Statistical Analysis Plan 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**

This study was sponsored by Actelion Pharmaceuticals.

Study sponsorship was transferred to Idorsia Pharmaceuticals in July 2018.

# STATISTICAL ANALYSIS PLAN

# FOR CSR

**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**

| | |
|---|---|
| Purpose of Analysis | Clinical Study Report |
| Investigational Drug | Cenerimod (ACT-334441) |
| Protocol Number | AC-064A201 |
| Actelion Document Number | D-17.230 |
| Document Status/Version Number | Final 1.0 |
| Date | 20 April 2017 |

| | |
|---|---|
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| Reviewer | [redacted] |
| Reviewer | [redacted] |
| Reviewer | [redacted] |
| Reviewer | [redacted] |
| Reviewer | [redacted] |
| Reviewer | [redacted] |
| Reviewer | [redacted] |
| Reviewer | [redacted] |
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# LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ACR | American College of Rheumatology |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ALP | Alkaline Phosphatase |
| ANA | Anti-nuclear antibodies |
| ANCOVA | Analysis of covariance |
| anti-dsDNA | Anti-double-stranded deoxyribonucleic acid |
| APL | Immunoglobulin A Phospholipid |
| AST | Aspartate aminotransferase |
| ATC | Anatomic therapeutic chemical |
| BLyS | B-lymphocyte stimulator |
| BP | Blood pressure |
| bpm | Beats Per Minute |
| CCM | Central Clinical Monitoring |
| CI | Confidence interval |
| CRP | C-reactive protein |
| CL | Confidence limit(s) |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| $C_{trough}$ | Measured plasma concentration at the end of one dosing interval |
| CXCL10 | C-X-C motif chemokine 10 |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDTA | Ethylenediaminetetraacetic acid |
| $E_{max}$ | Maximum effect |

| | |
|---|---|
| EOS | End-of-study |
| EOT | End-of-treatment |
| FAS | Full analysis set |
| FDA | (US) Food and Drug Administration |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FSFV | First subject first visit |
| FU | Follow-up |
| FVC | Forced vital capacity |
| GPL | Immunoglobulin G Phospholipid |
| HIV | Human immunodeficiency virus |
| HR | Heart rate |
| ICH | International Council for Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IgA | Immunoglobulin A |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| INR | International Normalized Ratio |
| IR | Interim safety review |
| IRT | Interactive response technology |
| LLN | Lower limit of the normal ranges |
| LLOQ | Lower limit of quantification |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCP | multiple comparison procedures |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MPL | Immunoglobulin M Phospholipid |
| LSLV | Last subject last visit |
| NA | Not applicable |

| | |
|---|---|
| OCT | Optical coherence tomography |
| PD | Pharmacodynamic |
| PGA | Physician's Global Assessment |
| PK | Pharmacokinetic |
| PPS | Per-protocol analysis set |
| QTcB | QT corrected for heart rate on the basis of Bazett's formula |
| QTCF | QT interval corrected for heart rate using Fridericia's formula |
| S1P | Sphingosine-1-phosphate |
| S1P1 | Sphingosine-1-phosphate receptor 1 |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical analysis plan |
| SAS | Statistical analysis system |
| SBP | Systolic blood pressure |
| SF-36v2 | 36-Item Short Form Health Survey v2 |
| SLE | Systemic lupus erythematosus |
| SLEDAI-2K | Systemic Lupus Erythematosus Disease Activity Index-2000 |
| SOC | System organ class |
| SDTM | Study Data Tabulation Model |
| SI | Standard International |
| TEAE | Treatment-emergent adverse event |
| TB | Tuberculosis |
| TBL | Total bilirubin |
| ULN | Upper limit of the normal ranges |
| ULQ | Upper limit of quantification |
| VPCs | Ventricular premature complexes |
| WBC | White blood cells |
| WHO | World Health Organization |
| WOCBP | Women of childbearing potential |

# 1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the analyses and data presentation of all endpoints for the final clinical study report (CSR) of study AC-064A201.

This analysis plan is based on or refers to the following documents:

**Table 1 Associated Documents**

[redacted]

Two additional SAPs were developed for:

- Closed sessions of the independent data monitoring committee (IDMC) and Interim Safety Review (IR). This is based on this CSR SAP and is written by the Independent Statistical Analysis Center and is not reviewed by Actelion.
- Periodic reviews for Central Clinical Monitoring (CCM) and open sessions of the IDMC. This document describes specific and dedicated analyses as documented in the CCM Plan and refers mainly to this CSR SAP in terms of statistical methods and data presentation.

The source data for the analyses described in this SAP are the Study Data Tabulation Model (SDTM) datasets, provided by CDDM as Statistical Analysis System (SAS) datasets.

# 2 STUDY DESIGN AND FLOW

Further details can be found in the protocol synopsis in Appendix A.

## 2.1 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 consists of four parallel treatment groups (including 0.5 mg, 1 mg, or 2 mg of ACT-334441 and placebo control). Approximately 48 subjects were randomized (1:1:1:1) via an interactive response technology (IRT) system to one of the 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.).

Subjects received ACT-334441 or placebo once daily (o.d.) for 12 weeks.

Interim safety review

An Interim Review (IR) was conducted by the IDMC when all subjects enrolled into Part A completed Visit 4 (Week 4), unless prematurely discontinued. The IDMC evaluated the safety profile of ACT-334441 in systemic lupus erythematosus (SLE) subjects and gave a recommendation to continue the study as planned (i.e., proceed to Part B).

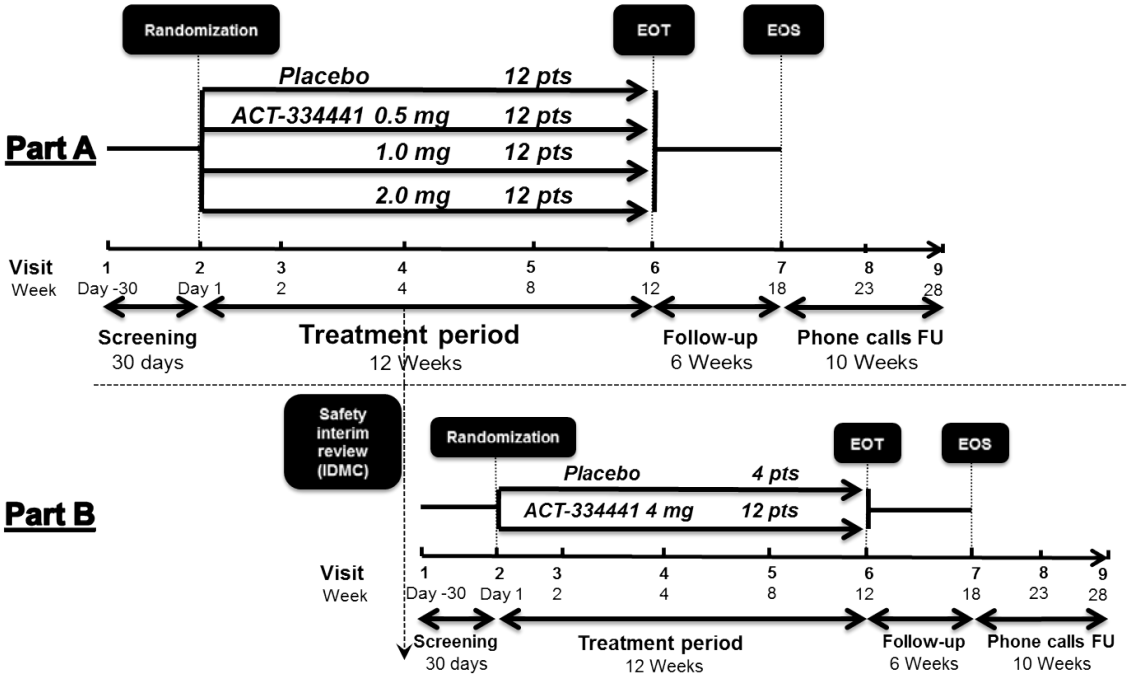
Part B

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

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

The study design is shown in Figure 1.

**Figure 1 Study design of AC-064A201 investigating ACT-334441 in SLE subjects**




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

## 2.2 Study visit and assessment schedule

See Table 2 for a detailed plan of the visit and assessment schedule.

## Table 2 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 | | | | |

| 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 | |
| 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 | | | | | | | | | | |
| Additional serum sample for viral serology*** | | | X | | | | | | | | | |
| ANA, anti-dsDNA antibodies, complement C3 and C4** | | X | X | | X | X | X | X | | | X | |
| Exploratory biomarkers** (11) | | | X | | X | X | X | X | | | | |
| Lymphocyte subsets*** (12) | | | 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 visits 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/TBL, 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; TBL = total bilirubin; WOCBP = women of childbearing potential.

# 3 OBJECTIVES

## 3.1 Main objective(s)

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

## 3.2 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.

# 4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

## 4.1 Changes to the analyses planned in the study protocol

### 4.1.1 Pharmacodynamic analysis set definition

Previously Read
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.

Now Reads:
The pharmacodynamics analysis set (PDS) includes all subjects who received at least 21 days of uninterrupted study treatment, with lymphocyte count measurements at baseline and post-baseline (namely, one sample taken at least 21 days after the first study treatment intake and no later than 7 days after the last study treatment intake and no study treatment interruption documented in the first 21 days).

Rationale for change:
To allow analysis of the primary endpoint, the change from baseline to end of treatment (EOT) in lymphocyte count, based on a value at baseline and a value 'under treatment' so that the expected drug dependent effect on the lymphocyte count is biologically meaningful and has sufficient time to reach the full effect on lymphocyte reduction.

### 4.1.2 Per-protocol analysis set definition

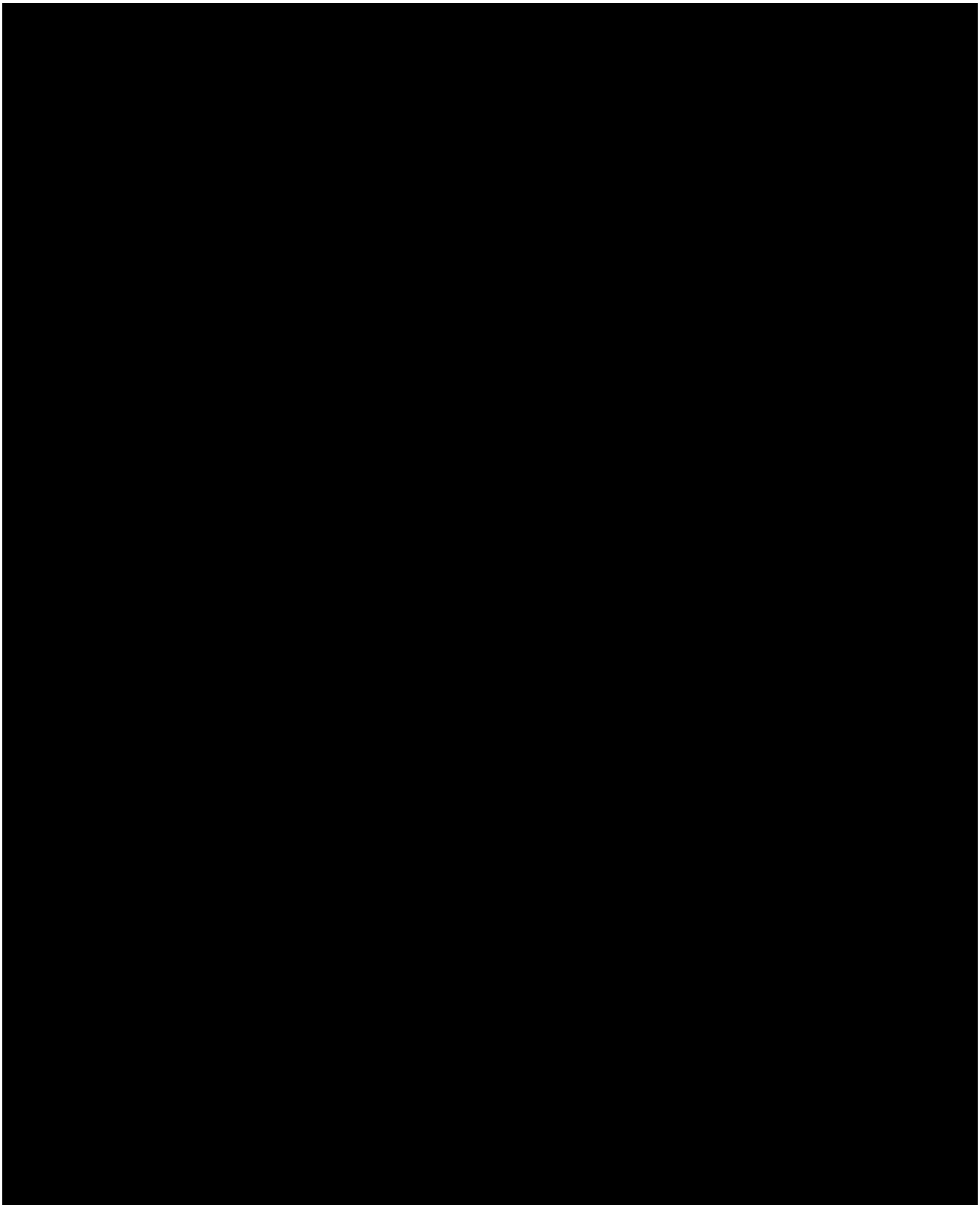
Previously Read
The Per-Protocol Set (PPS) comprises data from all subjects included in the Full Analysis Set (FAS) without selected important protocol deviations including but not limited to:

- 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.

Now Reads:

The Per-Protocol Set (PPS) comprises data from all subjects included in the Full Analysis Set (FAS) without relevant deviations which could affect the evaluation of the pharmacodynamic parameters (lymphocyte count) and the exploratory disease activity parameters (SLEDAI-2K, PGA).

The protocol deviations leading to exclusion from the PPS are listed in the below table.



[redacted]

Please note:

- If a subject is excluded from the PDS then he is also excluded from the PPS.
  *Rationale:* Insufficient pharmacodynamic effect is unlikely to show e.g. clinical improvement, but will confound the results.
- [redacted] If a subject presents with such protocol deviation (specifically, pregnancy test not performed 3 weeks apart), but no pregnancy occurred and all subsequent pregnancy tests were consistently negative during the trial, the subject can be included into the PPS.
  *Rationale:* Biologically this subject is not different from included subjects. However, an important protocol deviation has to be reported.
- [redacted]: If a subject presents with such protocol deviation, but the change of the immunologically active medication occurred at or after EOT, the subject can be included in the PPS.
  *Rationale:* The primary endpoint compares the change from baseline to EOT.

Rationale for change:
The definition of the PPS has been adapted to fully account for the study eligibility criteria.

### 4.1.3 Adverse events of special interest

The adverse events of special interest (AESIs) listed in the protocol have been amended/refined as follows:

| Previously Read | Now Reads |
|---|---|
| Effect on HR and rhythm related AEs<br>Hypotension related AEs | Effect on heart rate and rhythm AESI (including hypotension) |
| Cardiovascular related AEs | Cardiovascular AESI |
| Hypertension related AEs | Hypertension AESI |
| Hepatobiliary disorders / liver enzyme abnormality related AEs | Liver AESI (Hepatobiliary disorders/ liver enzyme abnormality) |
| Pulmonary related AEs | Pulmonary AESI |
| Eye disorders related AEs | Macular edema AESI |
| Infection related AEs | Infection AESI (only if reported as serious or severe) |
| | Herpetic infections AESI |
| Skin malignancy related AEs | Skin malignancy AESI |
| Malignancy (non-skin) related AEs | Non-Skin malignancy AESI |
| | Stroke AESI |
| | Seizure AESI |

Rationale for change:

Additional categories of AESI were included in order to monitor additional risks and/or observations reported with other S1P receptor modulators (such as fingolimod or ponesimod).

## 4.2 Changes in the conduct of the study / data collection

Not applicable.

## 4.3 Clarifications concerning endpoint definitions and related variables or statistical methods

### 4.3.1 Analysis visits

To allow analysis of data at the relevant planned (scheduled) visits, all recorded assessments, including unscheduled ones, are assigned to the most appropriate analysis visit according to the best fitting time-window for that visit (more details are given in Section 11). The visit windows are based on the number of days from first study treatment intake and from last study treatment intake.

### 4.3.2 Systemic Lupus Erythematosus Activity Index-2000 (SLEDAI-2K)

Naming convention

In this study, a modified SLEDAI-2K score is applied. The item related to leukopenia is excluded from the SLEDAI-2K scoring due to the mode of action of the compound (i.e. lymphocyte count reduction in peripheral blood).

*Rationale for change:* To make it more clear that the full SLEDAI-2K score has not been used in the study.

Additional variables/endpoints related to SLEDAI
For the modified SLEDAI-2K score, additional variables/endpoints are added:

- Value at baseline categorized as '≥ 6' and '< 6';
- Occurrence of an increase from baseline > 3 at each post-baseline analysis visit.

*Rationale for change:*
More granularity in the SLEDAI-2K categories is provided to better describe the disease severity and to assess lupus flares during the study.

A SLEDAI score of 6 is considered to be clinically relevant, because a score of > 5 has > 50% probability of requiring lupus-directed therapy [Nuttall 2013]. In turn, a SLEDAI-2K of < 6 is considered as mild disease, whereas a SLEDAI-2K of ≥6 points corresponds to moderate or severe SLE disease activity.

Reduction in the flare rate is a useful clinical trial endpoint even in a small trial. An increase in the global SLEDAI-2K score of >3 points is considered to distinguish SLE patients with persistently active disease versus those having a disease flare [Nuttall 2013, Nikpour 2009].

Additional endpoint related to arthritis
For subjects presenting arthritis, the number of affected joints is collected in the eCRF.

The following endpoints not listed in the protocol are defined:

- Number of affected joints, value at baseline;
- Number of affected joints and change from baseline to each post-baseline analysis visit.

*Rationale for change:*
Positive proof of concept (PoC) of the S1P1 receptor modulator ponesimod was achieved in the skin auto-immune disease psoriasis [Vaclavkova 2014]. In the subgroup of psoriasis patients with concomitant psoriatic arthritis, ponesimod also improved the joint pain score, giving rise to the hypothesis that S1P receptor modulation may improve arthritis. Accordingly, the number of arthritis affected joints in SLE patients is assessed during the study and proposed to be analyzed statistically.

### 4.3.3 Exploratory biomarkers variables

For exploratory biomarkers such as ANA titers or C-reactive protein (CRP), the planned analyses encompass the description of the values as a continuous variable (absolute value, absolute change from baseline and percent change from baseline). A selection of these biomarkers will be summarized as categorical variables.

*Rationale for change:* During the conduct of the study, it was realized that, for some biomarkers (ANA titers, CRP, anti-ribosomal P), more than one-third of the values are either recorded below the lower limit of quantification ('<1'; BLQ) or above upper limit of quantification ('>100'; ULQ). Considering this, descriptive results may be biased when the total number of BLQ and ULQ values is large; in these circumstances, the variables are described only as categorical variables.

### 4.3.4 24 hour Holter-ECG

An additional (exploratory) endpoint is defined for 'ECG Mean Heart rate (beats/min)', recorded during the diary period:

- Absolute time-matched change in ECG Mean Heart rate (beats/min) from Visit 1 (Screening) to Visit 2 (Randomization/ Day 1) at each hourly time point up to 24 hours post-dose.

*Rationale for change:* The descriptive analysis of hourly mean heart rate during screening and on Day 1 was planned but the analysis of the absolute time-matched change from Screening to Day 1 was subsequently considered to be relevant.

# 5 DEFINITIONS OF VARIABLES

## 5.1 Screening failures

A subject is considered a screening failure if the subject is screened but not subsequently randomized in the IRT System. Subjects screened twice (allowed by the protocol) and subsequently randomized are not counted as screening failures.

The primary reason for screening failure is documented on the 'Randomization' eCRF page (as the 'Primary reason why the subject was not randomized'). If a subject is considered a screening failure but no reason for screening failure is reported, the reason is categorized as 'Unknown'.

## 5.2 Subject characteristics

In the event that a subject is re-screened and the re-screening pages are completed, the data on the re-screening page supersedes that on the original screening page.

### 5.2.1 Demographics and other characteristics

The following characteristics are collected on the 'Demographics', 'Smoking Status' and 'Body Weight and Height' eCRF pages at Visit 1 (Screening):

- Age (years);
- Sex (categorized as: Male, Female);
- Woman of childbearing potential (No/Yes) ;
- Smoking status (categorized as: Current smoker/ Former smoker/ Never smoked);
- Race (categorized as: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other);
- Ethnicity (categorized as: Hispanic or Latino, Not Hispanic or Latino, Unknown);
- Body weight (kg);
- Height (cm);
- Country of enrolment (assigned in the eCRF based on the list of sites).

In addition, the following variables are derived:

- Age (years) in categories, mandatory for EudraCT (12 - 17, 18 - 64, 65 - 84);
- Age (years) in categories (18 - 30, 31 - 45, 46 - 65);
- Body mass index ($kg/m^2$); derived weight (kg) / [height (cm) / 100]$^2$.
- Body mass index ($kg/m^2$) in categories, based on the WHO classification (< 18.5, 18.5 – <25.0, 25.0 – <30.0, 30.0 – <35.0, 35.0 – <40.0, ≥ 40.0).

