
- Flecainide
- Ibutilide
- Ivabradine
- Lidocaine
- Lorajmine
- Lorcainide
- Metoprolol
- Mexiletine
- Morcizine
- Nadolol
- Phenytoin
- Pilocarpin
- Prajmaline
- Procainamide
- Propafenone
- Propranolol
- Quinidine
- Sotalol
- Sparteine
- Tedisamil
- Timolol
- Tocainide
- Verapamil
- Vernakalant

If, in the judgment of the investigator, it is in the best interests of the subject to receive any of the drugs listed above, study drug must be permanently discontinued.

Appendix 2 List of medications with risk of torsades de pointes

The use of the following QT-prolonging medications with a known risk of torsades de pointes at any time during the study is prohibited [see Section 5.2.5]:

- Arsenic trioxide
- Astemizole
- Anagrelide
- Azithromycin
- Bepridil
- Chlorpromazine
- Cisapride
- Citalopram
- Clarithromycin
- Cocaine
- Domperidone
- Dronedarone
- Droperidol
- Erythromycin
- Escitalopram
- Flecainide
- Halofantrine
- Haloperidol
- Levomethadyl
- Mesoridazine
- Methadone
- Moxifloxacin
- Ondansetron
- Pentamidine
- Pimozide
- Probucol
- Sevoflurane
- Sparfloxacin
- Sulpiride
- Terfenadine
- Thioridazine
- Vandetanib

If, in the judgment of the investigator, it is in the best interests of the subject to receive any of the drugs listed above, study treatment must be permanently discontinued.

Appendix 3 Adverse events of special interest

AESIs will include the anticipated risks of treatment with ACT-334441 or the known class effects or the events that may be related to SLE comorbidities (e.g., cardiovascular AEs) and will address the following safety areas:

- Effect on HR and rhythm related AEs
- Hypotension related AEs
- Hypertension related AEs
- Hepatobiliary disorders / liver enzyme abnormality related AEs
- Pulmonary related AEs
- Eye disorders related AEs
- Infection related AEs
- Skin malignancy related AEs
- Malignancy (non-skin) related AEs
- Cardiovascular related AEs

A list of AESIs (MedDRA preferred terms) will be defined in the SAP.

Appendix 4 Criteria for discharge from hospital on Day 1 and on the first day of re-initiation following treatment interruptions

At the time of discharge (i.e., 6 h post-dose) on Day 1 and on the first day of re-initiation of study treatment following drug interruptions, the following criteria must be met:

- ECG-derived resting HR > 45 bpm; and if HR < 50 bpm it must not be the lowest value post-dose
- SBP > 90 mmHg;
- QTcF < 500 ms;
- No persistent ECG abnormality (e.g., AV block second degree or higher) or ongoing AE requiring continued hospitalization.

Should the subject not meet the criteria for discharge 6 h post-dose, she/he will be monitored until 12 h post-dose with 12-lead ECG and BP measurements performed hourly and may be discharged after any of the hourly measurements, provided that discharge criteria are met until 12 h post-dose. If at 12 h post-dose, the subject does not meet discharge criteria, he/she must be permanently discontinued from study treatment. Subjects who are permanently discontinued should not be discharged from the monitored setting before vital signs return to near baseline values and until there are no persistent ECG abnormalities (e.g., AV block second degree or higher) or ongoing AE requiring continued hospitalization, or until a diagnosis is established.