### 5.2.2 Baseline disease characteristics

#### *5.2.2.1 SLE relevant disease history*

SLE relevant disease characteristics (as recorded or derived from the data captured on the 'Systemic Lupus Erythematosus Relevant Disease History' and 'History of Detectable ANA or Anti-dsDNA Testing' eCRF pages at Visit 1 [Screening]) include:

- Time from first SLE symptoms (years) calculated as follows:
  (date of informed consent - date of first SLE symptoms)/365.25.
- Time from SLE diagnosis (years) calculated as follows:
  (date of informed consent - date of SLE diagnosis)/365.25.
- Number of SLE symptoms according to ACR criteria [ACR 1997]:
  - met in the past
  - started more than 6 months prior to screening
  - ongoing at screening
  - met either serially or simultaneously (i.e., met in the past and started more than 6 months prior to screening)

  Number of SLE symptoms according to ACR criteria [ACR 1997] met in the past is calculated for each subject as the number of criteria for which the box 'Was this criterion ever met in the past?' is ticked 'Yes'. This number is categorized as 0-3, 4-11.

Number of SLE symptoms according to ACR criteria [ACR 1997] started more than 6 months prior to screening is calculated for each subject as the number of criteria for which the box 'Did it start more than 6 months prior to Screening?' is ticked 'Yes'. This number is categorized as 0-3, 4-11.

Number of SLE symptoms according to ACR criteria [ACR 1997] ongoing at screening is calculated for each subject as the number of criteria for which the box 'Ongoing at Screening?' is ticked 'Yes'. This number is categorized as 0-3, 4-11.

Number of SLE symptoms according to ACR criteria [ACR 1997] met either serially or simultaneously is calculated for each subject as the number of criteria for which the box 'Ongoing at Screening?' or 'Was this criterion ever met in the past?' is ticked 'Yes'. This number is categorized as 0-3, 4-11.

- Presence of a documented historical positive ANA or anti-dsDNA testing

  Presence of a documented historical positive ANA is equal to 'Yes' when the box 'ANA: Was a documented historical positive testing available?' is ticked 'Yes' on 'History of Detectable ANA or Anti-dsDNA Testing' eCRF. If there is no documented evidence of a test we do not know if the subject was positive or negative and therefore they are counted as having 'No documented evidence of a test'.

  Presence of a documented historical positive anti-dsDNA is equal to 'Yes' when the box 'Anti-dsDNA: Was a documented historical positive testing available?' is ticked 'Yes' on 'History of Detectable ANA or Anti-dsDNA Testing' eCRF. If there is no documented evidence of a test we do not know if the subject was positive or negative and therefore they are counted as having 'No documented evidence of a test'.

#### *5.2.2.2 Modified SLEDAI-2K and PGA*

The modified SLEDAI-2K relevant disease characteristics (as recorded and derived from the data on the 'Modified SLEDAI-2K' and 'Physician's Global Assessment' eCRF pages at Visit 1 [Screening]) include:

- SLEDAI-2K:
  - presence or not of each active descriptor,
  - mucocutaneous score,
  - musculoskeletal score,
  - sum of the mucocutaneous and musculoskeletal scores,
  - modified SLEDAI-2K total score,
  - modified SLEDAI-2K total score as a category ($\geq 6$ and $< 6$)

- Physician's Global Assessment (PGA) score.

Modified Systemic Lupus Erythematosus Activity Index-2000 (SLEDAI-2K)

The SLEDAI-2K is a disease activity index of SLE based on the presence of 24 descriptors in nine organ systems over the preceding 10 days. Descriptors of the SLEDAI-2K are documented as either present or absent. Each of the descriptors is weighted and the total score of SLEDAI-2K is the sum of all 24 (weighted) descriptor scores. The range of the total SLEDAI-2K score is 0 to 105, with higher scores representing higher disease activity.

In this study, a modified SLEDAI-2K score is applied. The item related to leukopenia is excluded from the SLEDAI-2K scoring due to the mode of action of the compound (i.e. lymphocyte count reduction in peripheral blood). Therefore, the modified SLEDAI-2K total score has only 23 descriptors and a maximum score of 104.

In addition the modified SLEDAI-2K score is categorized as '≥ 6' and '< 6'.

Physician's Global Assessment of disease (PGA)

The PGA is a 100 mm visual analog scale for the assessment of disease activity ranging from 0 to 3. The scale is anchored at 0="none", 1="mild", 2="moderate", 3="severe".

The PGA score is computed as follows in the 'Physician's Global Assessment (PGA)' eCRF form as: Length measured [mm] x 3 / 100

#### *5.2.2.3 Exploratory disease biomarker*

The following parameters are assayed by the central laboratory at baseline only at Visit 2: anti-Smith, anti-cardiolipin (IgA, IgG, IgM), anti-ribosomal P.

If the number of values recorded as below or above the limit of quantification is more than one third overall, the parameter is described only as a categorical variable.

Categories are defined using the limits of quantification (lower, upper) and/ or the reportable ranges provided by the central laboratory.

**Table 4 Exploratory disease biomarker evaluated at baseline only (in categories)**

| Parameter (unit) | LLQ | LLN | ULN | ULQ | Categorization |
|---|---|---|---|---|---|
| Cardiolipin IgA Antibody (APL) | 1 | NA | 12 | | <1, 1 - 11, 12 - 20, 21 -100, > 100 |
| Cardiolipin IgG Antibody (GPL) | 1 | NA | 15 | 100 | <1, 1 - 14, 15 - 20, 21 -100, > 100 |
| Cardiolipin IgM Antibody (MPL) | NA | NA | 12 | | <1, 1 - 11, 12 - 20, 21 -100, > 100 |
| Ribosomal P Protein Antibody (U/mL) | 20 | NA | 20 | | <20, ≥ 20 |
| Smith Antibody (mmol/L) | NA | | 100 | | < 100, ≥ 100 |

LLQ = Lower Limit of Quantification, LLN = Lower Limit of Normal, ULN = Upper Limit of Normal, ULQ = Upper Limit of Quantification

### 5.2.3 Other baseline characteristics

Other baseline characteristics, collected during screening include chest X-ray, contraceptive methods, tuberculosis test and optionally viral serology results. These are defined as collected on the eCRF and no derivation is required.

### 5.2.4 Medical history

Medical history includes clinically significant previous and/or concomitant diseases or diagnoses recorded on the 'Medical History (except SLE)' eCRF page. Reported terms are mapped to preferred terms using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at time of database closure.

The variables of interest are the preferred term and the primary System Organ Class (SOC).

Previous medical history are those diseases or diagnoses that are not ticked as ongoing at screening on the eCRF and with an end date before or equal to the study treatment start date. In the event of a partial end date that overlaps with first dose (e.g., May2013 and first dose occurred on 23May2013) or if an end date is missing, the medical history is considered as previous if ongoing is ticked 'No'. All other medical history terms are considered concomitant.

### 5.2.5 Previous and concomitant therapies

Therapies are collected on several dedicated eCRF pages:

- 'Previous non-SLE therapies'
- 'Concomitant non-SLE therapies'
- 'Previous SLE therapies'
- 'Concomitant (Background) SLE therapies

The reported names are coded using the WHO drug code dictionary and the anatomic therapeutic chemical (ATC) class according to the most current version at time of database closure. The variables of interest are the preferred term (standardized medication name) and the ATC code level 4.

#### *5.2.5.1 Previous non-SLE therapies*

A previous non-SLE therapy is any therapy for which the end date of therapy is prior to the start of study (i.e., signed informed consent) and reported in the 'Previous Non SLE therapies' page of the eCRF.

#### *5.2.5.2 Study-treatment concomitant non-SLE therapies*

A study-treatment concomitant non-SLE therapy is any therapy given for any reason except SLE that is either ongoing at the start of study treatment or is initiated between the start of the study treatment and Visit 7 (EOS) reported on the 'Concomitant medications' page of the eCRF.

#### *5.2.5.3 Previous SLE therapies*

A previous SLE therapy is any therapy administered for SLE and/or SLE manifestations as described in protocol section 5.2.2.1 reported on the 'Previous SLE therapies' page of the eCRF.

#### *5.2.5.4 Study-treatment concomitant SLE therapies*

A concomitant (background) SLE therapy is any therapy administered for SLE and/or SLE manifestations as described in protocol section 5.2.1.1 reported on the 'Background SLE therapies' page of the eCRF.

## 5.3 Study treatment exposure and compliance

Study treatment duration and compliance are defined for the treatment period.

### 5.3.1 Exposure

For each subject, the following exposure-related variables are derived from the 'Study Drug Log' eCRF form:

- Study treatment duration, defined as the number of days between start of study treatment and permanent treatment discontinuation of study treatment (both inclusive), regardless of interruption(s).
- Study treatment duration excluding treatment interruptions (days), defined as the study treatment duration minus study treatment interruptions.

Study treatment duration is also categorized (cumulatively) as: at least one day, at least 1 week, at least 4 weeks, at least 8 weeks, at least 11 weeks and at least 12 weeks.

### 5.3.2 Compliance with study treatment

Study treatment compliance is computed within the 'Study Drug Log Dispensing & Accountability' form of the eCRF at each dispensing/return visit as well as for the whole treatment period based on the visit dates.

In case of low compliance with the study drug (below 80%), the reason is collected in the eCRF (e.g., Treatment interrupted due to AE, Bottle not returned and study drug not taken).

The actual compliance over the study treatment period needs to be re-computed based on the actual study treatment duration according to the following formula:

$$\text{Compliance (\%)} = 100 \times \frac{\text{Total number of capsules dispensed - Total number of capsules returned}}{\text{Study treatment duration (days) x number of capsules prescribed per day (1)}}$$

### 5.3.3 Study treatment discontinuation

Reasons for premature discontinuation of study treatment are recorded on the 'Premature Discontinuation of Study Treatment' page of the eCRF.

A subject is considered to have discontinued from the study treatment prematurely if at least one reason is reported, or the reason for treatment discontinuation on the 'Study Drug Log' page of the eCRF is 'premature discontinuation'.

Subjects who complete study treatment as per protocol are those with a record in the eCRF Study Drug Log of 'Completed as per protocol'.

### 5.3.4 Study treatment interruptions and re-initiations

Study treatment interruptions at any time and re-initiations between Day 1 and Week 2 are recorded on the 'Study Drug Log' page of the eCRF.

A subject is considered to have had a study treatment interruption if the reason for treatment end is either 'Temporarily interrupted due to an AE' or 'Temporarily interrupted not due to an AE'.

## 5.4 Study discontinuation of the subject

Reasons for study discontinuation are recorded on the 'End of Study' page of the eCRF.

A subject is considered to have completed the study if 'Did the subject complete the study?' has been ticked as 'Yes'. A subject is considered to have discontinued from the study prematurely if 'Did the subject complete the study?' has been ticked as 'No'.

## 5.5 Pharmacodynamic variables

In this section, the variables include all lymphocyte count values as transferred by the central laboratory (i.e., all planned visits plus unscheduled visits) but exclude the local laboratory results (which are included in the safety analyses).

Details of the general computation rules for pharmacodynamic variables can be found in Section 11.

### 5.5.1 Main pharmacodynamic variable

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

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

The value at baseline is defined as the last non-missing value obtained from a sample taken prior to the first study treatment intake.

The value at EOT is defined last post-baseline value from a sample taken at least 21 days after the first study treatment intake (with no interruptions) and no later than 7 days after the last study treatment intake for the analyses on the PDS and on the PPS.

The value at EOT is defined as the last post-baseline value up to Week 12 for the analyses on the FAS (application of the intention-to-treat principle [ITT] utilizing the Last observation carried forward [LOCF] technique for missing data).

### 5.5.2 Other pharmacodynamic variables

Other PD variables comprise:

- Absolute values of total lymphocyte count at each analysis visit;
- Absolute change in total lymphocyte count from baseline at each analysis visit;
- Percentage change in total lymphocyte count from baseline at each analysis visit.

The analysis visits are defined in Section 11.1.1. Absolute change and percentage changes are calculated as defined in Section 11.

## 5.6 Pharmacokinetic variables

PK samples are collected at Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 12/ EOT), and Visit 7 (EOS).

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).

The following PK endpoint is defined:

- Cenerimod (ACT-334441) plasma concentrations at each analysis visit.

For analysis visits Weeks 2, 4, 8, samples must be taken 1 calendar day after the previous dose and before the next dose (see Section 11 for details of how this is handled).

For analysis visit Week 12, samples must be taken within 1 to 7 calendar days after the last dose (see Section 11 for details of how this is handled).

## 5.7 Efficacy variables

For the endpoints defined below, further details concerning the derivation of the corresponding analysis variables can be found in Section 11.

### 5.7.1 Primary efficacy variable

Not applicable.

### 5.7.2 Secondary efficacy variables

Not applicable.

### 5.7.3 Other efficacy variables

All efficacy variables evaluated in this study are considered exploratory.

#### *5.7.3.1 Exploratory disease activity variables*

- Modified Systemic Lupus Erythematosus Activity Index-2000 (SLEDAI-2K)

The following endpoints are defined:

  - Absolute values, absolute change and percent change in modified total SLEDAI-2K score from baseline to each post-baseline analysis visit (including EOT);
  - Absolute values, absolute change and percent change in SLEDAI-2K mucocutaneous subscore, musculoskeletal subscore, and combined mucocutaneous and musculoskeletal subscores from baseline to each post-baseline analysis visit (including EOT).

In addition, for the modified total SLEDAI-2K score, the following endpoints are defined:

  - Occurrence of an increase from baseline of > 3.

In addition, for subjects presenting with arthritis, the following endpoint is defined:

  - Number of affected joints at baseline;
  - Number of affected joints and change from baseline to each post-baseline analysis visit.

- Physician's Global Assessment of disease (PGA)

The following endpoints are defined:

  - Absolute value, absolute change and percent change in PGA score from baseline to each post-baseline analysis visit (including EOT).

#### *5.7.3.2 Exploratory biomarker variables*

- ANA, anti-dsDNA, complement factors and exploratory biomarkers

The following parameters are assayed by the central laboratory:

  - ANA, anti-dsDNA, complement C3 and C4 (all visits except Visit 3);
  - IgM, IgG, IgA, CRP, fibrinogen, and B lymphocyte stimulator (BLyS) (Visit 2 and Visits 4 to 7).

The following parameter is assayed by Translational Science Biology:

- C-X-C motif chemokine ligand 10 (CXCL10) (EDTA-plasma; Visit 2 and Visits 4 to 7).

The following endpoints are defined:

- Change in immunoglobulin serum levels (IgG, IgM, IgA) from baseline to each post-baseline analysis visit;
- Change in ANA and anti-dsDNA antibody titers from baseline to each post-baseline analysis visit;
- Change in serum complement components C3 and C4, CRP, fibrinogen, BLyS and CXCL10 from baseline to each post-baseline analysis visit.

If the number of values recorded as below or above the limit of quantification is more than one third overall, the parameter is only described as a categorical variable (value at each analysis visit).

Categories are defined using the reference ranges and the reportable ranges provided by the central laboratory.

**Table 5 Exploratory biomarker variables evaluated during the study**

| Parameter (unit) | Reference Ranges | Reportable Ranges | Categorization |
|---|---|---|---|
| ANA titer | < 40 | <40; >=640 | < 40, 40, 80, 160, 320, >=640 |
| anti-dsDNA (U/mL) | < 100 | 50; 1000 | < 1.0, 1.0 - 99.9, >= 100 |
| Complement C3 (g/L) | 0.9 ; 1.8 | 0.50; 1125.00 | < 0.90, 0.90 - 1.80, > 1.80 |
| Complement C4 (g/L) | 0.18 ; 0.45 | 0.40; 700.00 | < 0.05, 0.05 - 0.17, 0.18 - 0.45, > 0.45 |
| C Reactive Protein (mg/L) | < 8.00 | 4.00; 999.00 | < 4.00, 4.00 - 7.99 , >= 8.00 |
| Fibrinogen (g/L) | 2.1 ; 4.7 | 0.01; 7.0 | < 0.5, 0.5 - 1.0, 1.1 - 2.0, 2.1 - 4.7, 4.8 - 5.9, > 5.9 |
| Immunoglobulin A (g/L) | 0.4 ; 3.5 | 0.15; 54.00 | < 0.4, 0.4 -3.5, > 3.5 |
| Immunoglobulin G (g/L) | 6.5 ; 16 | 0.70; 340.00 | < 6.5, 6.5-16.0, >16.0 |
| Immunoglobulin M (g/L) | 0.5 ; 3 | 0.08; 33.00 | < 0.5, 0.5 - 3.0, > 3.0 |
| BAFF/ BLyS (pg/mL) | 584 ; 1186 | 63; 4000 | 63, 63-583, 584-1186, 1187-4000, >4000 |
| CXCL10 (ng/L) * | NA | NA | NA |

* assayed by Translational Science Biology at Actelion

For parameters considered as continuous variables, the change is evaluated in terms of absolute change and percent change from baseline to each post-baseline analysis visit.

- Blood lymphocyte subsets

Blood samples for lymphocyte subset analysis are taken at Visit 2 (Randomization/ Day 1), Visit 6 (EOT) and Visit 7 (EOS) and assayed by Translational Science Biology at Actelion.

The following endpoints are defined:

  - Change in blood lymphocyte subsets from baseline to EOT and EOS.

The complete list of parameters and units is provided in Section 11.

## 5.8 Safety variables

More details of the computation of safety variables can be found in Section 11.

### 5.8.1 Adverse events

All adverse events (AEs) occurring during the study period (from informed consent signature up to the EOS visit) are recorded on the eCRF. The original verbatim terms used by investigators to identify AEs are mapped to preferred terms (PT) using the most current version of the MedDRA dictionary at the time of database closure.

#### *5.8.1.1 Treatment-emergent adverse events*

A treatment-emergent adverse event (TEAE) is any AE temporally associated with the use of study treatment (from study treatment initiation until Visit 7 [EOS]) irrespective whether considered by the investigator to be related to study treatment or not.

An AE is considered a TEAE if the start date is after (>) the first study treatment intake or the start date is on the same day as the first study treatment intake and the answer to 'Did this adverse event start at visit 2 or on first day of re-initiation following study drug intake?' is equal to 'Yes' indicating that the AE started after first intake of study treatment.

#### *5.8.1.2 Related treatment-emergent adverse events*

An AE is considered related if the investigator ticked 'Yes' to the question 'Relationship to study treatment' or if it is missing.

### 5.8.2 Deaths

#### *5.8.2.1 All deaths*

Date of death and primary cause are recorded on the 'Death' eCRF page.

#### *5.8.2.2 Adverse events leading to death*

AEs with an outcome reported as 'death' are considered as AEs leading to death.

### 5.8.3 Serious adverse events

An AE is considered serious if the investigator ticked 'Yes' on the question 'Serious?' on the Adverse Event eCRF or if it is missing.

#### *5.8.3.1 Fatal serious adverse events*

An AE is considered fatal and serious if the investigator ticked 'Yes' on the question 'Serious?' and if the outcome is equal to 'Death' on the Adverse Event eCRF.

### 5.8.4 Adverse events leading to discontinuation of study treatment

These are AEs with 'Action taken with study drug' recorded as 'permanently discontinued' on the Adverse Event eCRF.

### 5.8.5 Other significant adverse events

#### *5.8.5.1 AE of special interest*

An AE is considered to be an AE of special interest (AESI) if it is treatment emergent and belongs to any of the categories listed below (the list of corresponding MedDRA PT is defined in the latest AESI list enclosed in Appendix 15.2.2):

- Effect on heart rate and rhythm AESI (including hypotension)
- Cardiovascular AESI
- Hypertension AESI
- Liver AESI (Hepatobiliary disorders/ liver enzyme abnormality)
- Pulmonary AESI
- Macular edema AESI
- Infection AESI
- Herpetic infections AESI
- Skin malignancy AESI
- Non-Skin malignancy AESI
- Stroke AESI
- Seizure AESI

#### *5.8.5.2 SLE flares reported as AEs*

These are AEs with 'Does this Adverse Event represent a clinical manifestation of SLE flare?' ticked 'Yes' on the 'Adverse Event' eCRF page.

### 5.8.6 Vital signs and body weight

Vital signs include Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP) (mmHg) and body weight (kg).

#### *5.8.6.1 Blood pressure*

SBP and DBP are collected at all visits. At Visit 1 (Screening), SBP and DBP are measured sequentially, twice in the supine and twice in the standing position. In this case

the mean of the two values by position as recorded in the eCRF is used for the analysis. At Visit 2 (Randomization/ Day 1) and at re-initiation, supine SBP and DBP are measured once pre-dose and then once hourly until 6 hours post-dose. At each post-baseline pre-dose assessment, SBP and DBP are measured twice in the supine position and the mean of the two values as recorded in the eCRF is use for the analysis.

The following endpoints are defined:

- Change from baseline to each post-baseline assessment up to EOS (i.e., each post-dose hourly time point on Day 1 and each post-dose analysis visit up to EOS);
- Occurrence of treatment emergent notable abnormalities in blood pressure.

The following analysis parameters are defined:

- Supine SBP (mmHg)
- Standing SBP (mmHg) (only at Visit 1)
- Supine DBP (mmHg)
- Standing DBP (mmHg) (only at Visit 1)

For supine SBP and DBP, the occurrence of treatment emergent notable abnormalities is assessed according to the criteria defined in the table below:

**Table 6 Notable abnormalities in blood pressure**

| Analysis Parameter | Analysis Criterion |
|---|---|
| Supine SBP (mmHg) | Value ≤ 90 and decrease ≥ 20 from baseline |
| | Value ≥140 and increase ≥ 20 from baseline |
| | Value ≥ 160 |
| Supine DBP (mmHg) | Value ≤ 50 and decrease ≥ 15 from baseline |
| | Value ≥ 90 and increase ≥ 15 from baseline |
| | Value ≥ 100 |

Abnormalities are defined for each post-baseline time point and analysis visit individually. In addition, the occurrence of at least one abnormality for each of the criterion is derived on the subject level on the following time intervals: on Day 1 (from 1 hour post-dose through to discharge), after Day 1 (from discharge through to EOT ) and at any post-baseline time point/analysis visit (from 1 hour post-dose through to EOS).