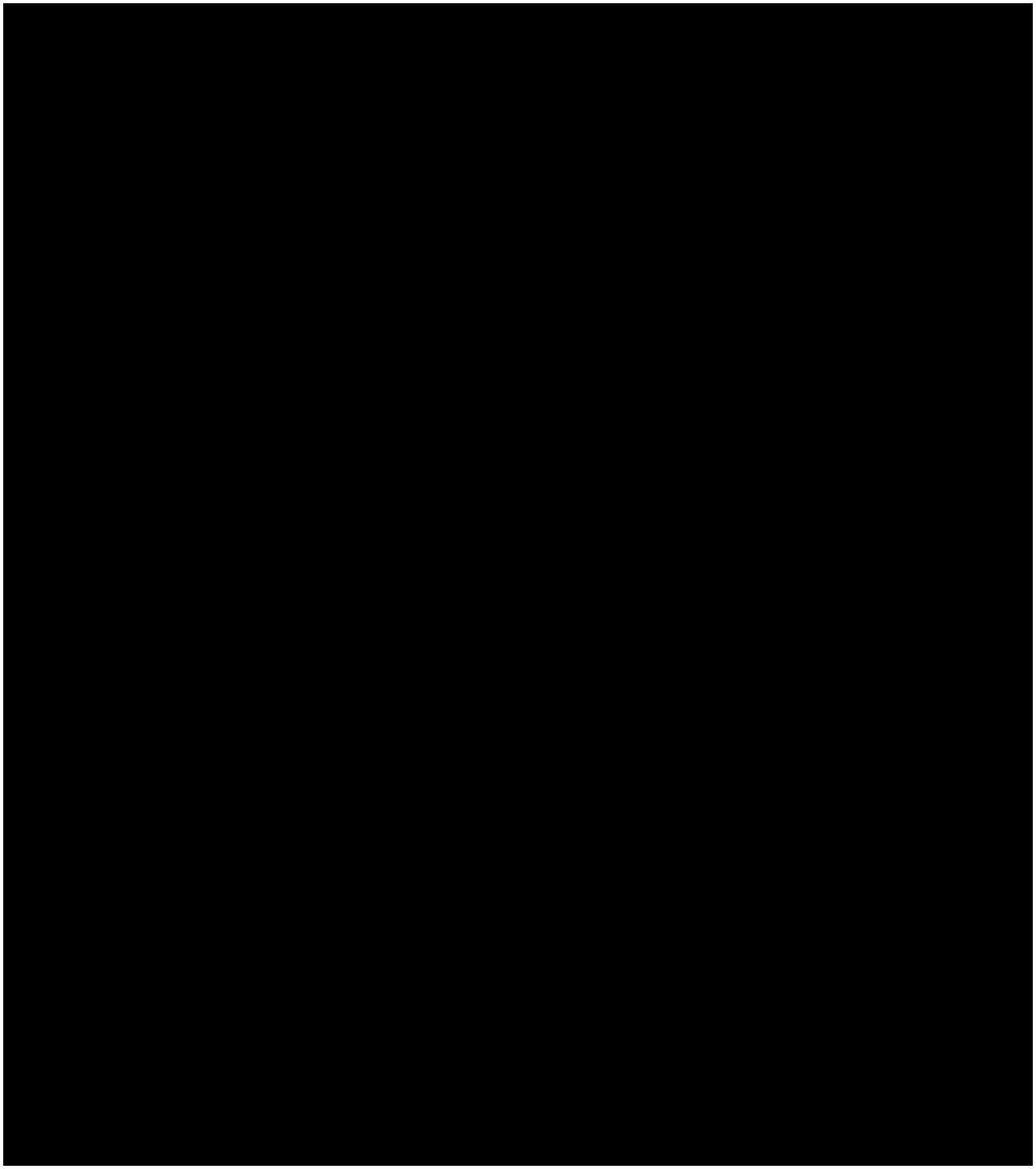
Appendix 5 American College of Cardiology / American Heart Association / American College of Physicians Training Requirements for Performance and Interpretation of Adult Transthoracic Echocardiography

	Cumulative Duration of Training	Minimum Total Number of Examinations Performed	Minimum Number of Examinations Interpreted
Level 1	3 months	75	150
Level 2	6 months	150 (75 additional)	300 (150 aditional)
Level 3	12 months	300 (150 aditional)	750 (450 aditional)

From: Quiñones 2003

Appendix 6 SLEDAI-2K: DATA COLLECTION SHEET

Enter weight in SLEDAI-2K score column if descriptor is present at the time of the visit or in the **preceding 10 days.**



Note that Leukopenia will not be evaluated for reasons of functional blinding [see Section 5.1.4.2] and CH50 will not assessed by central laboratory.

Hematuria, proteinuria and pyuria are evaluated by dipstick at each visit assessing SLEDAI-2K. If the dipstick results are positive, urine sample will be further analyzed as clinically indicated (i.e., microscopic analysis of WBC, RBC, casts, and protein quantification).

Appendix 7 Notable abnormalities for ECG, BP and laboratory variables

Notable abnormalities for ECG and BP

Notable abnormalities for ECG and BP that are related to the potential effects of ACT-334441 will address the following variables:

- Morphological ECG findings (defined as any abnormal finding not present prior to start of treatment)
- HR outliers (bpm), based on ECG
- PR interval (ms)
- QT/QTc interval (ms), based on Bazett's or Fridericia's formula
- BP (mmHg)

The definition of the abnormal values to be reported will be described in the SAP.

Laboratory abnormalities

Laboratory values below or above the normal range will be graded at three levels (H, HH, HHH for values above normal range and L, LL, LLL for values below the normal range) where L stands for "low", H for "high".

The term "marked abnormality" describes laboratory values above or below the thresholds, with grading of abnormalities at two levels: LL/HH and LLL/HHH. These thresholds have been defined by the sponsor in order to flag and/or communicate abnormal laboratory results from the central laboratory to the investigators, and for the purpose of standardized data analysis and reporting by the sponsor. The definitions of marked abnormal values are based mainly on the Common Terminology Criteria for Adverse Events (CTCAE) grading system (2010 v4.03) and, in specific cases (e.g., lymphocyte levels), are adjusted based on the known PD effect of the study drugs (e.g., LLL threshold for lymphocytes) [CTCAE 2010].

The term ALERT here corresponds to protocol-defined test result threshold requiring an action from the investigator as described in the protocol (e.g., repeat the test; interrupt or discontinue the study drug) and should not be confused with the term "call alert" used by the central laboratory for laboratory results, which will be communicated to the investigator. Not all ALERTS listed in this table will be "call alerts" from the central laboratory and vice versa.

PLEASE NOTE: Thresholds for abnormality of level L or H are not provided in this appendix but will be provided in the laboratory manual. Parameters for which no threshold is defined in Table 5 below may be defined in the central laboratory manual.

Table 5 Thresholds for marked laboratory abnormalities for ACT-334441

Parameter	LL	LLL	HH	HHH
Hemoglobin	< 100 g/L (< 10g/dL; < 6.2 mmol/L)	< 80 g/L (<8g/dL; < 4.9 mmol/L)	Increase in > 20 g/L above ULN or above baseline (if baseline is above ULN)	Increase in > 40 g/L above ULN or above baseline (if baseline is above ULN)
MCH	ND	ND	ND	ND
MCV	ND	ND	ND	ND
MCHC	ND	ND	ND	ND
Hematocrit	< 28% (female) < 32% (male)	< 20%	> 60% (male) > 55% (female)	> 65%
Platelet count	< 75 × 10 e9/L (< 75,000/mm3)	< 50.0 × 10 e9/L (<50,000/mm3)	> 600 × 10 e9/L	> 999 × 10 e9/L
RBC count	ND	ND	ND	ND
WBC count	ND	< 1.9 × 10e9/L	> 20.0 × 10e9/L (>20 000/mm3)	CTCAE (grade 3) > 100.0 × 10e9/L (>100 000/mm3)
Lymphocyte	ND	< 0.2 × 10e9/L (< 200/mm3) **ALERT*** **< 0.2 × 10e9/L (< 200/mm3)**	> 4.0 × 10e9/L (> 4000/mm3)	≥ 8 × 10e9/L (> 8000/mm3)
Neutrophils	< 1.5 × 10e9/L (< 1,500/mm3)	< 1.0 × 10e9/L (< 1000/mm3)	ND	ND
Eosinophils	ND	ND	> 5.0 × 10 e9/L or > 5% (> 5000 cells/mm3)	ND
Monocytes	ND	ND	ND	ND
Basophils	ND	ND	ND	ND
Polymorphonuclear leucocyte/Band cells	ND	ND	> 90%	> 95%
AST	ND	ND	≥ 3 ULN (U/L) **ALERT** **≥ 3 ULN**	≥ 5 ULN (U/L) **ALERT** **≥ 5 ULN** **≥ 8 ULN**
ALT	ND	ND	≥ 3 ULN (U/L) **ALERT** **≥ 3 ULN**	≥ 5 ULN (U/L) **ALERT** **≥ 5 ULN** **≥ 8 ULN**
Total bilirubin	ND	ND	≥ 2 ULN (umol/L) **ALERT** **≥ 2 ULN combined with ALT or AST ≥ 3 ULN**	≥ 5 ULN (umol/L)
Alkaline Phosphatase	ND	ND	> 2.5 ULN (U/L)	> 5 ULN (U/L)