#### *5.8.6.2 Body weight*

Body weight is collected at Visit 1 (Screening) and at Visit 6 (EOT). The following endpoint is defined:

- Change in body weight from baseline to EOT.

### 5.8.7 Electrocardiogram

#### *5.8.7.1 12-lead ECG variables and findings*

- 12-lead ECG variables

The 12-lead ECG measurements and qualitative ECG findings (e.g. rhythm, ectopy, conduction and morphology) are provided by the ECG central reader, along with the overall interpretation of the ECG (Normal/ Abnormal).

The following endpoints are defined:

- Absolute values and change from baseline to each post-baseline assessment up to EOS (i.e., each post-dose time point on Day 1 and each post-dose analysis visit up to EOS) for each parameter;
- Occurrence of treatment-emergent 12-lead ECG notable abnormalities;
- Occurrence of treatment-emergent 12-lead ECG qualitative abnormalities (medical review findings).

For the following ECG parameters, the occurrence of treatment emergent notable abnormalities is assessed according to the criteria defined in the table below.

**Table 7 Notable abnormalities in ECG parameters**

| Analysis Parameter | Analysis Variable(s) | Analysis Criterion |
|---|---|---|
| QTcB-Bazett's Correction Formula (ms) and QTcF-Fridericia's Correction Formula (ms) | Analysis value | - Value > 450 (male), Value > 470 (female)<br>- Value > 480<br>- Value > 500<br>- Value > 500 (male), Value > 520 (female) |
| | Change from baseline | - Increase from baseline > 30<br>- Increase from baseline > 60 |
| | Analysis value<br>Change from baseline | - Value > 450 and increase from baseline > 30<br>- Value > 450 and increase from baseline > 60 |
| Heart rate (bpm) | Analysis value | - Value < 40 |
| PR Duration (ms) | Analysis value | - Value > 200 |
| | Change from baseline | - Increase from baseline > 20 |
| | Analysis value<br>Change from baseline | - Value > 200 and increase from baseline > 20 |

Notable abnormalities are derived for each post-baseline analysis visit. In addition, the occurrence of at least one abnormality on Day 1 (from 1 hour post-dose to discharge), after Day 1 (from discharge on Day 1 through EOT) and at any post-baseline analysis visit (from 1 hour post-dose through EOS) is also derived for each parameter for each subject.

- 12-lead ECG findings

For each ECG, the cardiologist provides his overall interpretation (Normal/ Abnormal) and describes the potential findings by category. All findings reported post first dose are considered as treatment-emergent.

#### *5.8.7.2 24 hour Holter-ECG*

Holter-ECG monitoring is performed for 24 hours at Visit 1 (Screening) and at Visit 2 (Randomization/ Day 1). The 24 hour Holter-ECG parameter collected is the hourly mean heart rate (bpm).

The hourly records are time-matched between these two visits and the corresponding change for each matched time point is computed.

The following endpoints are defined:

- Occurrence of treatment-emergent Holter-ECG-Holter abnormalities on Day 1;
- Absolute time-matched hourly mean heart rate (bpm) change from Visit 1 (Screening) to Visit 2 (Randomization/ Day 1) at each hourly timepoint up to 24 hours post-dose for;

- Holter-ECG- variables

The following analysis parameter is defined:

- ECG Mean Heart rate (beats/min) .

For this analysis parameter, the following analysis variables are defined (see Section 11 for further details):

- Baseline value at each hourly time point (i.e. hourly measurements at Visit 1)
- Analysis value at each post-baseline assessment (i.e., hourly measurements at Visit 2)
- Absolute time-matched change from Visit 1 (Screening) to Visit 2 (Randomization/ Day 1) at each hourly time point.

- Holter-ECG qualitative findings

For each Holter-ECG, the cardiologist provides his overall interpretation (Normal/ Abnormal) and describes the potential findings in the comment section. Each finding reported for the Holter-ECG performed on Day 1 are considered treatment-emergent.

### 5.8.8 Echocardiography

Echocardiography is performed at Visit 1 (Screening) and Visit 6 (EOT). The presence/absence (i.e., Yes/No) of any abnormality is recorded in the eCRF.

### 5.8.9 Discharge from hospital at day 1/re-initiation

The subject's eligibility for discharge or study drug discontinuation at Visit 2 (Randomization/ Day 1) or study treatment re-initiation is independently assessed by the cardiac safety assessor and collected in the 'Discharge from Hospital at Day 1/Re-Initiation'. The variables of interest are:

- Actual time from first study treatment intake to discharge (hours);
- Time from first study treatment intake to discharge, derived from the actual time computed above (at 6 hours, after 6 through 12 hours, after 12 hours);
- Reason for non-discharge at 6 hours, as collected in the eCRF;
- Reason for non-discharge from 6 to 12 hours, as collected in the eCRF;

### 5.8.10 Laboratory

Laboratory test results are transferred from the central laboratory or, if assayed locally, entered in local laboratory eCRF. Assessments are performed at each scheduled visit from Visit 1 (Screening) to Visit 7 (EOS), and at unscheduled visits if required.

The following parameters are assayed:

- **Hematology**: Hemoglobin, hematocrit, platelets, MCH, MCV, MCHC, reticulocytes/erythrocytes, erythrocytes, leukocytes count with differential count (basophils, eosinophils, lymphocytes, neutrophils, monocytes, and basophils/ leukocytes, eosinophils/ leukocytes, lymphocytes/ leukocytes, monocytes/ leukocytes, neutrophils/ leukocytes);
- **Blood chemistry**: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin (TBL), direct bilirubin, lactate dehydrogenase, creatinine, blood urea nitrogen, urate, glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, protein, albumin, creatinine clearance;
- **Coagulation tests**: prothrombin time, INR, activated partial thromboplastin time;
- **Urine protein-to-creatinine ratio** (Visits 1, 2 and 6): Creatinine, protein, protein/ creatinine.

For women of childbearing potential, serum pregnancy tests are performed at Visit 1 (Screening) and Visit 7 (EOS) (central laboratory), and urinary pregnancy tests are performed at all other visits and collected in the dedicated eCRF page.

Urine dipsticks are used to perform the urinalysis at all visits (e.g., pH, glucose, proteins, blood, leukocytes) and the results are recorded in the dedicated eCRF page.

The following endpoints are defined:

- Absolute value and absolute change from baseline in laboratory parameters (hematology, blood chemistry, and urinalysis) at each post-baseline analysis visit up to EOS;
- Treatment-emergent laboratory test abnormalities based on reference ranges (central laboratory) and abnormality thresholds (as defined in appendix 7 of the study protocol and in Section 15.2).

For these abnormalities, additional criteria are defined to characterize the occurrence of treatment-emergent abnormalities during the treatment period in each direction separately (low and high).

Treatment-emergent liver function abnormalities occurring at any time post-baseline are identified according to the following criteria, where a subject is considered to have met the criteria if they have at least one abnormality based on the worst post-baseline value measured (up to EOS):

- ALT ≥ 3, ≥ 5, ≥ 8 x ULN;
- AST ≥ 3, ≥ 5, ≥ 8 x ULN;
- AST or ALT ≥ 3, ≥ 5, ≥ 8, x ULN;
- ALP ≥ 2 x ULN;
- TBL ≥ 2 x ULN;
- TBL ≥ 2 ULN combined with ALT ≥ 3 ULN;
- TBL ≥ 2 ULN combined with AST ≥ 3 ULN;
- INR ≥ 1.5, ≥2.5 x ULN;
- INR ≥ 1.5, ≥2.5 x baseline;
- INR ≥ 1.5 ULN combined with ALT ≥ 3 ULN;
- INR ≥ 1.5 ULN combined with AST ≥ 3 ULN;
- ALT ≥ 3 x ULN + TBL ≥ 2 x ULN + ALP < 2 x ULN;
- AST ≥ 3 x ULN + TBL ≥ 2 x ULN + ALP < 2 x ULN;

Please note that for criteria combining several parameters, the abnormality must be reported at the same visit (same sample date).

### 5.8.11 Spirometry

Spirometry is performed at all scheduled visits except Visit 2 (Randomization/ Day 1). Two spirometry assessments are performed at Visit 1 (Screening). For each test, the best values for 12 parameters are provided: Forced Expiratory Volume in 1 Second ($FEV_1$) (L), Forced Vital Capacity (FVC) (L), percent-predicted FEV1 (%), percent-predicted FVC (%), FEV1/FVC, Predicted FEV1 (L), Predicted FVC (L), Peak Expiratory Flow (L/s), Forced Expiratory Flow 25-75% (FEF) (L/s), Forced Expiratory Flow 25% (FEF)

(L/s), Forced Expiratory Flow 50% (FEF) (L/s) and Forced Expiratory Flow 75% (FEF) (L/s).

The following endpoints are defined:

- Absolute value, absolute change and percent change in $FEV_1$ and FVC from baseline at any post-baseline analysis visit (up to EOS);
- Occurrence of treatment-emergent decrease in $FEV_1$ or FVC of > 15% from baseline values at any post-baseline analysis visit.

The analysis visits are defined in Section 11.1.1 'Analysis visits'. Absolute value, absolute change and percentage change are calculated for all parameters as defined in Section 11.

The occurrence of treatment emergent abnormalities is assessed at each post-baseline analysis visit for $FEV_1$ (L) and FVC (L), on the value of the percent change from baseline as a decrease greater than 15%.

### 5.8.12 Optical coherence tomography test

The optical coherence tomography test (OCT) is performed at Visit 1 (Screening) and Visit 6 (EOT). The presence/ absence of any abnormality (i.e., Yes/No) and whether the finding is clinically significant is recorded in the eCRF.

### 5.8.13 Ophthalmological examination

Ophthalmological examinations are performed at each visit except Visit 2 (Randomization/ Day 1). The presence/ absence of any abnormality (i.e., Yes/No) and whether the finding is clinically significant is recorded in the eCRF.

### 5.8.14 Physical examination

A complete physical examination is performed at Visit 1 (Screening) and Visit 6 (EOT). A symptom-driven, abbreviated physical examination is performed at all other visits.
The observations are reported according to body system in the eCRF as either normal or abnormal, and whether the finding is clinically significant.

## 5.9 Quality of life variables

The SF-36v2™ questionnaire is used to assess the subject's quality of life. The SF-36v2™ is completed by the subject at Visit 2 (Randomization/ Day 1) and at Visit 6 (EOT).

The following endpoint is defined:

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

Full details of the derivations of the raw and norm-based domain scores and physical and mental component scores, and handling of missing data, are described in Section 11 and Appendix 15.2.

# 6 DEFINITION OF PROTOCOL DEVIATIONS

This section refers to all protocol deviations as recorded in a database according to the specifications provided in the protocol violations code list. They are categorized as:

- Important protocol deviations
  - Protocol deviation at screening before randomization
  - Protocol deviation for eligibility criteria at screening (only for randomized subjects)
  - Protocol deviation after randomization
- Minor protocol deviations

Deviations that lead to exclusion of subjects from the Per-protocol set are described in Section 7.1.3 and in more detail in Section 11.2.3.

# 7 ANALYSIS SETS

## 7.1 Definitions of analysis sets

### 7.1.1 Screened analysis set

The screened analysis set (SCR) includes all subjects who were screened and received a subject number.

### 7.1.2 Full analysis set

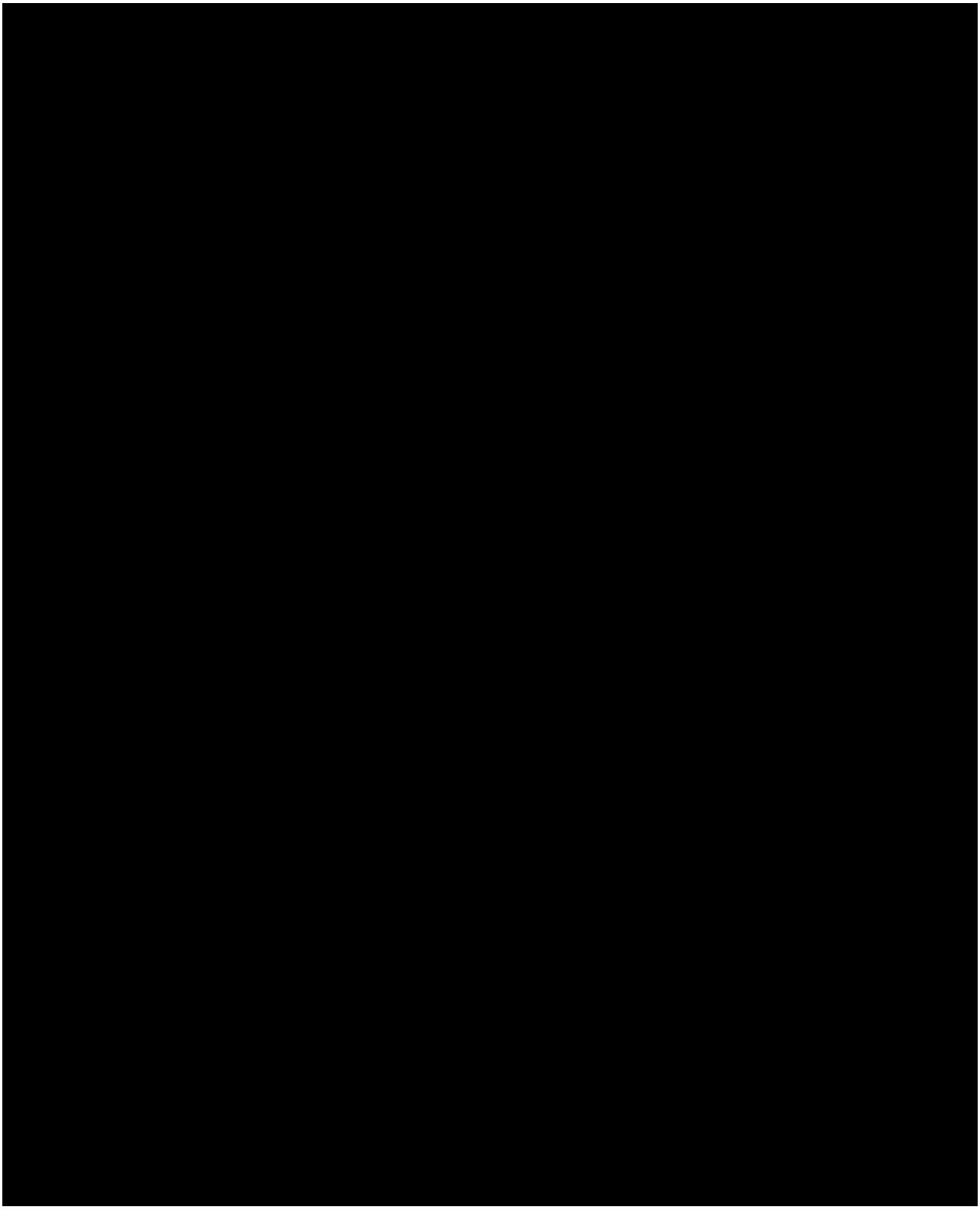
The full analysis set (FAS) includes all subjects randomized to a study treatment. In order to adhere to the intention-to-treat (ITT) principle as far as possible:

- Subjects are evaluated according to the study treatment to which they were randomized (which may be different from the study treatment they have received).

### 7.1.3 Per-protocol analysis set

The Per-Protocol Set (PPS) comprises data from all subjects included in the FAS without relevant deviations which could affect the evaluation of the PD parameters (lymphocyte count) and the exploratory disease activity parameters (SLEDAI-2K, PGA).

The protocol deviations leading to exclusion from the PPS are listed in the below table.



[redacted]

Please note:

- If a subject is excluded from the PDS then he is also excluded from the PPS.
  *Rationale:* Insufficient pharmacodynamic effect is unlikely to show e.g. clinical improvement, but will confound the results.
- [redacted] If a subject presents with such protocol deviation (specifically, pregnancy test not performed 3 weeks apart), but no pregnancy occurred and all subsequent pregnancy tests were consistently negative during the trial, the subject can be included into the PPS.
  *Rationale:* Biologically this subject is not different from included subjects. However, an important protocol deviation has to be reported.
- [redacted]: If a subject presents with such protocol deviation, but the change of the immunologically active medication occurred at or after EOT, the subject can be included in the PPS.
  *Rationale:* The primary endpoint compares the change from baseline to EOT.

### 7.1.4 Safety analysis set

The safety analysis set (SAF) includes all subjects who received at least one dose of study treatment. Unless otherwise stated, any analysis using the SAF uses all available safety data up to EOS.

Subjects are analyzed based on treatment actually received.

### 7.1.5 Other analysis sets

#### *7.1.5.1 Pharmacodynamic Analysis Set*

The Pharmacodynamics Analysis Set (PDS) includes all subjects who received at least 21 days of study treatment, with lymphocyte count measurements at baseline and post-baseline (namely, one sample taken at least 21 days after the first study treatment intake and no later than 7 days after the last study treatment intake with no treatment interruption documented in the first 21 days).

Subjects are analyzed according to the treatment received.

#### *7.1.5.2 Pharmacokinetic Analysis Set*

The pharmacokinetic analysis set (PKS) includes all randomized subjects who received at least one dose of ACT-334441 and provided at least one blood sample for PK evaluation.

Subjects are analyzed based on treatment received.

## 7.2 Usage of the analysis sets

Overall summary of study disposition, screening failures and including reasons for screening failure are summarized using the SCR.

Overview of analysis sets, study completion/discontinuation, protocol deviations, demographics and baseline disease characteristics, medical history and previous/ concomitant medications are summarized for the FAS. Demographics and baseline disease characteristics are also summarized on the PDS.

Study treatment completion/discontinuation, treatment exposure, safety and quality of life are summarized using the SAF.

For pharmacodynamics (PD), the main and supportive analyses are performed on the PDS, FAS and PPS. All other analyses (exploratory disease activity, exploratory biomarkers) are performed on the FAS and on the PPS.

The PKS is used for the analyses of the PK endpoints.

Listings are prepared using the SCR, unless otherwise specified.

Table 9 rovides an overview of the analysis set usage for the main variables of the study.

**Table 9 Overview of the different analysis sets and their usage**

| Analyses/ Data Displays | Screened analysis set (SCR) | Full analysis set (FAS) | Safety Analysis Set (SAF) | Per-protocol Analysis set (PPS) | Pharmaco-dynamics Analysis set (PDS) | Pharmaco-kinetics Analysis set (PKS) |
|---|---|---|---|---|---|---|
| Subject disposition | ✓ | ✓ | (✓) | | | |
| Protocol deviations | | ✓ | | | | |
| Analysis sets | | ✓ | | | | |
| Demographic characteristics | | ✓ | (✓) | | ✓ | |
| Baseline disease characteristics | | ✓ | | | ✓ | |
| Medical history | | ✓ | | | | |
| Previous and concomitant medications | | ✓ | | | | |
| Treatment exposure/ compliance | | ✓ | ✓ | | | |
| Main PD endpoints | | ✓ | | ✓ | ✓ | |
| Other PD endpoints | | ✓ | | | | |
| Safety | | | ✓ | | | |
| Pharmacokinetic variables | | | | | | ✓ |
| --Exploratory disease activity | | ✓ | | ✓ | | |
| Quality of life | | | ✓ | | | |
| Exploratory biomarkers | | ✓ | | ✓ | | |

# 8 DEFINITION OF SUBGROUPS

Not applicable as no subgroups were defined in the protocol. Due to the small number of subjects per dose it was decided that subgroups would not be explored in the CSR SAP.

# 9 GENERAL STATISTICAL METHODOLOGY

This section describes in general terms the statistical models and methods applied.

## 9.1 Statistical methods for binary data

### 9.1.1 Confidence interval for a proportion

*Statistical considerations*.

For proportions, two-sided $(1-\alpha)\%$ Clopper-Pearson Confidence Intervals (CIs) [Clopper 1934] are calculated.

*SAS Code*

The Clopper-Pearson CIs are calculated using SAS code similar to:

```
data events;
  set events; * containing - for each group - numbers of subjects (n) and 'events' (e);
  p=round(100*e/n);
  lo=round(100*betainv(.025, e, n-e+1));
  up=round(100*betainv(.975, e+1, n-e));
  if lo=. then lo=0;
  if up=. then up=100;
run;
```

## 9.2 Statistical methods for continuous data

### 9.2.1 Multiple Comparison Procedure and Modeling (MCP-Mod) approach

Dose-response data are analyzed using the MCP-Mod approach [Bretz 2005]. In brief, this methodology consists of two steps:

1. Multiple Comparisons Procedures (MCP) step to establish a dose-response signal (i.e., the dose-response curve is not flat) using multiple comparison procedures.
2. Modeling (Mod) step to estimate the dose-response curve and target doses using modeling techniques.