INR	ND	ND	≥ 1.5 ULN** or ≥ 1.5 times above baseline if on anticoagulation **ALERT** **≥ 1.5 combined with ALT or AST ≥ 3 ULN**	≥ 2.5 ULN** or ≥ 2.5 times above baseline if on anticoagulation
Activated partial thromboplastin time prolonged (aPTT)	ND	ND	> 1.5 - 2.5 × ULN	> 2.5 × ULN
Lactate dehydrogenase	ND	ND	ND	ND
Creatinine	ND	ND	> 1.5 ULN (umol/L) or > 1.5 × baseline	> 3 ULN (umol/L) or > 3 × baseline
Creatinine Clearance (eGFR)	<60 ml/min/1.73m^2	<30 ml/min/1.73m^2	ND	ND
Urea	ND	ND	> 2.5 ULN (mmol/L)	> 5 ULN (mmol/L)
Uric acid	ND	ND	> 0.59 mmol/L (>10 mg/dL)	> 0.72 mmol/L (>12 mg/dL)
Proteinuria	ND	ND	≥1.0 g/24h	≥3.5 g/24h
Protein/creatinine ratio	ND	ND	>100 mg/mmol***	>300 mg/mmol***
Albumin	< 30 (g/L)	< 20 (g/L)	ND	ND
Protein total	ND	ND	ND	ND
C-reactive protein	ND	ND	ND	ND
Glucose (Non-diabetic Fasting)	< 3.0 (mmol/L) (< 55 mg/dL)	< 2.2 (mmol/L) (< 40 mg/dL)	> 8.9 (mmol/L) (> 160 mg/dL)	> 13.9 (mmol/L) (> 250 mg/dL)
Potassium	< 3.2 (mmol/L)	< 3.0 (mmol/L)	> 5.5 (mmol/L)	> 6.0 (mmol/L)
Sodium	ND	< 130 (mmol/L) (< 130 mEq/L)	> 150 (mmol/L) (> 150 mEq/L)	> 155 (mmol/L) (> 155 mEq/L)
Calcium (corrected for albumin)	< 2.0 (mmol/L) (< 8.0 mg/dL)	< 1.75 (mmol/L) (< 7.0 mg/dL)	> 2.9 (mmol/L) (> 11.5 mg/dL)	> 3.1 (mmol/L) (> 15.5 mg/dL)
Chloride	ND	ND	ND	ND
Triglyceride	ND	ND	> 3.42 (mmol/L)	> 11.4 (mmol/L)
Cholesterol	ND	ND	> 7.75 (mmol/L)	> 12.92 (mmol/L)
Fibrinogen	< 0.75 - 0.5 LLN or 25 - < 50% decrease from baseline	< 0.25 LLN or < 75% decrease from baseline or absolute value < 50 mg/dL	ND	ND
IgG	ND	ND	ND	ND
IgM	ND	ND	ND	ND
IgA	ND	ND	ND	ND

ANA	ND	ND	ND	ND
Anti-dsDNA	ND	ND	ND	ND
C3	ND	ND	ND	ND
C4	ND	ND	ND	ND
Anti-Sm	ND	ND	ND	ND
Antiribosomal P	ND	ND	ND	ND
Anti-cardiolipin IgA	ND	ND	ND	ND
Anti-cardiolipin IgG	ND	ND	ND	ND
Anti-cardiolipin IgM	ND	ND	ND	ND
Serum pregnancy test	ND	ND	ND	Positive **ALERT: Positive**

ALT = alanine aminotransferase; ANA = anti-nuclear antibodies; anti-dsDNA = anti-double-stranded DNA; anti-Sm = anti-Smith; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = Mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; ND = not defined; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell.

*If lymphocyte count < 800 cells/µl at EOS visit, an alert will be sent.** HH and HHH based on CTCAE 2010 v4.03 [CTCAE 2010]. However, an Alert will be sent when INR ≥ 1.5 based on the guidance for monitoring liver test abnormalities from Food and Drug Administration (FDA) [FDA 2009]. ***Source for protein/creatinine ratio thresholds: http://www renal.org/information-resources/the-uk-eckd-guide/proteinuria#sthash.jdT5cPIP.dpbs.

Appendix 8 Corticosteroid conversion table

Corticosteroid Conversion Table		
Glucocorticoid	**Approximate equivalent dose (mg)**	**Half---life (hr)**
Short-Acting		
Cortisone	25	8-12
Hydrocortisone	20	8-12
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6-0.75	36-54
Dexamethasone	0.75	36-54

1. Dixon JS. Second-line Agents in the Treatment of Rheumatic Diseases. Informa Health Care, 1991. (456).
2. Meikle AW and Tyler FH. Potency and duration of action of glucocorticoids. Am J of Med 1977;63;200.
3. Webb R, Singer M. Oxford Handbook of Critical Care. Oxford ; New York : Oxford University Press, 2005.

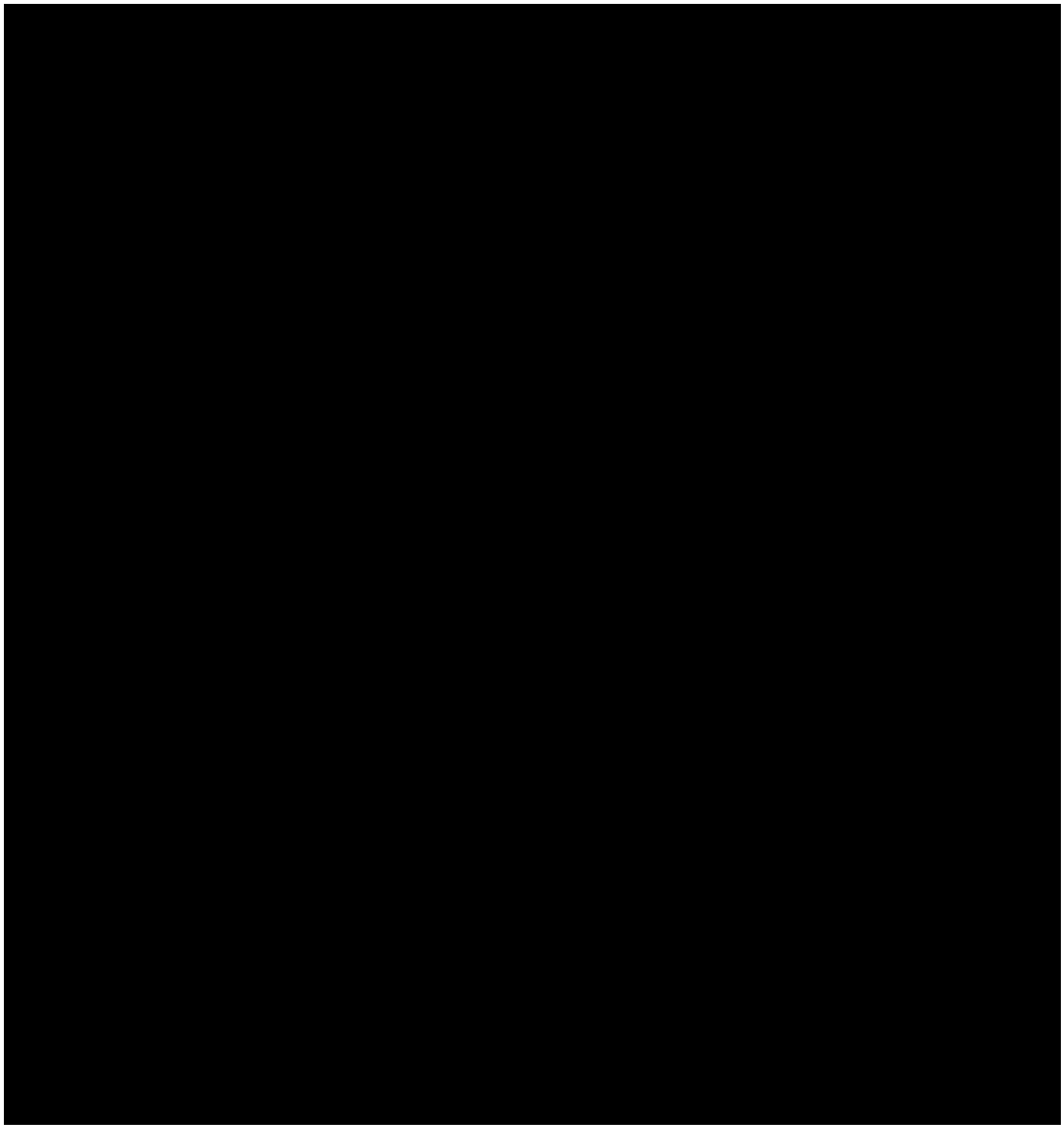
Source: http://med.umkc.edu/docs/em/Corticosteroid_Table.pdf