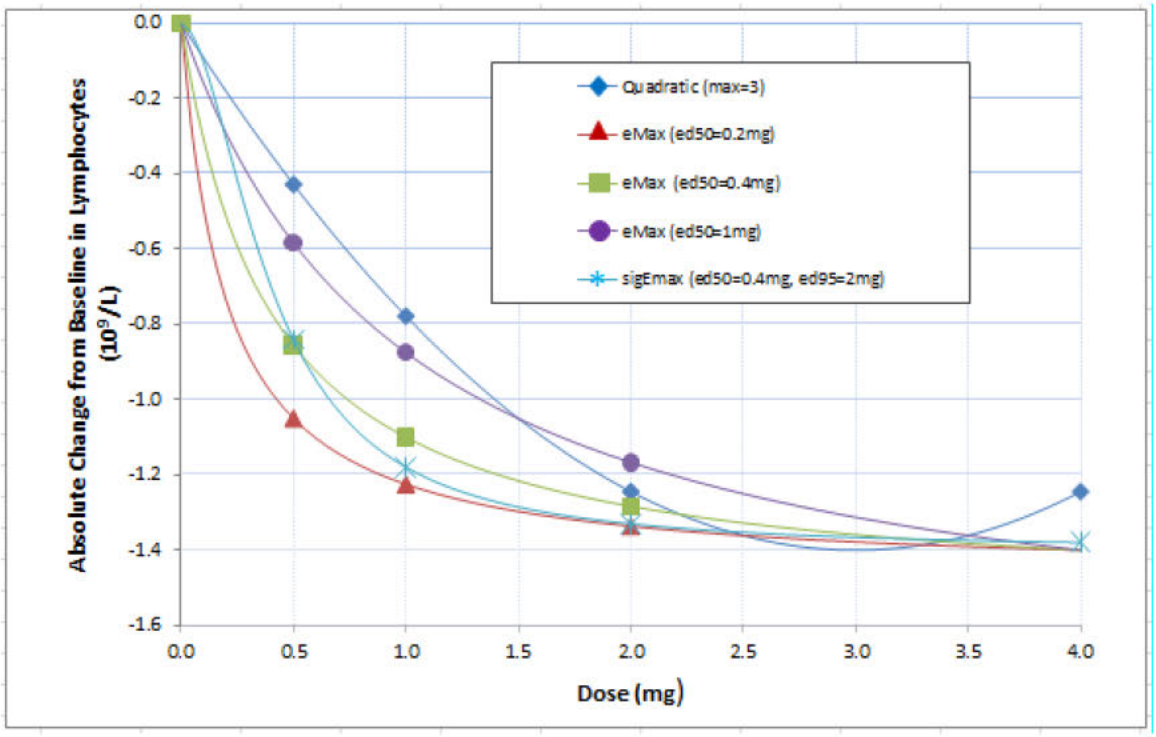
In this study five models have been pre-specified in the protocol for consideration in all MCP-Mod analyses: $E_{max}$ (with three different starting values for ED50), quadratic, and sigmoidal $E_{max}$. See Table 10 for the parameterization of the dose-response models and Figure 2 as illustration of their basic shapes. The initial values for the parameters are needed in the MCP step of the procedure. They will be estimated in the Mod step based on the actual data.

**Table 10 Parameterization of Models considered in MCP-Mod analyses**

| Model | Response* | Initial value(s) for parameters |
|---|---|---|
| Emax | E0 + Emax • *dose*/($ED_{50}$ + *dose*) | $ED_{50}$ = 0.2 |
| Emax | E0 + Emax • *dose*/($ED_{50}$ + *dose*) | $ED_{50}$ = 0.4 |
| Emax | E0 + Emax • *dose*/($ED_{50}$ + *dose*) | $ED_{50}$ = 1.0 |
| Quadratic | E0 + beta1 • dose + beta2 • dose^2 | beta2/beta1 = -0.167 |
| Sigmoidal Emax | E0 + Emax • *dose*^h/($ED_{50}$^h + *dose*^h) | $ED_{50}$=0.4, h=1.829 |

*Dose = 0, 0.5, 1.0, 2.0 and 4.0

**Figure 2 Dose-response curves considered in MCP-Mod procedure**




The null hypothesis of 'no dose-response' will be rejected if at least one of the five multiple comparison tests has an adjusted p-value < 0.05. All statistically significant models (i.e., with a multiplicity adjusted p-value < 0.05) are fitted in the Mod step and for each model Akaike's Information Criterion (AIC) is calculated. The smaller the value of AIC (= model deviance + 2 times the number of model parameters), the better the fit. The analysis is performed using the R-package *DoseFinding* [Bornkamp 2016].

The basic R-code is similar to:

```
library(DoseFinding)
doses <- c(0, 0.5, 1.0, 2.0, 4.0)
s <- sEmax(ed50=0.4, ed95=2)
candMod <- Mods(      emax = c(0.2, 0.4, 1.0)
               ,   sigEmax = s
               , quadratic = -0.167
               ,     doses = doses
               ,   placEff = 0
               ,    maxEff = -70% reduction from of the mean baseline value
               , direction = "decreasing"
               )
MMfit <- MCPMod(       dose = TRTDOSEP
                ,      resp = CHG
                ,      data = LYM
                , addCovars = ~BASE
                ,    models = candMod
                ,     delta = -1.4(arbitrary to run model, target dose not estimated)
                )
```

In the *Mods* function call the candidate models are specified, together with the assumed placebo and maximum effects. In the call to the *MCPMod* function, LYM is a data frame with objects TRTDOSEP (Planned Dose for Period 01), CHG (for Absolute change from baseline), and BASE (for Baseline Value) and delta is a target difference vs. placebo. The object *MMfit* is summarized to obtain the MCP test, parameter estimates, target dose and AIC. These elements go in a summary table. The object is plotted to display the fitted dose-response curves.

### 9.2.2 Analysis of Variance

For the analysis of quality of life variables, on the absolute change from baseline for each score, the mean treatment differences for each ACT-334441 dose compared to placebo and their corresponding 95% confidence intervals are provided using a One-way analysis of variance (ANOVA) with treatment group as a factor in the model.

*Statistical considerations*

In analysis of variance, a continuous response variable, known as a *dependent variable*, is measured under experimental conditions identified by classification variables, known as *independent variables*. The variation in the response is assumed to be due to effects in the classification, with random error accounting for the remaining variation.

Adjusted means are calculated by fitting the following fixed effects analysis of variance (ANOVA) model,

$$Y_{ik} = \mu + \alpha_i + \varepsilon_{ik}$$

where

- $Y_{ik}$ is the absolute change from baseline of the $k^{th}$ subject in treatment group i;
- $\mu$ is the overall mean;
- $\alpha_i$ is the main effect of treatment group i;

- $\varepsilon_{ik}$ are error terms which are normally distributed with a mean of zero and variance $\sigma^2$ ( $\varepsilon_{ijk} \sim N(0,\sigma^2)$ ( $\varepsilon_{ijk} \sim N(0,\sigma^2)$ ( $\varepsilon_{ijk} \sim N(0,\sigma^2)$ ).

*Validation:*

The normal distribution of the variables is evaluated by means of the Shapiro-Wilk test and graphically (stem and leaf plot and normal probability plot) in each treatment group. The homogeneity of variances across treatment groups is assessed using Hartley's test.

*SAS Code*

The SAS statements used to calculate the means and the between-group differences are similar to:

```
ods output ESTIMATES = DIFF;
ods output LSMeanCL = LSM;

proc glm data = changes ;

  by TESTNO TESTCD TEST  ;
  class TRTGRPPS;
  model CHANGE = TRTGRPPS/ss3;
  lsmeans TRTGRPPS / tdiff stderr cl;

  estimate "Group A minus Group E" TRTGRPPS  1   0   0   0  -1;
  estimate "Group B minus Group E" TRTGRPPS  0   1   0   0  -1;
  estimate "Group C minus Group E" TRTGRPPS  0   0   1   0  -1;
  estimate "Group D minus Group E" TRTGRPPS  0   0   0   1  -1;

run;
quit;
```

### 9.2.3 Analysis of Covariance

For analyses involving the absolute and/or the percent changes from baseline for a studied parameter, the mean treatment differences for each ACT-334441 dose compared to placebo and their corresponding 95% confidence intervals are provided using an Analysis of Covariance (ANCOVA) including baseline value as a covariate and with treatment group as a factor in the model.

*Statistical considerations*

The model used for this analysis is a general linear model studying treatment effect with baseline value of studied parameter (as fixed effect) as covariate:

$$Y_{ik} = \gamma X_{ik} + a_i + \varepsilon_{ik}$$

where:

- $Y_{ik}$ is the response from the $k^{th}$ subject that received treatment i,
- $X_{ik}$ is the baseline value of the analysed variable for the $k^{th}$ subject that received treatment i,
- $\gamma$ denotes the common slope of the baseline covariate,

- $a_i$ denotes the intercept of the $i^{th}$ treatment,
- $\varepsilon_{ik} \sim$ iid $N(0, \sigma_\varepsilon^2)$ denotes the experimental unit error associated with the $k^{th}$ subject that received treatment i.

The model can also be written in matrix notation as:

$$Y = X\beta + \varepsilon$$

where:

- Y is the vector of observations,
- X is the design matrix of the fixed effects and baseline factors,
- $\beta$ is the unknown vector of the fixed effects and baseline factors,
- $\varepsilon$ is the unobserved vector of independent and identically distributed random errors, such as $\varepsilon \sim N(0,R)$ where $R = \sigma_\varepsilon^2\ \sigma_\varepsilon^2\ \sigma_\varepsilon^2 I_n$.

Estimations:

The estimate $\hat{\beta}$ of $\beta$ is given by:

$$\hat{\beta} = (X'X)^- X'Y$$

$$\text{with } Var(\hat{\beta}) = (X'\hat{R}^{-1}X)^- = \hat{C}$$

Confidence interval:

The Sum of Squares (SS) using a LS-means contrast is used for computing $SS_{(H0:\ L\beta = 0)}$ (where $L\beta$ denotes a linear estimable combination of the fixed effects):

The 95% confidence interval of $\hat{\beta}\ \hat{\beta}\ \hat{\beta}$ is given by:

$$L\hat{\beta} \pm t_{\hat{\nu},0\,975}\ \sqrt{L\hat{C}L'}$$

where:

- $\hat{\nu}$ denotes the approximate degrees of freedom by Satterthwaite,
- $t_{\hat{\nu},0\,975}$ is the $0.975^{th}$ quantile of the t-distribution with $\hat{\nu}$ degrees of freedom.

The least-squares approach provides estimates of the linear parameters that are unbiased and have minimum variance among linear estimators.

The treatment effect is estimated by the difference of the LS-means of each studied treatment group.

*Validation:*

Residual normality and homoscedasticity will be studied using graphs and descriptive statistics.

*SAS Code*

The SAS statements used to calculate the adjusted means and the between-group differences are similar to:

```
ods output ESTIMATES = DIFF;
ods output LSMeanCL = LSM;

proc glm data = changes ;

  by TESTNO TESTCD TEST  ;
  class TRTGRPPS;
  model CHANGE = TRTGRPPS BASELINE /ss3;
  lsmeans TRTGRPPS / tdiff stderr cl;

  estimate "Group A minus Group E" TRTGRPPS  1   0   0   0  -1;
  estimate "Group B minus Group E" TRTGRPPS  0   1   0   0  -1;
  estimate "Group C minus Group E" TRTGRPPS  0   0   1   0  -1;
  estimate "Group D minus Group E" TRTGRPPS  0   0   0   1  -1;

run;
quit;
```

# 10 STATISTICAL ANALYSES

This study is performed in two parts: part A with four treatment groups (including 0.5 mg, 1 mg, or 2 mg of ACT-334441 and placebo control) and part B with two treatment groups (including 4 mg of ACT-334441 and placebo control). In all analyses the assumption is made that the data from part A and part B can be combined, in particular the subjects randomized to placebo in any part of the study are analyzed as one group. This assumption is investigated for the main pharmacodynamics endpoint in a sensitivity analysis.

## 10.1 Overall testing strategy

An optimized contrast test according to the Multiple Comparison Procedure and Modeling (MCP-Mod) approach [Bretz 2005] for each considered dose-response model is performed. The existence of dose-response effects on the change from baseline in lymphocytes counts at EOT is tested using the maximum of the model-based contrast tests using a one-sided 0.05 alpha. Multiplicity adjusted p-values are calculated using the Dunnett-distribution which controls the type 1 error.

All other statistical testing are performed at a two-sided significance level of 0.05 using 95% Confidence Limits (CLs).

In all analyses of secondary and other efficacy variables, no correction will be made for multiple testing.

## 10.2 General rules for data presentations

This section describes the general rules applied for all data displays, unless otherwise specified in each corresponding section.

SAS version 9.4 is used for the preparation of all tables, listings and figures.

Listings are sorted by country, site, treatment group, subject number and timing (dates, times and/or visits as applicable) and will display all subjects.

Names of outputs begin with T for Table, F for Figure and L for Listing, the next 2 digits represent the ADaM dataset the output is based on (e.g. LB for laboratory), followed by a numerical number and finally there is a suffix that indicates the analysis set (e.g., SAF for Safety Analysis Set).

Data are listed and summarized using appropriate descriptive statistics:

- Number of non-missing observations, mean, standard deviation, minimum, Q1, median, Q3 and maximum for continuous variables.
- Number of non-missing observations, and frequency with percentage per category for categorical variables. Denominators for percentages are the number of subjects in the pertinent analysis set and treatment group, unless otherwise specified.

### Table layout and format

- Placebo is the first column on the left with ACT-334441 dose groups ordered (left to right) in ascending order of dose and where appropriate the total is in the right most column.
- Placebo corresponds to the pooled subjects randomized in 'Placebo Control (Part A)' and 'Placebo Control (Part B)'.

Example table layout:

| | Placebo (N=XX) | ACT-334441 0.5 mg (N=XX) | ACT-334441 1.0 mg (N=XX) | ACT-334441 2.0 mg (N=XX) | ACT-334441 4.0 mg (N=XX) | Total (N=XX) |
|---|---|---|---|---|---|---|
| <XXXXXXXXXX> | XX (XX.X) | XX (XX.X) | XX (XX.X) | XX (XX.X) | XX (XX.X) | XX (XX.X) |

## 10.3 Display of subject disposition, protocol deviations and analysis sets

A listing of the randomization scheme and codes is produced for randomized subjects only (ICH E3 16.1.7).

### 10.3.1 Subject disposition

An overview of the recruitment for each country/site is presented for the FAS by treatment group and overall in a table.

An overview of the subject disposition over the course of the study is presented for the SCR by treatment group (except for Screened and Re-Screened which are only summarized for the total column) and overall in a table and comprises the number of subjects:

- Screened,
- Re-screened
- Randomized
- Treated
- Completed/ prematurely discontinued the study treatment
- Completed/ prematurely discontinued the study

#### *10.3.1.1 Screening failures*

The number of subjects screened, randomized, failed screening and reasons for screening failure are summarized for the SCR in a table and in a listing. For subjects that fail screening twice, only the reason of the last failure is reported in the summary table. All reasons for screening failure are included in the listing together with the screening failure date.

#### *10.3.1.2 Discontinuation from study*

For the FAS, the number and percentage of subjects who completed the study as per protocol, discontinued the study and the reasons for study discontinuation are summarized by treatment group and overall. Study completion/discontinuation details and the reasons for study discontinuation are also presented in a listing.

#### *10.3.1.3 Discontinuation of study treatment*

For the SAF, the number and percentage of subjects who completed the study treatment as per protocol, discontinued the treatment prematurely and the reasons for study treatment discontinuation are summarized by treatment group and overall. The study treatment completion/discontinuation details and reasons for study treatment discontinuation are also presented in a listing.

### 10.3.2 Protocol deviations

Minor and important protocol deviations are displayed in a listing. This listing includes all deviation descriptions, identifiers and categories. A second listing may be generated to list the ‘other’ protocol deviations. Subjects without any protocol deviations are not included in these listings.

Protocol deviations (minor and important) are summarized by treatment group and overall for the FAS. Protocol deviations are also summarized by country and treatment group for the FAS.

### 10.3.3 Analysis sets

The number and percentage of subjects included and excluded in each analysis set are summarized in a table, by treatment group and overall for the FAS.

The inclusion/ exclusion of subjects in each analysis set and the reasons are listed for all screened subjects.

In addition, the number and percentage of subjects included in the FAS but excluded from the PPS are summarized in a table as well as the reason of exclusion.

A listing is produced to present the subjects for whom the randomization code was broken at site or sponsor office. It contains the date of unblinding and the reason for unblinding.

## 10.4 Analyses of subject characteristics

### 10.4.1 Demographics

Demographic characteristics [variables defined in Section 5.2.1] are summarized by treatment group and overall, using descriptive statistics for continuous and categorical data using the FAS. Body weight and height are tabulated by gender.

A listing is produced on the SCR for the demographic characteristics. Smoking habits are presented in a separate listing for the SCR.

### 10.4.2 Baseline disease characteristics

Baseline disease characteristics [defined in Section 5.2.2] are summarized by treatment group and overall using appropriate descriptive statistics for the FAS. The variables related to the SLE relevant disease history and history of detectable ANA or anti-dsDNA testing are summarized in one table, and the variables related to modified SLEDAI-2K at baseline (active descriptors, sub-scores and scores) and PGA in a second table, and exploratory biomarkers (anti-Smith, anti-cardiolipin [IgA, IgG, IgM], anti-ribosomal P) in a third table. Listings are presented for the SCR.

### 10.4.3 Other baseline characteristics

Other baseline disease characteristics [defined in Section 5.2.3] are listed for the SCR.

### 10.4.4 Medical history

Previous and concomitant medical history (diseases/diagnoses) [defined in Section 5.2.4] are summarized separately, by treatment group and overall using the FAS. The number and percentage of subjects with at least one medical history are presented overall and by SOC and individual PT within each SOC.

SOCs/PTs are sorted by descending frequency of the number of subjects in the highest-dose group. If the frequencies of SOCs or PTs are the same, alphabetical order is used.

One listing is produced for the SCR.

### 10.4.5 Previous and concomitant therapies

Previous and concomitant therapies [defined in Section 5.2.5] are summarized separately as follows:

- 'Previous non-SLE therapies'
- 'Study treatment concomitant non-SLE therapies'
- 'Previous SLE therapies'
- 'Study treatment concomitant (Background) SLE therapies'

Number and percentage of subjects having received at least one therapy are presented overall, by ATC class (level 4) and PT within each ATC class. ATC classes are sorted by descending frequency of the number of subjects in the highest-dose treatment group. If the frequencies of ATC class are the same, alphabetical order is used. The same rule applies for PTs within ATC class.

### 10.4.6 Other subject characteristics

The information 'woman of childbearing potential' as well as the contraceptive methods and the results of the serum and urinary pregnancy tests conducted during study are presented in a listing for the SCR.

## 10.5 Analysis of study treatment exposure and compliance

### 10.5.1 Exposure

Exposure characteristics for the study treatment [defined in Section 5.3.1] are summarized by treatment group using descriptive statistics for continuous and categorical data, for the SAF. The listing is produced for the SCR The study treatment duration (days) is also tabulated by end of treatment status (completed, premature discontinuation) and overall.

Study treatment interruptions data [defined in Section 5.3.4] are summarized by treatment group using descriptive statistics for categorical data using the SAF. The reasons for treatment interruptions are included in the exposure listing.

### 10.5.2 Compliance with study treatment

The overall compliance to the study treatment [defined in Section 5.3.2] is summarized by treatment group using descriptive statistics for continuous and categorical data, for the FAS. The listing is produced for the SCR.

## 10.6 Analysis of the main pharmacodynamic variable(s)

This section describes the analysis of the main pharmacodynamic endpoint (i.e., change in lymphocyte count from baseline to EOT), as defined in in Section 5.5.1.

The objective is to demonstrate a dose response of ACT-334441 on the lymphocyte count reduction from baseline in peripheral blood in subjects with SLE.

### 10.6.1 Hypothesis and statistical model

The null hypothesis is that there is no dose response in terms of lowering the lymphocyte count (p, which is a negative value for 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-

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

### 10.6.2 Handling of missing data

In the main analysis the lymphocyte count is analyzed at EOT which for the majority of patients is Week 12. This is effectively imputation utilizing the LOCF technique i.e., using data from Week 4 (i.e. at least 21 days after the first study treatment intake) later to impute for missing Week 12 values. This is justified given the maximum effect on lymphocyte counts is expected to be achieved at 4 weeks, since in the AC-064-101 study that investigated cenerimod in healthy subjects, multiple doses resulted in mean lymphocyte count-time profiles that "plateaued" at 20–23 days of treatment in all dose groups [Cenerimod IB, section 5.2.5.2]. Subjects with missing baseline lymphocyte counts and/or no lymphocyte count at or after Week 4 are excluded from the main analysis on the PDS.

The analysis by visit includes a 'Complete Case' analysis at Week 12 which allows for an assessment of the effect of LOCF. The analysis on the FAS is also at EOT which uses LOCF from the last post-baseline visit with no time restriction.

### 10.6.3 Main analysis

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

Definition of a set of likely dose-response relations (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
- 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 is 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 is fitted to the data. As a sensitivity analysis, all remaining significant models are fitted to the data, and model-based dose response estimates are calculated. A table summarizing the t-statistic and adjusted p-value for each curve is presented by decreasing adjusted p-value.

A plot of the estimated dose-response curve with 95% CIs is presented along with the observed response at each dose. A table summarizing the estimates (and standard error) of each dose-response curve parameters and the AIC will also be presented.

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

This analysis is performed on the PDS.

### 10.6.4 Supportive/sensitivity analyses

These analyses (MCP-Mod and ANCOVA) are replicated on the FAS.

The assumption that the data from part A and part B can be pooled in a single analysis [Section 10] is investigated by performing separate ANCOVAs for the two parts. Within part A, comparisons are conducted between first 3 treatment groups (0.5 mg, 1.0 mg and 2.0 mg) and placebo (Part A) and within part B between the 4$^{th}$ treatment group (4.0 mg) and placebo (Part B). The differences vs. placebo obtained from these models are compared with the corresponding differences from the main analysis. This sensitivity analysis is performed for the PDS and FAS.