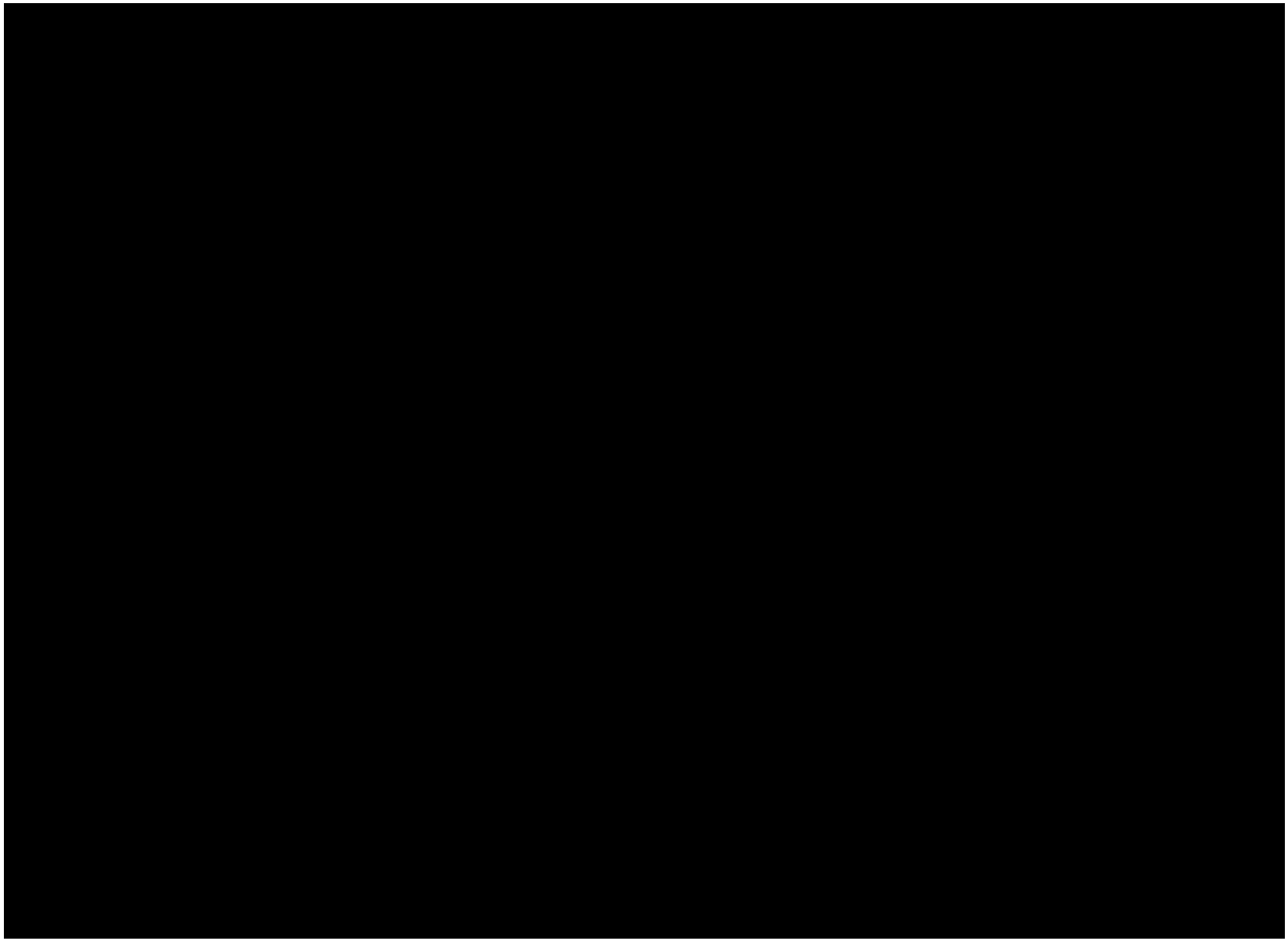
Appendix 9 Physician's Global Assessment Visual Analog Scale