### 10.6.5 Subgroup analyses

Not applicable.

## 10.7 Analysis of the other pharmacodynamic variables

Quantitative descriptive statistics for absolute value, absolute change from baseline and percent change from baseline are presented by analysis visit and treatment group. These analyses are performed on the FAS.

## 10.8 Analysis of other efficacy variables

#### *10.8.1.1 Exploratory disease activity endpoints*

- Main analysis

For all the SLEDAI-2K variables (including number of affected joints) and the PGA variable [defined in Section 5.7.3.1], an ANCOVA model including baseline value as a covariate and treatment group as a factor is applied to the absolute change from baseline to EOT for each variable on the FAS and PPS. The difference in least squares means between each ACT-334441 dose and placebo is computed and the 95% confidence intervals for the differences are estimated.

- Secondary analysis

For the SLEDAI-2K (including number of affected joints) and PGA variables [defined in Section 5.7.3.1], separate summaries of quantitative descriptive statistics for absolute values, absolute change from baseline and percent change from baseline are presented by analysis visit and treatment group.

For modified SLEDAI-2K total score, the summaries are also presented stratified by baseline category (baseline total SLEDAI-2K score < 6, baseline total SLEDAI-2K score ≥ 6, overall).

In addition, for the modified total SLEDAI-2K total score, the occurrence of an increase from baseline > 3is tabulated by analysis visit and treatment group.

The evolution of the values over time (PGA score, modified SLEDAI-2K score and number of affected joints) is provided in graphical format for each parameter from baseline to EOS visit (one figure per endpoint, one boxplot per treatment group and analysis visit).

All these analyses are performed on the FAS.

Listings are produced on the SCR. For PGA and SLEDAI-2K score, it displays the absolute values, the absolute change and the percent change from baseline to each post-baseline assessment, the values taken into account for the analysis are flagged.

In addition, for the modified SLEDAI-2K, the value at each analysis visit for each descriptor is included in a listing.

#### *10.8.1.2 Exploratory biomarker*

For exploratory biomarkers [defined in Section 5.7.3.2], separate summaries of quantitative descriptive statistics for absolute values, absolute change and percent change from baseline are presented by analysis visit and treatment group (including geometric mean and associated 95% CI).

For exploratory biomarkers for which categories have been used, the number and percentage of subjects with a value in each category are summarized by analysis visit and treatment group.

## 10.9 Analysis of safety variables

The SAF is used to perform all safety analyses.

For the tabulations by analysis visit and time points (e.g. values over time for blood pressure measurements, ECG), if multiple values are available (unscheduled visits/ retests), the examination closest to the planned visit/ time point is chosen [see Section 11 for more details].

However, for the summaries of treatment-emergent abnormalities over the study period, all safety data collected up to EOS are considered.

All safety data are included in listings, with specific flags for the treatment-emergent or values taken into account in the analyses.

### 10.9.1 Adverse events

All AEs captured from signature of informed consent up to EOS are reported in the subject listings which include data collected in eCRF as well as the coded terms (SOC, PT) and a flag for treatment-emergent.

For displays of AEs summarizing counts on the event level (i.e. total number of events), the denominator for calculating percentage is the number AEs occurring in a given treatment group. For displays of events by period of onset, the denominator is the number of AEs occurring in a given treatment group during the relevant period of onset. For displays of AEs summarizing counts on the subject level (i.e. total number of subjects experiencing events), the denominator for percentages is the number of subjects in the SAF for a given treatment group.

For all tables, aggregate counts for total number of subjects, events and associated percentages, and total number of subjects, events and associated percentages per SOC and PT are also included (as applicable).

For tables presented by SOC and PT, SOCs/PTs are sorted by descending frequency of the number of subjects in the highest-dose group. If the frequencies of SOCs or PTs are the same, alphabetical order is used.

For tables presented by PT, PTs are sorted by descending frequency of the number of subjects in the highest-dose treatment group. If the frequencies of PTs are the same, alphabetical order is used.

The following displays of adverse events are provided:

- An overview of treatment-emergent adverse events (TEAEs) by treatment group with the following counts and percentages:
  - Subjects with at least one TEAE;
  - Subjects with at least one serious TEAE;
  - Subjects with fatal serious TEAE;
  - Subjects with at least one non-serious TEAE;
  - Subjects with at least one severe TEAE;
  - Subjects with at least one drug-related TEAE;
  - Subjects with at least one drug-related serious TEAE;
  - Subjects with at least one TEAE leading to study drug discontinuation.
- The number and percentage of TEAEs, and subjects experiencing TEAEs, by period of onset (on Day 1 post-dose, after Day 1, overall), treatment group, SOC and PT.
- The number and percentage of subjects with TEAEs by treatment group and PT.
- The number and percentage of subjects with related TEAEs, by treatment group and PT. If an adverse event (PT) occurs more than once for a subject during the treatment period, the strongest relationship to study treatment is taken into account.
- The number of subjects with TEAEs, by treatment group, severity/ intensity and PT. If an adverse event (PT) occurs more than once for a subject during the treatment period, the maximal severity is taken into account.

### 10.9.2 Deaths and other serious adverse events

#### *10.9.2.1 Death*

<u>All deaths</u>

The number and percentage of subjects who died after the start of the treatment are summarized per treatment group, including the reported causes of death. A listing including all deaths is provided.

<u>Fatal SAEs</u>

The following displays of fatal SAEs are provided:

- The number and percentage of subjects with fatal SAEs by treatment group, SOC and PT.

- The number and percentage of subjects with fatal SAEs, by treatment group and PT.
- The number and percentage of subjects with related fatal TEAEs by treatment group and PT.

Fatal SAEs are included and flagged in the listing of all SAEs.

#### *10.9.2.2 Serious adverse events*

The following displays of SAEs are provided:

- The number and percentage of treatment-emergent SAEs, and subjects experiencing treatment-emergent SAEs, by period of onset (on Day 1 post-dose, after Day 1, overall), treatment group, SOC and PT.
- The number and percentage of subjects with treatment-emergent SAEs by treatment group and PT.
- The number and percentage of subjects with related treatment-emergent SAEs, by treatment group and PT. If an adverse event (PT) occurs more than once for a subject during the treatment period, the strongest relationship to study treatment is taken into account.

A listing including all SAEs is provided.

#### *10.9.2.3 Adverse events leading to study treatment discontinuation*

The following displays of TEAEs leading to study treatment discontinuation are provided:

- The number and percentage of subjects experiencing TEAEs leading to study treatment discontinuation, by period of onset (on Day 1 post-dose, after Day 1, overall), treatment group, SOC and PT.
- The number and percentage of subjects with TEAEs leading to study treatment discontinuation by treatment group and PT.
- The number and percentage of subjects with related TEAEs leading to study treatment discontinuation, by treatment group and PT

A listing including all AEs leading to study treatment discontinuation is provided.

#### *10.9.2.4 Other significant adverse events*

The number and percentage of subjects who experienced after the first study treatment at least one adverse event of special interest (AESI), at least one AESI within each category and at least one AESI within each preferred term is summarized by treatment group.

The relative risk of having a specific AESI in each dose group compared to placebo is summarized in a table and presented in a figure (forest plots).

A listing including all AESIs is provided.

### 10.9.3 Electrocardiography (ECG)

#### *10.9.3.1 12-lead ECG variables and findings*

The following displays of ECGs are provided:

- Quantitative descriptive statistics for absolute values of ECG parameters by treatment group and analysis visit and time point.
- Quantitative descriptive statistics for the absolute change from baseline to 1h, 2h, 3h, 4h, 5h and 6 h post-dose on Day 1 and each post-baseline analysis visit by treatment group and parameter.
- Boxplots of absolute values at baseline and all post-baseline analysis visits and time points: one figure per parameter and per treatment group. Notable abnormality thresholds are displayed on the plots as an overlay.
- Notable ECG abnormalities for QTcB, QTcF, HR, PR and QRS are summarized by treatment group by presenting the number and percentage of subjects with any abnormality at each post-baseline analysis visit and time point, at any time on Day 1 (from 1 hour post-dose to discharge), at any time after Day 1 (from discharge on Day 1 up to EOT), and at any time post-baseline (from 1 hour post-dose to EOS), 95% Clopper-Pearson confidence intervals are presented for the proportions.
- The number and percentage of subjects with any treatment-emergent ECG qualitative abnormalities at any time (ECG findings) by category and reported term are summarized by treatment group.

The denominator for percentages is the number of subjects with at least one post-baseline assessment in the considered interval.

All ECG data (parameters and findings) are listed by treatment group, subject and visit. All post-treatment notable abnormalities are flagged and qualitative abnormalities (as transferred by the ECG central reader) are listed.

#### *10.9.3.2 24 hour Holter-ECG*

Quantitative descriptive statistics are presented for the hourly mean heart rate (bpm) by time interval for measurements performed on Visit 2 (Randomization/ Day 1).

The hourly records are time-matched between Visit 1 (Screening) and Visit 2 (Randomization/ Day 1) and quantitative descriptive statistics for the corresponding change by time interval are presented.

The evolution of the values over time for the hourly mean heart rate (bpm) on Visit 2 (Randomization/ Day 1) is provided in graphical format (mean and 95% CI for the absolute value for each time interval and treatment group).

The evolution of the change from time-matched screening holter on day 1 for the hourly mean heart rate (bpm) is similarly provided in a graphical format (mean and 95%CI for the time-matched change for each time interval and treatment group)

Treatment-emergent Holter-ECG findings are tabulated by treatment group.

All Holter-ECG data are listed by treatment group, subject and visit. A listing of all Holter-ECG abnormalities is also provided.

### 10.9.4 Laboratory tests

Descriptive summary statistics by analysis visit and treatment group are provided for observed values and absolute changes from baseline by category (hematology/ coagulation, chemistry, urinalysis). Data are displayed in SI units as provided by the central laboratory.

Values from local labs are not included in the different summaries but are included in the listings.

For categorical urinalysis parameters (dipstick), qualitative descriptive statistics for recorded values are presented by parameter and visit.

Treatment-emergent laboratory abnormalities are summarized by lab category, parameter and severity over the study treatment period. For each parameter, the severity is based on the position of the value against reference ranges (central laboratory) and additional thresholds for significance (see appendix 7 of the study protocol) and the worst abnormality is considered in each direction separately (Low and High). In addition, for the liver tests, the number and percentages of subjects with values above the normal ranges, or with abnormal values that are of a certain size (e.g., twice the upper limit of the normal ranges; see section 5.1.10.5, figure 3 of the study protocol) are presented along with their 95% Clopper-Pearson confidence intervals. For each parameter, the maximum highest value recorded during the treatment period is taken into account.

The denominator for percentages is the number of subjects with at least one post-baseline assessment.

All data are presented in the listings:

- hematology, chemistry, coagulation, urinalysis
- urinary dipstick
- viral serology (if assay is required)/ tuberculosis test results are listed along with the other baseline characteristics

- serum and urinary pregnancy tests results are listed along with the childbearing potential information

### 10.9.5 Vital signs and body weight

For body weight, a summary table presenting the value at baseline, value at Visit 6 (EOT) and the change from baseline is produced by treatment group.

Standing SBP and DBP (mmHg) are not included in the summary tables but included in the listings.

For supine SBP and DBP (mmHg), the following displays are provided:

- Quantitative descriptive statistics for absolute values by treatment group and analysis visit and time point.
- Quantitative descriptive statistics for the absolute change from baseline to 1h, 2h, 3h, 4h, 5h and 6 h post-dose on Day 1 and each post-baseline analysis visit by treatment group and parameter. This table is repeated for the measurements taken on day of study drug re-initiation, if applicable.
- Boxplots of absolute values at baseline and all post-baseline analysis visits and time points: one figure per parameter and per treatment group. Notable abnormality thresholds are displayed on the plots as an overlay.
- Notable BP abnormalities are summarized by treatment group by presenting the number and percentage of subjects with any abnormality at each post-baseline analysis visit and time point, at any time on Day 1 (from 1 hour post-dose to discharge), at any time after Day 1 (from discharge on Day 1 up to EOT), and at any time post-baseline (from 1 hour post-dose to EOS), 95% Clopper-Pearson confidence intervals are presented for the proportions.

The denominator for percentages is the number of subjects with at least one post-baseline assessment in the considered interval.

All data (values and changes) are listed by treatment group, subject and visit. All marked abnormalities are flagged.

### 10.9.6 Spirometry

Quantitative descriptive statistics are presented by parameter, by analysis visit and treatment group. In addition, a summary table presenting the absolute change from baseline to each visit up to EOS is produced. Similarly the percent change from baseline to each visit up to EOS are presented by visit and by treatment group.

The number and percentage of subjects with a decrease in $FEV_1$ or FVC of > 15% from baseline value is provided for each visit, by analysis visit and treatment group, each with 95% Clopper-Pearson confidence intervals. In addition, the number and percentage of

subjects with a 15% decrease in $FEV_1$ or FVC at one visit, 2 consecutive visits, 3 consecutive visits, and more than 3 visits during the treatment period is presented.

The evolution of the values over time is provided in graphical format for $FEV_1$ (L), FVC (L) and $FEV_1$/FVC (one figure per parameter: one boxplot per treatment group and analysis visit, from baseline to EOS).

All data (values and changes) are listed by treatment group, subject and visit. All marked abnormalities are flagged.

### 10.9.7 Physical examination

A listing presents the findings of physical examination (Clinical significance and details) by treatment group, subject number, body system and visit number.

### 10.9.8 Ophthalmological examination and OCT

A listing presents the findings of ophthalmological examination (Clinical significance and details) by treatment group, subject number, visit and by type of examination (optical coherence tomography test, ophthalmological examination).

### 10.9.9 Echocardiography

A listing presents the findings of echocardiography (Clinical significance and details) by treatment group, subject number and visit.

## 10.10 Analysis of quality of life variables

For each score (8 domain scores, 2 component scores), quantitative descriptive statistics are presented for each analysis visit (baseline and EOT) and for the change from baseline to EOT by treatment group for the SAF. Additionally, the mean treatment differences for each ACT-334441 dose compared to placebo and their corresponding 95% CIs are provided using an ANOVA with treatment group as a factor in the model.

If the data are non-normally distributed or should the assumptions underlying the ANOVA model (normality of the residuals, homogeneity of the variance) not be fulfilled, the same comparisons between treatment groups will also be performed using a non-parametric one-way ANOVA.

For the reported health transition item, qualitative descriptive statistics are presented for each visit by treatment group.

## 10.11 Analysis of pharmacokinetic variables

For PK variables [defined in Section 5.6], quantitative descriptive statistics (including geometric mean and 95% CI) for ACT-334441 plasma concentrations are presented by visit and treatment group for the PKS. It includes only data from samples that are taken according to the protocol i.e.,

- For Week 2, 4 and 8: trough samples, i.e., samples taken before dosing and one day after the previous dose
- For Week 12: samples taken within 1 to 7 days following the last dose.

The evolution of the values over time is provided in graphical format (one figure: one boxplot per treatment group and analysis visit, from baseline to EOS).

A listing of individual data is produced on the SCR.

# 11 GENERAL DEFINITIONS AND DERIVATIONS

## 11.1 Phases, periods, visits

Assessments that are summarized in the report are those defined in the study protocol and recorded at the corresponding visits in the eCRF.

### 11.1.1 Analysis visits

To allow analysis of data at the relevant planned (scheduled) visits, all recorded assessments, including unscheduled ones, are assigned to the most appropriate analysis visit according to the best fitting time-window for that visit [see Table 11]. The visit windows are based on the number of days from first study treatment intake. In the majority of cases it is expected that the analysis visit is the same as the scheduled visit.

**Analysis Relative Day** is estimated for several assessments (e.g., vital signs, laboratory data, physical examination). It refers to the number of days elapsed since first study treatment intake date plus 1 (e.g., Day 1 is the day of first study treatment intake). For dates prior to first study treatment intake, study day is the negative number of days elapsed between the date under consideration and the day of first study treatment intake. Therefore, the study day is never 0.

**Analysis Relative Day to EOT** is estimated for several assessments (e.g., vital signs, laboratory data, physical examination). It refers to the number of days elapsed since last study treatment intake date (e.g., Analysis Relative Day to EOT is null when the date of assessment and the date of last study treatment intake are equal).

**Analysis Window Difference from Target** is defined as the absolute difference between **Analysis Relative Day** and **Analysis Window Target**. It is necessary to adjust for the fact that there is no day 0 in the event that Analysis Relative Day and Analysis Window Target are not of the same sign.

**Table 11 Study phases, period and analysis visits**

| Period | Phase | Analysis Visit (N) | Analysis Visit | Analysis Window Beginning Time point (Days) | Analysis Window Ending Time point (Days) | Analysis Window Valid Relative Range (Days) | Analysis Window Target (Days) |
|---|---|---|---|---|---|---|---|
| | Screening phase | 1 | Screening | Lowest | -1 | -30; -1 | . |
| 1 | Treatment phase | 2 | Day 1 | 1 | 1 | 1; 1 | 1 |
| 1 | Treatment phase | 3 | Week 2 | 2 | 21 | 2; 21 | 15 |
| 1 | Treatment phase | 4 | Week 4 | 22 | 42 | 22; 42 | 29 |
| 1 | Treatment phase | 5 | Week 8 | 43 | 70 | 43; 70 | 57 |
| 1 | Treatment phase | 6 | Week 12 | 71 | 105 | 71; 105 | 85 |
| | Follow-up phase | 7 | EOS* | 106 | 196 | 106; 196 | 127 |

*for EOS, it is either Analysis Relative Day > 105 or Analysis Relative Day to EOT> 42.

***Please note for that subjects who were not randomized, all assessments must be assigned to Analysis Visit 1 (Screening).***

## Additional expressions

### End of treatment (EOT)

For analyses ran on the FAS or the SAF, an additional observation (AVISITN = 6.1, AVISIT = 'End-of-treatment', DTYPE = 'LOCF') is created for all subjects with at least one post-baseline assessment available. It is populated with the latest non-missing value assigned from analysis visit Week 2 to analysis visit Week 12 according to the LOCF principle.

In addition, for analyses ran on the PDS or the PPS, an extra observation (AVISITN = 6.2, AVISIT = 'End-of-treatment', DTYPE = 'LOCF') is created for all subjects with at least one non-missing post-baseline assessment performed at least 21 days after the first study treatment intake but no later than 7 days after the last study treatment intake. It is populated with the latest value available fitting these criteria.

**On Day 1 (post-dose)**

For 12 lead ECG and blood pressure measurements, an additional observation (AVISITN = 2.5, AVISIT = 'During day 1', DTYPE = 'MINIMUM' and/or DTYPE = 'MAXIMUM') is created for all subjects with at least one post-baseline assessment performed on Day 1, after first study treatment intake, and is populated according to the worst observation carried forward (WOCF) principle.

**From discharge on day 1 through EOT**

For 12 lead ECG and blood pressure measurements, an additional observation (AVISITN = 7.1, AVISIT = 'From Week 2 through Week 12', DTYPE = 'MINIMUM' or/and DTYPE = ''MAXIMUM') is created for all subjects with at least one post-baseline assessment performed after discharge on Day 1 and up to Week 12 and is populated according to the WOCF principle.

**During Study Period**

For 12 lead ECG and blood pressure measurements, an additional observation (AVISITN = 7.2, AVISIT = 'During study period', DTYPE = 'MINIMUM' and/or DTYPE = ''MAXIMUM') is created for all subjects with at least one post-baseline assessment performed from Day 1, after first study treatment intake, up to EOS and is populated according to the WOCF principle.

### 11.1.2 Retests and multiple assessments in the same visit window

Unless specified otherwise, for findings (e.g., 12 lead ECG, laboratory data), in the case of multiple results in the same analysis visit/ time point, the results included in summary tables are selected according to the following rules:

- Prior to first study drug administration

  For the same parameter and the same subject, only the latest non-missing result available prior to first study drug administration is retained for analysis.

- After first study drug administration

  For the same parameter and the same subject in the same visit window, only the result of the first non-missing assessment (closer to the target day) is retained for analysis. In case of equidistant values from the planned time point, the last assessment is considered for the analyses. Where multiple assessments fall on the same day, then the latest is used.

The records to be taken into account in the analysis are to be flagged (the variable **Analysis Record Flag** is defined to support the selection of the right assessment). All results are listed.

## 11.2 Analysis variables

### 11.2.1 General

**Baseline value** is defined as the last non-missing value before date and time of first dose intake of double-blind treatment.

**Analysis value** is defined as the value at the visit (numeric result in standard units).

**Absolute change from baseline** is defined as post-baseline value minus baseline value, i.e., a positive sign indicates an increase as compared to baseline.

**Percent change from baseline** is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100.

**Ratio to baseline** is defined as the value at the visit divided by the value at baseline (if the baseline value is > 0).

**Analysis Date** is defined as the numeric SAS date derived from the Date/Time of assessment. It can be an imputed date [cf. section 12 for more details].

**Analysis Start Date** is defined as the numeric SAS date derived from the Start Date/Time of an event. It can be an imputed date [cf. section 12 for more details].

**Analysis End Date** is defined as the numeric SAS date derived from the End Date/Time of an event. It can be an imputed date [cf. section 12 for more details].

**Analysis End Relative Day** is estimated for several assessments, including AE end, treatment interruptions, concomitant medication end. It refers to the number of days between the end of the specific event and the first study treatment intake.

### 11.2.2 Subject Level Data

This dataset regroups information from Demographics (DM), Disposition (DS), Death Details (DD), Vital Signs (VS), Exposure (EX), Subject Visits (SV), Reproductive System (RP), Substance Use (SU) domains and their supplemental domains.

***Subject demographics***

**Age, Age Units, Sex:** retrieved from the DM domain or, in case of re-screening, retrieved from the supplemental domain.

**Childbearing potential:** latest information to be retrieved from the RP domain (the information recorded for a RE-SCREENING supersedes information collected at SCREENING).

**Race, Ethnicity, Country:** the information has to be retrieved from the DM domain. Variables to facilitate the production of the summary tables have to be created (e.g., numeric code to enable the correct display order or the long value in proper case).

Variables related to substance use (**Smoking habits, Number of cigarettes smoked, Number of years quit, Year quit)** are retrieved from Substance Use domain.

**Weight (kg) and Height (cm) at baseline:** the latest information has to be retrieved from the VS domain (prior to first intake).

***Population flags***

**Screened Subject Flag** is assigned to Y for all subjects who have a record in the DM domain.

**Re-Screened Subject Flag** is assigned to:

- Y for subjects who have a record in the SV domain with a visit number equal to 1.1
- N otherwise.

**Randomized Population Flag** is assigned to:

- Y for all subjects who have a record in DS domain with a Standardized Disposition Term equal to RANDOMIZED
- N otherwise.

**Full Analysis Set Population Flag** is assigned to:

- Y for all subjects who have a record in DS domain with a Standardized Disposition Term equal to RANDOMIZED
- N otherwise.

**Safety Analysis Set Population Flag** is assigned to

- Y for all subjects who have a record in EX domain corresponding to the first study treatment administration (Group ID =DAY 1 /RE-INITIATION)
- N otherwise.

**Per-protocol Population Flag** is assigned to:

- Y for all subjects included in the Full Analysis Set who have no record in the DV domain flagged as ‘leading to exclusion from PPS’
- N otherwise.

**Pharmacokinetic Analysis Set Population Flag** is assigned to:

- Y for all subjects included in the Safety Analysis Set who have at least one non-missing ACT-33341 concentration available post-baseline
- N otherwise.

**Pharmacodynamic Analysis Set Population Flag** is assigned to:

- Y for all subjects:
  - included in the Safety Analysis Set,
  - with an available baseline value for lymphocyte count (from a sample taken from ICF through first study treatment),
  - with an available post-baseline value for lymphocyte count (from a sample taken at least 21 days after the first study treatment intake but no later than 7 days after the last study treatment without treatment interruption documented in the first 3 weeks).
- N otherwise.

***Treatment variables***

**Randomization Number** is extracted from the DS domain, from the Reference ID variable, for records with a Standardized Disposition Term equal to RANDOMIZED.

**Planned Arm Code, Description of Planned Arm, Actual Arm Code** and **Description of Actual Arm** are retrieved from the DM domain.

The actual treatment variables are derived similarly to the planned treatment variables according to the following table:

| Planned Arm Code | Description of Planned Arm | Planned Treatment for Period 01 (N) | Planned Treatment for Period 01 | Planned Dose for Period 01 |
|---|---|---|---|---|
| A | ACT-334441 0.5mg | 2 | ACT-334441 0.5 mg | 0.5 |
| B | ACT-334441 1.0 mg | 3 | ACT-334441 1.0 mg | 1.0 |
| C | ACT-334441 2mg | 4 | ACT-334441 2.0 mg | 2.0 |
| D | Placebo Control (Part A) | 1 | Placebo | 0 |
| E | ACT-334441 4mg | 5 | ACT-334441 4.0 mg | 4.0 |
| F | Placebo Control (Part B) | 1 | Placebo | 0 |

***Trial dates***

**Date of Informed Consent Obtained** is extracted from the DS domain.

**Date of Randomization** is extracted from the DS domain.

**Date/time of Randomization** is extracted from the DS domain.

**Date of First Exposure to Treatment** is defined as the date/time of first study drug intake. It is the earliest treatment start date/time recorded in the EX domain.

**Date of Last Exposure to Treatment** is the date/time of last double-blind drug intake. It is the latest treatment end date/time recorded in the EX domain.

***Death variables***

**Date of Death** is extracted from the DS domain, where there is a record with Standardized Disposition Term equal to DEATH.

**Death Relative Day to EOT** is computed as the number of days between the date of first exposure to treatment and the end of treatment date.

**Death Relative Day** is computed as the number of days between the date of first exposure to treatment and the date of death.

**Death Dictionary-Derived Term** is extracted from the Death Details domain. It is equal to 'Character Result/Finding in Std Format' where Death Detail Assessment Name equals to Primary Diagnosis.

**Death Reported Term** is extracted from the Death Details domain. It is equal to Result or Finding as Collected where Death Detail Assessment Name equals to Primary Diagnosis.

***Screening variables***

**Date of Screening** is extracted from the SV domain as the start date of visit 1.

**Date of Screen Failure** is extracted from the DS domain.

**Reason for Screen Failure** is extracted from the DS domain. It is equal to:

- Subject withdrew consent, when there is a record with subcategory equal to RANDOMIZATION and a Standardized Disposition Term equal to WITHDRAWAL BY SUBJECT,
- Subject not eligible, when there is a corresponding record in the DS domain with a Standardized Disposition Term equal to SCREEN FAILURE and a Reported Term equal to NOT ELIGIBLE PER INCLUSION/EXCLUSION CRITERIA,
- Other, when there is a corresponding record in the DS domain with a category equal to OTHER EVENT and a Standardized Disposition Term equal to OTHER.

**Reason Spec for Screen Failure** is extracted from the DS domain. It is equal to the Reported Term from the record with a category equal to OTHER EVENT and a Standardized Disposition Term equal to OTHER.

*Conditional (if there is at least one re-screening visit performed)*

**Date of Re-Screening** is extracted from the SV domain as the start date of visit 1.1

***End of treatment variables***

**End of Treatment Date** is derived from DS domain where category equals to DISPOSITION EVENT epoch equals to TREATMENT.

**End of Treatment Day** is computed as the number of days between the date of first exposure to treatment and the end of treatment date.

**End of Treatment Status** is defined as Completed, Discontinued *or Ongoing*. It is equal to:

- *Ongoing, as long as there is no corresponding record in the DS domain*
- Completed, when there is a corresponding record in the DS domain with a Standardized Disposition Term equals to COMPLETED
- Discontinued, when there is a corresponding record in the DS domain with a Standardized Disposition Term not equals to COMPLETED.

***End of study variables***

**End of Study Date** is derived from DS domain where category equals to DISPOSITION EVENT, subcategory equals to STUDY and epoch equals to FOLLOW-UP.

**End of Study Day** is computed as the number of days between the date of first exposure to treatment and the end of study date.

**End of Study Status** is defined as Completed, Discontinued or Ongoing. It is equal to:

- *Ongoing, as long as there is no corresponding record in the DS domain*
- Completed, when there is a corresponding record in the DS domain with a Standardized Disposition Term equals to COMPLETED
- Discontinued, when there is a corresponding record in the DS domain with a Standardized Disposition Term not equals to COMPLETED.

***Accidental unblinding variables***

**Unblinding category** is populated, if there is a record in DS with a Standardized Disposition Term equals to equal UNBLINDED TREATMENT, with the contents of the Category for Disposition Event.

**Unblinding date/ time** is populated, if there is a record in DS with a Standardized Disposition Term equals to equal UNBLINDED TREATMENT, with the contents of the Start date/ time of the Disposition Event.

**Event that Triggered the Request** is populated, if there is a record in DS with a Standardized Disposition Term equals to equal UNBLINDED TREATMENT, with the contents of the Reported Term for the Disposition Event.

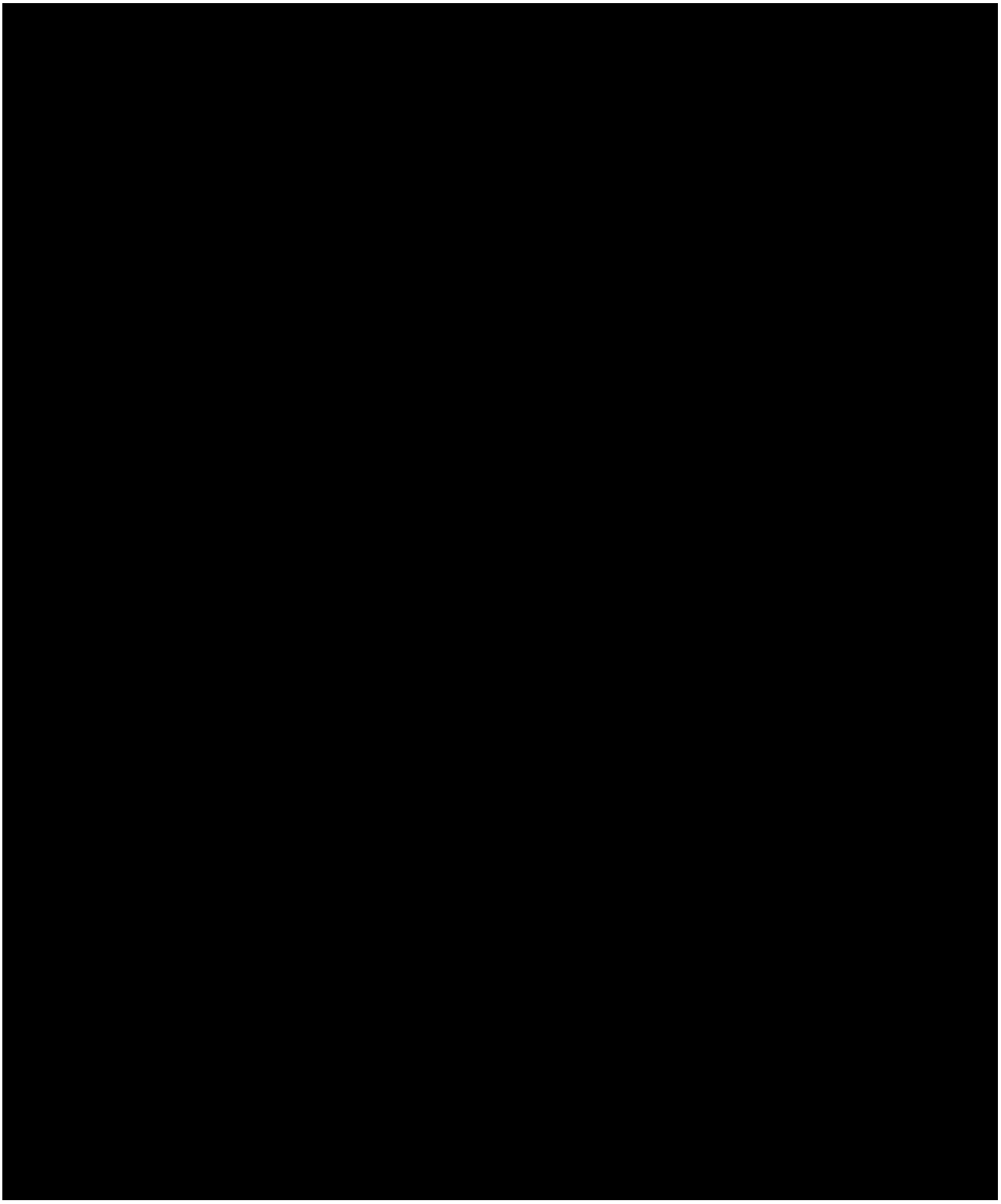
**Action Taken Following the Unblinding** is populated, if there is a record in DS with a Standardized Disposition Term equals to equal UNBLINDED TREATMENT, with the Data Value where the Variable Qualifier Name is equal to DSACNOTH.

### 11.2.3 Protocol Deviations Data

This dataset contains information from Protocol Deviations (DV) Domain and its supplemental domain, in an Occurrence Data Structure (OCCDS).

The presence of deviations affecting the assessment the efficacy leads to exclusion from the PPS. The following codes have been selected:

[redacted]



[redacted]

Please note:

- If a subject is excluded from the PDS then he is also excluded from the PPS.
  *Rationale:* Insufficient pharmacodynamic effect is unlikely to show e.g. clinical improvement, but will confound the results.
- [redacted] If a subject presents with such protocol deviation (specifically, pregnancy test not performed 3 weeks apart), but no pregnancy occurred and all subsequent pregnancy tests were consistently negative during the trial, the subject can be included into the PPS.
  *Rationale:* Biologically this subject is not different from included subjects. However, an important protocol deviation has to be reported.
- [redacted]: If a subject presents with such protocol deviation, but the change of the immunologically active medication occurred at or after EOT, the subject can be included in the PPS.
  *Rationale:* The primary endpoint compares the change from baseline to EOT.

### 11.2.4 Concomitant medications Data

This dataset regroups information from Concomitant/Prior Medications (CM) and its supplemental domain, in an Occurrence Data Structure (OCCDS).

**Previous therapy flag** is equal to Y when the therapy is reported on the corresponding eCRF 'Previous Non SLE Therapies' page (corresponds to Category equal to 'GENERAL' and Subcategory equal to 'PRIOR')

**Concomitant therapy flag** is equal to Y when the therapy is reported on the corresponding eCRF 'Concomitant Medication' page (Category equal to 'GENERAL' and Subcategory equal to 'CONCOMITANT')

**Previous SLE therapies flag** is equal to Y when the therapy is reported on the corresponding eCRF 'Previous SLE Therapies' page (Category equal to 'SLE SPECIFIC' and Subcategory equal to 'PRIOR')

**Concomitant (Background) SLE therapy flag** is equal to Y when the therapy is reported on the corresponding eCRF 'Background SLE Therapies' page (Category equal to 'SLE SPECIFIC' and Subcategory equal to 'CONCOMITANT')

### 11.2.5 Study treatment exposure and compliance

#### *11.2.5.1 Exposure*

This dataset regroups information from Exposure (EX) Domain and its supplemental domain, in a Basic Data Structure (BDS).

The following parameters are defined:

**Re-initiation performed** is defined to Y if there is more than one record in the EX domain with Group ID equals to 'DAY 1 /RE-INITIATION', equals to N otherwise.

**Study treatment duration (days)** is defined as the number of days between start of study treatment and permanent treatment discontinuation of study treatment (both inclusive), regardless of interruption, i.e.,

Latest end date of Treatment - Earliest start date of treatment intake +1.

It is also categorized as (non-exclusive mutually): at least 1 day, at least 1 week (7 days), at least 4 weeks (28 days), at least 8 weeks (56 days) and at least 11 weeks (77 days).

**Study treatment duration (days)**, excluding interruptions, is defined as the total number of days of all treatment intervals (end date of interval minus start date of interval + 1 [in days], excluding overlaps).

#### *11.2.5.2 Compliance (based on drug accountability)*

This dataset regroups information from Drug Accountability (DA) Domain and its supplemental domain, in a Basic Data Structure (BDS).

### 11.2.6 Pharmacodynamic data

This dataset contains information from Laboratory Test Findings (LB) domain in a BD structure. It is limited to the parameter named 'Lymphocyte' as measured by the central laboratory.

**Baseline**, **Absolute value at each post-baseline assessment**, **Absolute and percent change from baseline to each post-baseline assessment** variables are populated as described in the general section.

### 11.2.7 Adverse event data

This dataset contains information from Adverse Events (AE), its supplemental domain and Healthcare Encounters (HO) domain in an Occurrence Data Structure.

Events are considered '**Pre-treatment**' if the onset date is prior to the date of first study treatment intake or if it occurs on the day of the intake when the answer to 'Did this adverse event start at visit 2 or on first day of re-initiation following study drug intake?' is equal to 'No'.

Events are considered '**With onset on day 1**' if the onset date is equal to the first study treatment intake and the answer to 'Did this adverse event start at visit 2 or on first day of re-initiation following study drug intake? ' is answered 'Yes'.

Events are considered '**With onset after day 1**' if the onset date is later than the first study treatment intake.

Events are considered '**Treatment Emergent**' if the onset date is equal to the first study treatment intake and the answer to 'Did this adverse event start at visit 2 or on first day of re-initiation following study drug intake? ' is answered 'Yes' or if the onset date is later than the study treatment intake.

**Analysis Severity/Intensity** is derived if there are missing values in the original SDTM variable. If the original value is missing, it is imputed as 'SEVERE'.

**Analysis Causality** is defined as equal to the Causality recorded in the original SDTM variable as RELATED/ NOT RELATED. If the original value is missing, it is imputed as RELATED.

For serious adverse events requiring or prolonging hospitalization, the following variables are populated: Hospitalization Start Date, Hospitalization End Date, Hospitalization Start Relative Day, Hospitalization End Relative Day.

Events are considered '**Adverse events leading to discontinuation of study treatment'** when action taken with study treatment is recorded as 'permanently discontinued' on the Adverse Event eCRF (in the original SDTM variable 'DRUG WITHDRAWN').

***Adverse Events of special interest (AESI)***

The definitions for adverse events of special interest are based on systematic approach using Standardized MedDRA Queries (SMQ). The current proposal is based on S1P1 projects_AESI definitions_MedDRA version 19.0_09Sep2016. The following safety areas are addressed by the pre-defined adverse events of special interest:

| Protocol wording | Excel Sheet Name | Criterion name | Criterion label |
|---|---|---|---|
| Effect on HR and rhythm related AEs<br>Hypotension related AEs | Bradyarrhythmia<br>Hypotension | AESI01FL+<br>AESI02FL=<br>AESI14FL | Bradyarrhytmia flag +<br>Hypotension flag<br>= Effect on heart rate and rhythm flag |
| Cardiovascular related AEs | Cardiovascular | AESI03FL | Cardiovascular flag |

| Protocol wording | Excel Sheet Name | Criterion name | Criterion label |
|---|---|---|---|
| Hypertension related AEs | Hypertension | AESI04FL | Hypertension flag |
| Hepatobiliary disorders /liver enzyme abnormality related AEs | Liver | AESI05FL | Liver flag |
| Pulmonary related AEs | Pulmonary | AESI06FL | Pulmonary flag |
| Eye disorders related AEs | Macular edema | AESI07FL | Macular edema flag |
| Infection related AEs | Infections | AESI13FL | Infection (if serious or severe) flag |
| Missing/ New | Herpetic infection | AESI08FL | Herpetic infection flag |
| Skin malignancy related AEs | Skin malignancies | AESI09FL | Skin malignancy flag |
| Non-Skin malignancy related AEs | Non-skin malignancies | AESI10FL | Non-skin malignancy flag |
| Missing/ New | Stroke | AESI11FL | Stroke flag |
| Missing/ New | Seizures | AESI12FL | Seizure flag |

### 11.2.8 Medical history data (general)

This dataset contains information from Medical History (MH) Domain, its supplemental domain, in an occurrence data structure. It is restricted to the records with category equal to GENERAL.

For diseases and diagnoses, an additional **End Reference Time Point** is set up to 'START OF TREATMENT'.

For **previous medical history,** the **End Relative to Reference Time Point** is equal to BEFORE.

For **concomitant medical history,** the **End Relative to Reference Time Point** is equal to ONGOING.

### 11.2.9 Medical history data, SLE specific

This dataset contains information from Medical History (MH) Domain (restricted to category equal to SYSTEMIC LUPUS ERYTHEMATOSUS RELEVANT DISEASE HISTORY) and its supplemental domain, in a basic data structure.

Each criterion is mapped into a parameter. The analysis value is equal to the occurrence of the pre-specified event.

In addition, the following parameters are derived:

- **Time from first SLE symptoms (years) to informed consent signature** is calculated as follows: (Informed consent date - date of first symptoms)/365.25.

- **Time from SLE diagnosis (years) to informed consent signature** is calculated as follows: (Informed consent date - date of SLE diagnosis)/365.25.

- **Number of SLE symptoms** according to ACR criteria [ACR 1997] **met in the past** is calculated for each subject as the number of observations with Event Pre-Specified equal to Y and Occurrence equal to Y and End Relative to Reference Time Point equal to BEFORE.
- **Number of SLE symptoms** according to ACR criteria [ACR 1997] **started more than 6 months prior to screening** is calculated for each subject as the number of observations with Event Pre-Specified equal to Y and Occurrence equal to Y and Did it start more than 6 months prior? equal to Y.
- **Number of SLE symptoms** according to ACR criteria [ACR 1997] **ongoing at screening** is calculated for each subject as the number of observations with Event Pre-Specified equal to Y and Occurrence equal to Y and End Relative to Reference Time Point equal to ONGOING.
- **Number of SLE symptoms** according to ACR criteria [ACR 1997] **met either serially or simultaneously** is calculated for each subject as the number of observations with Event Pre-Specified equal to Y and Occurrence equal to Y.

  For each **Number of SLE symptoms** computed, the analysis value is further categorized in 0-3 and 4-11.

- **Presence of a documented historical positive ANA** is equal to Y when there is at least one observation in LB Domain with Group ID equal to 'PREVIOUS TESTINGS' and Lab Test or Examination Short Name equal to 'ANA'.

- **Presence of a documented historical positive anti-dsDNA** is equal to Y when there is least one observation in LB Domain with Group ID equal to 'PREVIOUS TESTINGS' and Lab Test or Examination Short Name equal to 'ADSDNA'.

### 11.2.10 Discharge from hospital data

The dataset is an extraction from the HO domain (Reported terms equal to 'HOSPITALIZATION AT RANDOMIZATION'), merged to its supplemental domain, in a basic data structure.

The following parameters/ analysis value are defined:

**Actual time from first study treatment intake to discharge (hours)** is calculated as follows: (date/ time of first study treatment intake - date/ time of discharge)/ 3600.