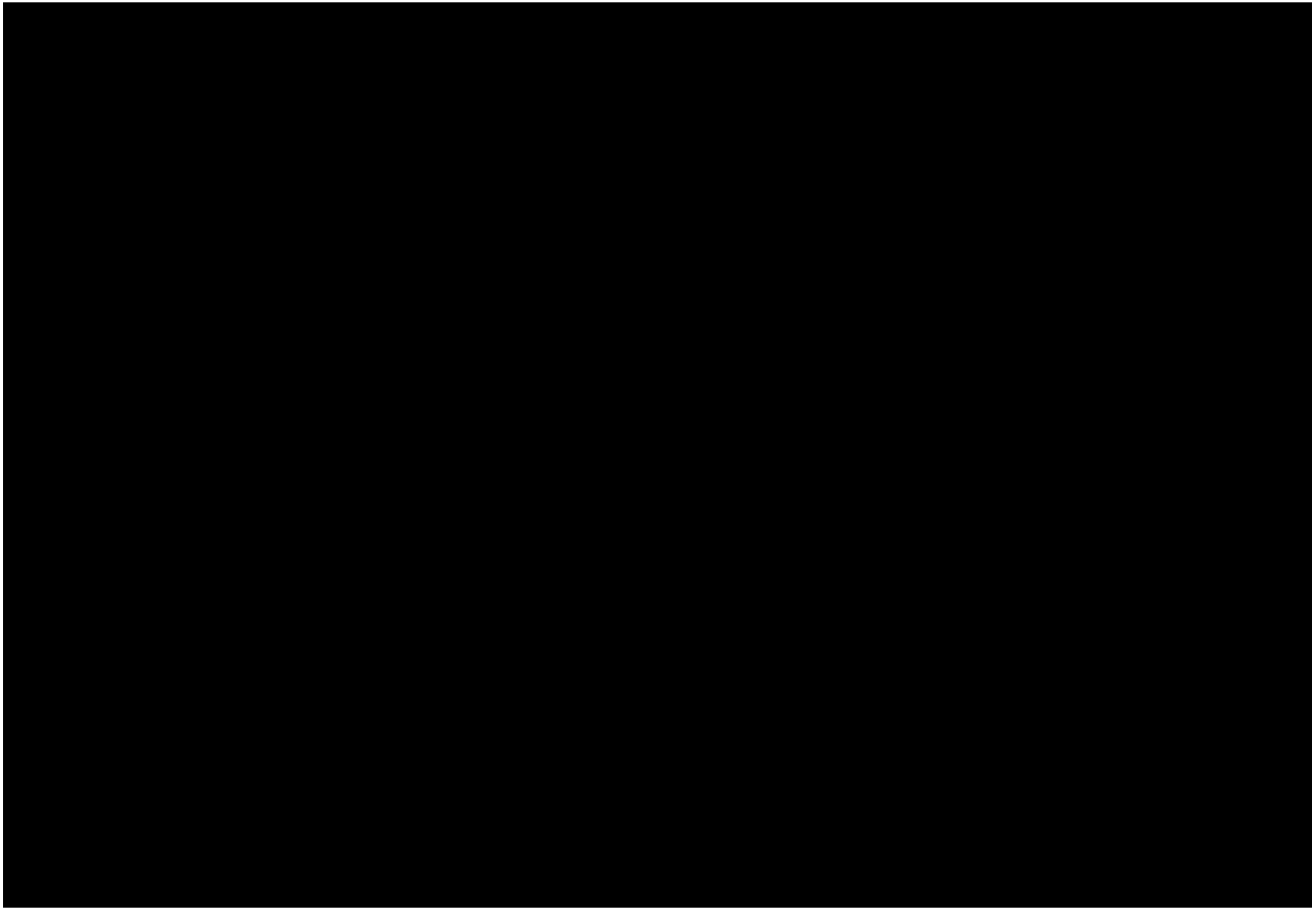
From: Petri 2005

Appendix 10 SF-36v2™

United States (English) SF-36v2 Standard







[redacted]