**Time from first study treatment intake to discharge** is defined as follows:

- Equal to '6 hours' when the answer to 'Was the subject discharge at 6h after study drug intake?' is equal to 'Yes',

- Equal to 'from 6 through 12 hours' when the answer to 'Was the subject discharge up to 12h after study drug intake?' is equal to 'Yes',
- Equal to 'after 12 hours' when the answer to 'Was the subject discharge up to 12h after study drug intake?' is equal to 'No'.

### 11.2.11 12-lead ECG, parameters data

This dataset contains data extracted from the Electrocardiogram Results (EG) Domain, restricted to the observations with Category equal to ('MEASUREMENT' or 'INTERPRETATION') and Method equal to '12 LEAD STANDARD' in a basic data structure.

The following analysis parameters are defined:

| **ADaM variables** | | | **SDTM variables** | | |
|---|---|---|---|---|---|
| **Parameter (N)** | **Parameter Code** | **Parameter** | **Test Short Name** | **Test Name** | **Standard Units** |
| 2 | EGHRMN | Heart rate (bpm) | EGHRMN | ECG Mean Heart Rate | beats/min |
| 3 | PRMEAN | PR Duration (msec) | PRMEAN | Summary (Mean) PR Duration | msec |
| 4 | QRSDUR | QRS Duration (msec) | QRSDUR | Summary (Mean) QRS Duration | msec |
| 6 | QTCB | QTcB-Bazett's Correction Formula (msec) | QTCB | QTcB - Bazett's Correction Formula | msec |
| 7 | QTCF | QTcF-Fridericia's Correction Formula (msec) | QTCF | QTcF - Fridericia's Correction Formula | msec |
| 5 | QTMEAN | QT Duration (msec) | QTMEAN | Summary (Mean) QT Duration | msec |
| 1* | RRMEAN | RR Duration (msec) | RRMEAN | Summary (Mean) RR Duration | msec |
| 8 | INTP | Interpretation | INTP | Interpretation | |

*Included in the listings but excluded from summary tables

For these analysis parameters (1 to 7), **Baseline**, **Absolute value at each post-baseline assessment and Absolute change from baseline to each post-baseline assessment** variables are populated as described in the general section.

The occurrence of abnormalities, as defined in table 'treatment emergent notable abnormalities', is populated for each post-baseline assessment individually. In addition, the occurrence of at least one 'Low' and at least one 'High' treatment-emergent

abnormality is derived on the subject level at the following time points: from 1 hour post-dose on Day 1 up to discharge, from discharge on Day 1 through EOT and at any time post-baseline.

There is also a parameter defined corresponding to the interpretation of the cardiologist. Additional comments he may have are extracted from the Comments (CO) Domain.

### 11.2.12 12-lead ECG, findings data

The dataset contains the observations extracted from the EG Domain with Category equals to 'FINDING' and Method equals to '12 LEAD STANDARD', in an occurrence data structure. Each finding is mapped now into an event.

Findings are considered '**Treatment Emergent**' if the date/time of the ECG is after the first study treatment intake.

### 11.2.13 24 hour Holter-ECG, parameters data

This dataset contains, in a basic data structure, only 2 tests extracted from EG Domain for Method equal to '12 LEAD HOLTER':

- 'ECG Mean Heart Rate', on observations with Category equal to 'MEASUREMENT' and Subcategory equal to 'DIARYP' (Diary Period)
- 'Holter Overall Interpretation'

For parameter equal to 'Mean Heart Rate (bpm)', the following variables are defined:

**Analysis Flag**

If several ECG (ECG reference ID) are available for 'V1 - Screening visit', only the most recent is taken into account (Group ID equal to ''REPEAT').

**Analysis time point**

For Holters performed during screening period, the analysis time point for each hourly measurement is defined with respect to the study treatment intake on Day 1. Let's assume a Holter (screening) starting on 05-FEB-2017 at 11:03 and a first study treatment intake on 03-MAR-2017 at 10:53. On Day 1, the 1$^{st}$ hour starts at 10:53 and ends at 11:53. It is time-matched with the screening record starting at 11:03 and ending at 12:03.

For Holters performed on day 1, the analysis time point for each hourly measurement is defined with respect to the study drug intake. It is equal to 0 for records with a start time of the interval prior to time of study drug intake.

**Absolute change from baseline** (time-matched change from Visit 1 (Screening) to Visit 2 (Randomization/ Day 1)' ) is defined as post-baseline value minus baseline value for each hourly time-matched measurement, i.e., a positive sign indicates an increase as compared to baseline.

For parameter equal to 'Holter Overall Interpretation', the analysis value is the opinion of the cardiologist recorded as 'NORMAL' or 'ABNORMAL'.

### 11.2.14 24 hour Holter-ECG, findings data

This dataset regroups information from EG Domain (restricted to observations with Test equal to 'Holter Overall Interpretation') and the CO Domain. It contains any additional comments from the central reader mapped into a basic data structure.

For each Holter, the cardiologist provides his overall interpretation as 'NORMAL', 'ABNORMAL' and describes the potential findings in the comment section.

The findings to be extracted from the comment field(s) are the following:

**Table 13 Potential Holter-ECG Findings**

| | Reported Term | Preferred Term |
|---|---|---|
| 1 | FREQUENT VPCS ( IN HOURS) | FREQUENT VPCS ( IN HOURS) |
| 2 | FREQUENT VPCS (GREATER THAN 30 VPCS IN ONE HOUR) | FREQUENT VPCS (GREATER THAN 30 VPCS IN ONE HOUR) |
| 3 | NONSUSTAINED VENTRICULAR TACHYCARDIA ( ) | NONSUSTAINED VENTRICULAR TACHYCARDIA |
| 4 | SUSTAINED VENTRICULAR TACHYCARDIA ( ) | SUSTAINED VENTRICULAR TACHYCARDIA |
| 5 | TORSADE DE POINTES | TORSADE DE POINTES |
| 6 | VENTRICULAR FIBRILLATION OR VENTRICULAR FLUTTER ( ) | VENTRICULAR FIBRILLATION OR VENTRICULAR FLUTTER |
| 7 | FREQUENT SHORT EPISODES OF NONSUSTAINED SUPRAVENTRICULAR TACHYCARDIA | FREQUENT SHORT EPISODES OF NONSUSTAINED SUPRAVENTRICULAR TACHYCARDIA |
| 8 | ATRIAL FIBRILLATION ( ) | ATRIAL FIBRILLATION |
| 9 | ATRIAL FLUTTER ( ) | ATRIAL FLUTTER |
| 10 | MOBITZ I (WENCKEBACH) 2ND DEGREE AV BLOCK ( ) | MOBITZ I (WENCKEBACH) 2ND DEGREE AV BLOCK |
| 11 | 2:1 AV BLOCK ( ) | 2:1 AV BLOCK |
| 12 | HIGH GRADE AV BLOCK ( ) | HIGH GRADE AV BLOCK |
| 13 | MOBITZ II 2ND DEGREE AV BLOCK ( ) | MOBITZ II 2ND DEGREE AV BLOCK |
| 14 | COMPLETE HEART BLOCK ( ) | COMPLETE HEART BLOCK |
| 15 | PAUSE GREATER THAN 3.0 SECONDS (LONGEST PAUSE SECONDS) | PAUSE GREATER THAN 3.0 SECONDS |
| 16 | AVERAGE HEART RATE LESS THAN OR EQUAL TO 40 FOR ANY ONE HOUR | AVERAGE HEART RATE LESS THAN OR EQUAL TO 40 FOR ANY ONE HOUR |

| | Reported Term | Preferred Term |
|---|---|---|
| 17 | MARKED SINUS BRADYCARDIA ( ) | MARKED SINUS BRADYCARDIA |
| 18 | INTERMITTENT ECTOPIC ATRIAL RHYTHM | INTERMITTENT ECTOPIC ATRIAL RHYTHM |
| 19 | INTERMITTENT JUNCTIONAL RHYTHM | INTERMITTENT JUNCTIONAL RHYTHM |
| 20* | OTHER: <FREE TEXT> | OTHER |
| 21* | NO DATA OBTAINED | NO DATA OBTAINED |
| 99* | COMMENTS: <FREE TEXT> | COMMENTS |
| 100* | GOOD QUALITY | GOOD QUALITY |
| 101* | ARTIFACT | ARTIFACT |
| 102* | SIGNIFICANT ARTIFACT- THROUGHOUT | SIGNIFICANT ARTIFACT- THROUGHOUT |
| 103* | BASELINE WANDER | BASELINE WANDER |
| 104* | MISSING LEADS | MISSING LEADS |
| 105* | HIGH OR LOW AMPLITUDE SIGNAL | HIGH OR LOW AMPLITUDE SIGNAL |
| 106* | 60 HZ NOISE | 60 HZ NOISE |

* Not summarized, only presented in the listings.

### 11.2.15 Laboratory Data (Safety labs)

This dataset contains data extracted from the Laboratory Test Findings (LB) Domain and its supplemental domain, excluding biomarkers and previous testings for Anti-Double Stranded DNA and Antinuclear Antibodies, in a basic data structure.

To facilitate the reporting, parameter category (numeric and character) are defined based on the Category and Method:

| Parameter Category (N) | Parameter Category | Source |
|---|---|---|
| 1 | HEMATOLOGY | HEMATOLOGY |
| 2 | CLINICAL CHEMISTRY | CHEMISTRY |
| 3 | COAGULATION TESTS | COAGULATION |
| 4 | VIRUS SEROLOGY | IMMUNOLOGY |
| 6 | URINALYSIS, DIPSTICK | Category = 'URINALYSIS' and Method = 'DIPSTICK' |
| 7 | URINE PROTEIN-TO-CREATININE RATIO | Category = 'URINALYSIS' |
| 8 | TEST FOR TUBERCULOSIS | IMMUNOLOGY |
| 9 | PREGNANCY TEST | CHEMISTRY |
| 9 | PREGNANCY TEST | URINALYSIS |

Some parameters being assayed in the serum and in the urine (assay and dipstick), parameters need to be renamed depending on Category, Method and Specimen Type:

The parameter code (no longer than 8 characters) corresponds to:

- the Test Code for Category equal to 'CHEMISTRY', 'COAGULATION' and 'HEMATOLOGY',
- the concatenation of 'U' and the Test Code for Category equal to 'URINALYSIS',
- the concatenation of 'UD' and the Test Code for Category equal to 'URINALYSIS' and Method equal to 'DIPSTICK'.

The parameter corresponds to the concatenation of:

- the Category,
- the Lab Test or Examination Name,
- the Standard Units in brackets.

For the parameters assayed as a continuous variable, **Baseline**, **Absolute value at each post-baseline assessment, Absolute and percent change from baseline to each post-baseline assessment** variables are populated as described in the general section.

For the parameters assayed as a categorical variable (e.g., Protein), the analysis value is defined only as a character value.

**Analysis Reference Range Indicator** is derived to identify marked abnormalities according the ***Adapted table 5*** from the study protocol [included in Section 15]. It is only defined for results coming from the central laboratory, it is based on the normal range indicator provided by ACM (L, LL, H, HH) and augmented or modified according to the adapted table 5.

### 11.2.16 Exploratory biomarker data

This dataset contains the following parameters, assayed by the central laboratory, except for Blood lymphocyte subsets, from the LB Domain, mapped into a basic data structure.

**Baseline** is defined as the last non-missing value (numeric result in standard units) before date and time of first dose intake of double-blind treatment. Values below the lower limit of quantification (for example: LLQ = 2) recorded as "< LLQ" are set to half that limit (i.e., LLQ/2). Values recorded above or equal the upper limit of quantification are set to the upper limit. No imputation is performed for values recorded greater than the ULQ.

**Baseline value in categories** is defined from numeric and character results in standard units using the categorization depicted in the corresponding sections.

**Analysis value** is defined as the value at the visit (numeric result in standard units). Values below the lower limit of quantification (for example: LLQ = 2) recorded as "<

LLQ" are set to half that limit (i.e., LLQ/2). Values recorded above or equal the upper limit of quantification are set to the upper limit. No imputation is performed for values recorded greater than the ULQ.

**Analysis value in categories** is defined from numeric and character results in standard units using the categorization depicted in the corresponding sections.

**Absolute and percent change from baseline to each post-baseline assessment** variables are populated as described in the general section.

#### *11.2.16.1 Baseline disease characteristics, Exploratory disease biomarker*

The following parameters are assayed by the central laboratory at Visit 2 only: anti-Smith, anti-cardiolipin (IgA, IgG, IgM), anti-ribosomal P.

#### *11.2.16.2 Exploratory biomarker variables*

The following parameters are assayed by the central laboratory:

- 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) ;

The following parameters are assayed by Translational Science Biology at Actelion:

- CXCL10 (EDTA-plasma; Visit 2 and Visits 4 to 7).

For the antinuclear antibody (ANA) test, 2 results (2 records) are provided by the central laboratory, only one observation is kept:

| Character Result in Std Format for Antinuclear Antibodies | Character Result in Std Format for Antinuclear Antibodies Titer | Analysis Value | Analysis Category 1 | Analysis Category 2 |
|---|---|---|---|---|
| NEGATIVE* | NOT APPLICABLE *(Vendor Name = ACM EUROPE)* | 20 | NEGATIVE | < 40 |
| NEGATIVE* | <40 *(Vendor Name = ACM US)* | 20 | NEGATIVE | < 40 |
| POSITIVE | 40 | 40 | POSITIVE | 40 |
| POSITIVE | 80 | 80 | POSITIVE | 80 |
| POSITIVE | 160 | 160 | POSITIVE | 160 |
| POSITIVE | 320 | 320 | POSITIVE | 320 |
| POSITIVE | >=640 | 640 | POSITIVE | >= 640 |

* In case the qualitative test for ANA is negative, ACM US reports '<40' and ACM Europe 'Not applicable' for the titer result.

For the other analysis parameters, **Baseline**, **Absolute value at each post-baseline assessment, Absolute and Percent change from baseline to each post-baseline assessment** variables are populated as described in the general section.

- Blood lymphocyte subsets

The list of parameters assayed by Translational Science Biology at Actelion is provided below:

**Table 14 Lymphocyte subsets: parameters and units**

| Category | Specimen Type | Lab Test | Lab Test Code | Original Units | Conventional Units | Standard Units |
|---|---|---|---|---|---|---|
| CHEMISTRY | Plasma | CXCL10 | CXCL10 | pg/mL | pg/mL | ng/L |
| HEMATOLOGY | Blood | B cells | BCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Naïve B cells | NAIVBCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Pre-germinal center B cells | PRGCBCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Post-germinal center memory B cells | PSGCMBCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Double-negative B cells | DNEGBCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Classical (Chain switched) memory B cells | CSMEMBCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | IgD+ memory B cells | IGDMBCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | CD20-/CD38+ B cells | CD20_38BC | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Plasma cells | PLSMCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | CXCR3+ B cells | CXCR3 | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Transitional B cells | TRANBCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Plasmablast-like cells | PLSPCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | T cells | TCE | cells/µL | 10^3 µL | 10^9/L |

| Category | Specimen Type | Lab Test | Lab Test Code | Original Units | Conventional Units | Standard Units |
|---|---|---|---|---|---|---|
| HEMATOLOGY | Blood | T helper (Th) | TH | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th central memory (CM) | TH_CM | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th naïve | TH_N | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th effector memory (EM) | TH_EM | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th EM RA+ (EMRA) | TH_EMRA | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | T regulatory (Treg) | TREG | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Double negative T cells (DNT) | DNEGTCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | T cytotoxic (Tc) | TCE_CYTOX | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Tc CM | TCCM | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Tc naïve | NAIVTCE | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Tc EM | TCE_EM | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Tc EMRA | TCE_EMRA | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th follicular (Tfh) | TH_F | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th1 | TH1 | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th2 | TH2 | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th17 | TH17 | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Th1/Th17 | TH1TH17 | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Tc CXCR5+ | CXCR5 | cells/µL | 10^3 µL | 10^9/L |
| HEMATOLOGY | Blood | Tc CXCR3+ | CXCR3 | cells/µL | 10^3 µL | 10^9/L |

**Analysis value** is defined as the value at the visit (numeric result in standard units). Original results recorded as below the lower limit of quantification (LLOQ) are set to half of the LLOQ value.

**Baseline**, **Absolute value at each post-baseline assessment, Absolute and Percent change from baseline to each post-baseline assessment** variables are populated as described in the general section.

### 11.2.17 Vital Signs Data

This dataset contains information from the Vital Signs (VS) Domain, mapped into a basic data structure.

#### *11.2.17.1 Blood pressure*

For Supine SBP / DBP (mmHg):

**Baseline** is defined as the mean (computed in the eCRF) of the 2 measurements performed on Visit Day 1, at pre-dose (Category equal to 'MEAN'). If missing, it is replaced by the last non missing value recorded prior to the first dose.

**Analysis value** is defined as the value at the visit/ time point (numeric result in standard units). For assessments performed on Visit Day 1, after pre-dose, the analysis value at the time point is retrieved from the record available. For all visits performed after Day 1, the analysis value is retrieved from the record populated with VSCAT = 'MEAN'.

Abnormalities, as defined in table 'treatment emergent notable abnormalities' are populated for each post-baseline assessment individually. In addition, the occurrence of at least one 'Low' and at least one 'High' treatment-emergent abnormality is derived on the subject level for the following time intervals: on Day 1 (from 1 hour post-dose up to discharge), after Day 1 (from discharge on Day 1 through Visit 7 (EOS)) and at any time post-baseline.

For Standing SBP / DBP (mmHg), only the **Analysis value** at the visit is populated.

#### *11.2.17.2 Body weight*

For Body weight (kg), **Baseline**, **Absolute value at each post-baseline analysis visit and Absolute change from baseline to each post-baseline analysis visit** variables are populated as described in the general section.

### 11.2.18 Questionnaires Data

This dataset contains information from the Questionnaire (QS) Domain and its supplemental domain, mapped into a basic data structure.

- Modified Systemic Lupus Erythematosus Activity Index-2000 (SLEDAI-2K)

The QS Domain contains the 23 individual descriptors but also the total SLEDAI-2K score and the combined musculoskeletal and mucocutaneous manifestations subscores.

Two additional parameters are created:

The **Mucocutaneous Score** is defined as the weighted sum of each of the individual descriptors for the applicable organ class, i.e. mucosal ulcers, rash, and alopecia. It can be computed by summing up the standardized result for each descriptor.

The **Muscoloskeletal Score** is defined as the weighted sum of each of the individual descriptors for the applicable organ class, i.e. arthritis and myositis. It can be computed by summing up the standardized result for each descriptor.

The usual **Baseline**, **Absolute value at each post-baseline analysis visit**, **Absolute and percent change from baseline to each post-baseline analysis visit** variables are defined for the total score and for the 3 sub-scores based on the numeric result (standardized).

The **Baseline Category** is defined, for the total score only, as '≥ 6' and '< 6'.

The **Occurrence of an increase from baseline > 3, > 6, > 12** are defined, for the total score only, at each visit, based on the absolute change from baseline.

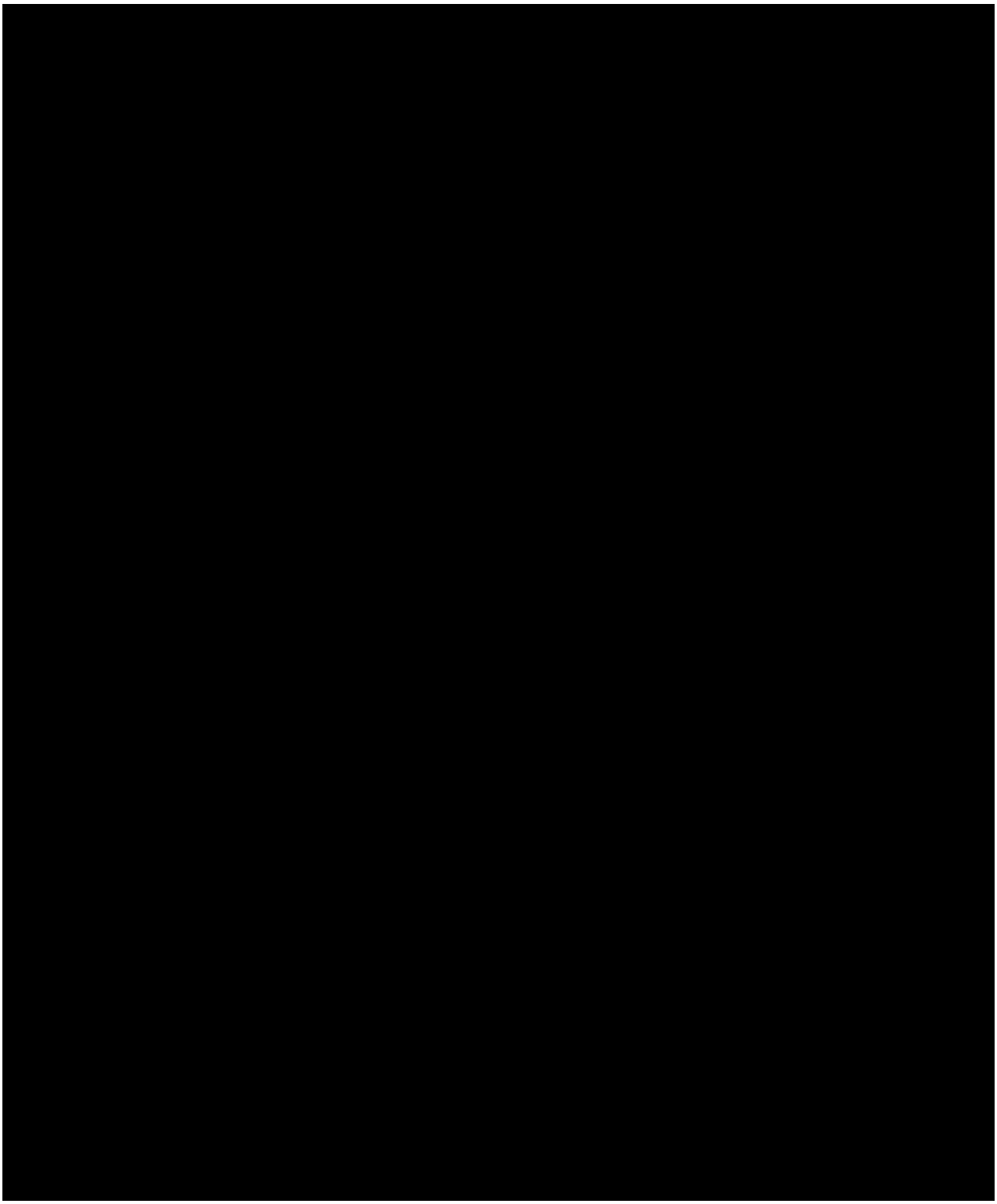
- Physician's Global Assessment of disease (PGA)

The QS Domain contains the original value recorded on the eCRF (length from 0 to 100 mm) and the standardized value (from 0.00 to 3.00).

The usual **Baseline**, **Absolute value at each post-baseline analysis visit**, **Absolute and percent change from baseline to each post-baseline analysis visit** variables are defined based on the numeric result (standardized).

- 36-Item Short Form Health Survey v2 (SF 36v2™) questionnaire

The QS Domain contains the original value (decode format) recorded on the eCRF (eg., 'Excellent', 'All of the time') and the standardized value as specified in the SF-36 v2 manual.



The **Analysis value (Character)** is defined for the 'parent records' only and contains the Finding in Original Units.

The **Baseline value (Character)** is defined for the 'parent records' only and contains the Finding in Original Units.

For all derived parameters (especially raw scores, norm-based scores and the health transition item), **Baseline** and **Change from baseline** are populated as described in the general section.

### 11.2.19 Spirometry Data

The dataset contains the information from the Respiratory System Findings (RE) and its supplemental domain, in a basic data structure, restricted to the 'best' records populated by the independent central reader (Sponsor-Defined Identifier equal to '0').

| Test Code | Test Label | Test Unit | Parameter (N) | Parameter Code | Parameter |
|---|---|---|---|---|---|
| FVC | Forced Vital Capacity | L | 1 | FVC | Forced Vital Capacity (FVC) (L) |
| FEV1 | Forced Expiratory Volume in 1 Second | L | 2 | FEV1 | Forced Expiratory Volume in 1 Second (FEV1) (L) |
| FEV1FVC | FEV1/FVC | RATIO | 3 | FEV1FVC | FEV1/FVC |
| FEV1PRED | Predicted FEV1 | L | 4 | FEV1PRED | Predicted FEV1 (L) |
| FEV1PP | Percent Predicted FEV1 | % | 5 | FEV1PP | Percent Predicted FEV1 (%) |
| FVCPRED | Predicted FVC | L | 6 | FVCPRED | Predicted FVC (L) |
| FVCPP | Percent Predicted Forced Vital Capacity | % | 7 | FVCPP | Percent Predicted FVC (%) |
| PEF | Peak Expiratory Flow | L/s | 8 | PEF | Peak Expiratory Flow (L/s) |
| FEF2575 | Forced Expiratory Flow 25-75% | L/s | 9 | FEF2575 | Forced Expiratory Flow 25-75% (FEF) (L/s) |
| FEF25 | Forced Expiratory Flow 25% | L/s | 10 | FEF25 | Forced Expiratory Flow 25% (FEF) (L/s) |
| FEF50 | Forced Expiratory Flow 50% | L/s | 11 | FEF50 | Forced Expiratory Flow 50% (FEF) (L/s) |
| FEF75 | Forced Expiratory Flow 75% | L/s | 12 | FEF75 | Forced Expiratory Flow 75% (FEF) (L/s) |

In this dataset, the 12 parameters are considered highly dependent, the results of different 'best' records cannot be mixed. The definition of **Analysis Record Flag** is slightly modified here, it is valid for a set (date/ time) of 'best' values i.e.,

- Prior to first study drug administration

The latest set of 'best' values carrying the highest FVC (L), with the highest quality, is retained for analysis.
If more than one set of 'best' values is done on the same day then an 'Acceptable' test is taken in preference to a 'Borderline' test. If all sets on one day have the same quality (BTR Grade Code equal to 'Acceptable' or 'Borderline') then the highest value is taken. If after this, there are still two sets with either the same value and the same quality then the last set using the time of assessment is used.

- After first study drug administration
  The first set of 'best' values carrying the highest FVC (L), with the highest quality, is retained for analysis.
  If more than one set of 'best' values is done on the same day then an 'Acceptable' test is taken in preference to a 'Borderline' test. If all sets on one day have the same quality (BTR Grade Code equal to 'Acceptable' or 'Borderline') then the set of 'best' values carrying the lowest FVC (L) is taken.

For each parameter, the **Baseline** Value is extracted from the same set of 'best' values identified thanks to the **Analysis Record Flag** defined above. It can be defined as the highest of the best value(s) populated by the independent central reader (Sponsor-Defined Identifier equal to '0') on valid assessments (BTR Grade Code equal to 'Acceptable' or 'Borderline') performed before first study treatment intake. If more than one set of tests is done on the same day then an 'Acceptable' test is taken in preference to a 'Borderline' test. If all tests on one day have the same quality (BTR Grade Code equal to 'Acceptable' or 'Borderline') then the highest value is taken. If after this, there are still two tests with either the same value and the same quality then the last test using the time of test is used.

For each parameter, the **Analysis value** is extracted from the same set of 'best' values identified thanks to the **Analysis Record Flag** defined above. It can be defined as the best value populated by the independent central reader (Sponsor-Defined Identifier equal to '0') on valid assessments (BTR Grade Code equal to 'Acceptable' or 'Borderline') at each post-baseline visit. If several best values of the same quality are available at the same visit, the highest value is taken in preference to a highest value (i.e., the value leading to the lowest change from baseline).

**Absolute and percent change from baseline to each post-baseline analysis visit** variables are populated as described in the general section (except for Predicted FVC (L) and Predicted $FEV_1$ (L) which hold constant values).

For FVC (L) and $FEV_1$ (L), for each post-baseline assessment, if the percent change from baseline is lower than -15%, the criterion 'Decrease from baseline > 15%' is populated to Y.

### 11.2.20 Pharmacokinetics Concentrations Data

The dataset contains the information from the Pharmacokinetics Concentration (PC) and its supplemental domain, in a basic data structure.

**Analysis value** is defined as the value at the visit (numeric result in standard units). Original results recorded as below the lower limit of quantification (LLOQ) are set to zero.

**Analysis Relative Time** is defined, for Visits 3 to 5, as the amount of time between the PK sample and the next study drug intake, expressed in minutes (**Analysis Relative Time Unit** is defined as 'MINUTES').

**Analysis Relative Day** is defined, for Visits 3 to 7, as the number of days elapsed between the last dose andand the PK samplingsampling.

In addition to the **Analysis Record Flag** populated as described in the general section, a second **Analysis Record Flag** is created to identify samples taken under the expected conditions i.e.,

- For analysis ofof Visits 33 to 5: samples taken before the morning dose and one day after the last dose
- For analysis visits Week 12 and EOT: samples taken within 1 to 7 days following the last dose.

### 11.2.21 Physical examination data

The dataset contains the information from the Physical Examination (PE) and its supplemental domain, in a basic data structure. No derivations are needed.

### 11.2.22 Childbearing potential data, contraception, and pregnancy test data

This dataset contains the information from the Reproductive System Findings (RP) domain together with the results of the pregnancy tests recorded in LB domain.

## 12 HANDLING OF MISSING/INCOMPLETE DATE AND TIME FIELDS

This section describes some general principles to be followed in the case of missing or incomplete dates/times. Missing parts for specific dates/times are changed into acceptable non-missing values as described in the below Table 15.

**Table 15 Handling of missing date and time**

| Type of date/time | Imputation method when date/time is incomplete | Imputation method when date/time is missing |
|---|---|---|
| Start of study treatment *(Randomized subjects only)* | Day is missing (i.e., "yyyy.mm")<br>Whichever is the later of "yyyy mm.01" or the date of randomization | Date of randomization (IVRS) |
| | Day and month are missing (i.e., "yyyy")<br>Whichever is the later of "yyyy.01.01" or the date of randomization | |
| End of study treatment *(Randomized subjects only)* | Day is missing (i.e., "yyyy.mm")<br>Whichever is the earlier of "yyyy mm.28/29/30/31" and the Visit 6 (EOT) date | Date of V6 - (Premature) End of Treatment |

| Type of date/time | Imputation method when date/time is incomplete | Imputation method when date/time is missing |
|---|---|---|
| | Day and month are missing (i.e., "yyyy")<br>Whichever is the earlier of "yyyy.12.31" and the Visit 6 (EOT) date | |
| Start Date of Adverse Event *(Randomized subjects only)* | Day is missing (i.e., "yyyy.mm")<br>If month and year of the episode = month and year of first study treatment intake then<br>Start date=date of first study treatment intake,<br>otherwise<br>Start date= yyyy.mm.01 | Date of first study treatment intake |
| | Day and month are missing (i.e., "yyyy")<br>If year of the episode = year of first study treatment intake then<br>Start date = date of first study treatment intake,<br>otherwise<br>Start date= yyyy.01.01 | |
| End Date of Adverse Event *(Randomized subjects only)* | Day is missing (i.e., "yyyy.mm")<br>If the year and the month are the same as the year and the month of last visit then<br>End date= Last visit date,<br>otherwise<br>End date=yyyy.mm.28 or 29 or 30 or 31 | No approximation, the AE is considered as ongoing in the analysis |
| | Day and month are missing (i.e., "yyyy")<br>If the year is the same as the year of last visit then<br>End date= Last visit date,<br>otherwise<br>End date=yyyy.12.31 | |
| Date of first SLE symptoms | Day is missing (i.e., "yyyy.mm")<br>If the year and the month are the same as the year and the month of screening then<br>Start date= Screening date,<br>otherwise<br>Start date=yyyy.mm.01 | Date of V1 - Screening |
| | Day and month are missing (i.e., "yyyy")<br>If the year is the same as the year of screening then<br>Start date= Screening date,<br>otherwise<br>Start date=yyyy.01.01 | |

| Type of date/time | Imputation method when date/time is incomplete | Imputation method when date/time is missing |
|---|---|---|
| Date of SLE diagnosis | Day is missing (i.e., "yyyy.mm")<br>If the year and the month are the same as the year and the month of screening then<br>Start date= Screening date,<br>otherwise<br>Start date=yyyy.mm.01 | Date of V1- Screening |
| | Day and month are missing (i.e., "yyyy")<br>If the year is the same as the year of screening then<br>Start date= Screening date,<br>otherwise<br>Start date=yyyy.01.01 | |
| Start Date of Medication | Day is missing (i.e., "yyyy.mm")<br>If the year and the month are the same as the year and the month of screening then<br>Start date= Screening date,<br>otherwise<br>Start date=yyyy.mm.01 | Date of V1- Screening |
| | Day and month are missing (i.e., "yyyy")<br>If the year is the same as the year of screening then<br>Start date= Screening date,<br>otherwise<br>Start date=yyyy.01.01 | |
| End Date of Medication | Day is missing (i.e., "yyyy.mm")<br>If the year and the month are the same as the year and the month of last visit then<br>End date= Last visit date,<br>otherwise<br>End date=yyyy.mm.28 or 29 or 30 or 31 | No approximation, the medication is considered as ongoing in the analysis |
| | Day and month are missing (i.e., "yyyy")<br>If the year is the same as the year of last visit then<br>End date= Last visit date,<br>otherwise<br>End date=yyyy.12.31 | |

# 13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

[redacted]

# 14 REFERENCES

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# 15 APPENDICES

## 15.1 Protocol Synopsis

A.

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| 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**<br>• To investigate the pharmacodynamics (PD) of ACT-334441 in adult subjects with systemic lupus erythematosus (SLE).<br>• To investigate the safety and tolerability of ACT-334441 in adult subjects with SLE.<br>**Exploratory objectives**<br>• To investigate the pharmacokinetics (PK) of ACT-334441 in adult subjects with SLE.<br>• 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.<br>This study is divided in two parts:<br>• **Part A**: Four parallel treatment groups (including 0.5 mg, 1 mg, or 2 mg of ACT-334441 and placebo control).<br>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).<br>• **Part B:** Two parallel treatment groups (including 4 mg ACT-334441 and placebo control).<br>Note: Subjects enrolled in Part A are not eligible to participate |

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| | in Part B. |
| PERIODS | **There will be three periods in Part A and Part B.**<br><br>**Screening period**:<br><br>This period starts up to 30 days before randomization and includes the **Screening visit** and the pre-randomization assessments.<br><br>**Treatment period**:<br><br>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.<br><br>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.<br><br>**Follow-up period**:<br><br>Subjects will undergo an **End-of-Study (EOS)** Visit 6 weeks after the last dose of study treatment.<br><br>**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 DISCONTINUATION CRITERIA AND STUDY-SPECIFIC CRITERIA FOR INTERRUPTION / CLINICAL STUDY STOP | **Study treatment discontinuation**<br><br>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 (telephone calls follow-up for pregnancy and SAEs).<br><br>**Study-specific criteria for interruption / stopping of the clinical study or Part B**<br><br>• 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 study treatment due to meeting any of the |

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| | 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.<br>• 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).<br>**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.]).<br>**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.<br>2. Men or women ≥ 18 and ≤ 65 years of age.<br>3. Women of childbearing potential as defined in Section 4.5.1:<br>• must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization at least 3 weeks apart;<br>• must agree to undertake a urine pregnancy test as indicated in Table 1 (bi-weekly/ monthly) during |

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| | the study and up to 16 weeks after study treatment discontinuation;<br>• must use methods of contraception, as described in Section 4.5.2, from the Screening visit until 16 weeks after study treatment discontinuation.<br>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].<br>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.<br>6. History or presence at Screening of positive anti-nuclear antibodies (ANA) or anti-double-stranded DNA (anti-dsDNA) antibodies.<br>7. Currently treated for at least 30 days prior to Randomization with stable doses of one or more of the following background medications:<br>• Non-steroidal anti-inflammatory drugs (NSAIDs),<br>• Corticosteroids (≤ 10 mg/day prednisolone or equivalent),<br>• Anti-malarials (≤ 400 mg/day hydroxychloroquine, ≤ 500 mg/day chloroquine, ≤ 100 mg/day quinacrine)[#],<br>• Mycophenolate mofetil (≤ 2 g/day)[#],<br>• Azathioprine (≤ 2 mg/kg/day)[#],<br>• Methotrexate (≤ 20 mg/week)[#].<br><br>[#]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**<br>1. Breastfeeding, pregnant women or women planning to become pregnant during the study.<br>**SLE disease**<br>2. Subjects with active lupus nephritis (defined by proteinuria > 1 g/24 h, or equivalent using spot urine |

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| | 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.<br>3. Subjects presenting with a SLEDAI-2K score > 12 at Screening or at Randomization.<br>**Cardiovascular**<br>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).<br>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.<br>6. History or presence of ischemic heart disease.<br>7. History or presence of myocarditis or endocarditis.<br>8. Presence of valvular heart disease associated with symptoms or hemodynamic change.<br>9. History of syncope associated with cardiac disorders.<br>10. History or presence of cardiac failure.<br>11. Systemic arterial hypertension not controlled by medication according to investigator judgment.<br>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.<br>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.<br>14. Known pulmonary arterial hypertension of functional class III or IV.<br>**Pulmonary**<br>15. History or presence of severe respiratory disease or |

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| | pulmonary fibrosis, based on medical history, lung function and chest X-ray (CXR) performed at Screening or within 3 months prior to Screening.<br>16. Bronchial asthma or chronic obstructive pulmonary disease.<br>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.<br>**Treatments**<br>18. Treatment or planned treatment with the following medications*:<br>a. Within 15 days or 5 half-lives of the medication, whichever is longer, prior to Randomization:<br>o β-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR-lowering systemic therapy (list of drugs provided in Appendix 1).<br>o QT-prolonging drugs with known risk of torsades de pointes, for any indication (list of drugs provided in Appendix 2).<br>o Short- and long-acting β2-agonists (e.g., albuterol, levalbuterol, formoterol, terbutaline salmeterol).<br>b. Within 30 days or 5 half-lives of the medication, whichever is longer, prior to Randomization:<br>o Cyclophosphamide, cyclosporine, tacrolimus, sirolimus, etc.,<br>o Pulse methylprednisolone<br>o Vaccination with live vaccines.<br>c. Within 90 days prior to Randomization:<br>o Belimumab, leflunomide,<br>o 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).<br>d. Within 12 months prior to Randomization:<br>o B cell-depleting biological agents such as rituximab or ocrelizumab.<br>e. Any time prior to Randomization:<br>o Alemtuzumab, sphingosine-1-phosphate (S1P) modulators (e.g., fingolimod). |

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| | *For immunosuppressants or anti-inflammatory drugs not listed among the fordidden medications, the investigator should discuss adequate wash-out time with the sponsor.<br>**Infection and infection risk**<br>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.<br>20. Ongoing known bacterial, viral or fungal infection that is of clinical concern in the judgment of the investigator.<br>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.<br>22. Hepatitis B and C, congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at Screening.<br>23. Negative antibody test for varicella-zoster virus at Screening.<br>**Malignancy**<br>24. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation.<br>**Transplantation**<br>25. History or presence of bone marrow or solid organ transplantation.<br>**Ophthalmology**<br>26. Presence of macular edema or active uveitis.<br>**Metabolic and hepatic**<br>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.<br>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.<br>29. TBL > 1.5-fold upper limit of normal (ULN; unless in the context of known Gilbert's Syndrome). |

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| | 30. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2-fold ULN.<br>**Hematology**<br>31. Hemoglobin < 9 g/dL.<br>32. White blood cell count < 2500/μL ($2.5 \times 10^9$/L).<br>33. Lymphocyte count < 800 /μL ($0.8 \times 10^9$/L).<br>34. Platelets < 75,000/μL ($75 \times 10^9$/L).<br>**Renal**<br>35. Proteinuria > 1.0 g/24 hour or equivalent using spot urine protein-to-creatinine ratio.<br>36. Estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$.<br>**Other categories**<br>37. History of clinically significant drug or alcohol abuse.<br>38. Known allergy to S1P receptor 1 modulators or any of the ACT-334441 formulation excipients.<br>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.<br>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**<br>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.<br><br>**Placebo**<br>Placebo matching ACT-334441 capsules administered orally o.d. in the morning. |

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| CONCOMITANT THERAPY | **Allowed concomitant therapy**<br>• i.v. atropine in the event of symptomatic bradycardia [see study-specific criteria for permanent discontinuation of study treatment in Section 5.1.10;<br>• Dilating eye drops, mydriatics, including parasympathetic antagonists (e.g., tropicamide) or sympathetic agonists (e.g., phenylephrine) for topical use;<br>• Vaccination with non-live vaccines;<br>• 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);<br>• Topical treatment therapy including topical use of corticosteroid;<br>• 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;<br>• Stable NSAID chronic therapy. Therapy is not to be started or stopped during the study;<br>– Temporary use and/or dose change for treatment of non-SLE-related conditions (e.g., headache, menstrual cramps) is allowed;<br>• 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.<br>**Forbidden concomitant medication**<br>• Immunosuppressives not listed in allowed concomitant medication such as cyclophosphamide, cyclosporine, |

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| | leflunomide, sirolimus, tacrolimus, etc.;<br>• Immunosuppressive or immunomodulatory biological agents (e.g., belimumab, i.v. immunoglobulin, rituximab, S1P modulators other than ACT-334441);<br>• β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR-lowering therapy (as listed in Appendix 1);<br>• QT-prolonging drugs with known risk of torsades de pointes (list of drugs provided in Appendix 2);<br>• Short- and long-acting $\beta_2$-agonists (e.g., albuterol, levalbuterol, formoterol, terbutaline salmeterol);<br>• Vaccination with live vaccines. |
| ENDPOINTS | **Pharmacodynamic endpoints**<br>• Change in total lymphocyte count from baseline to EOT<br>• Change in total lymphocyte count from baseline to each post-baseline assessment<br>**Safety endpoints**<br>The treatment-emergent period is defined as the time from first study treatment intake up to 6 weeks (inclusive) after last study treatment intake.<br>• Treatment-emergent adverse events (AEs), SAEs, and adverse events of special interest (AESI[#]);<br>• AEs leading to premature discontinuation of study treatment;<br>• 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;<br>• Occurrence of treatment-emergent 12-lead ECG outliers (e.g., HR, PR, QTc defined in the Statistical Analysis Plan [SAP]);<br>• Occurrence of treatment-emergent 12-lead ECG abnormalities;<br>• Occurrence of treatment-emergent ECG-Holter |

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| | abnormalities on Day 1;<br>• Change in SBP and DBP from baseline up to EOS;<br>• Change in $FEV_1$ and FVC, expressed in absolute value (L) and percent value from baseline up to EOS;<br>• Occurrence of treatment-emergent decrease of $FEV_1$ or FVC > 15% from baseline values;<br>• Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline up to EOS;<br>• 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);<br>• Change in protein-to-creatinine ratio from baseline to EOT;<br>• Change in body weight from baseline to EOT.<br>[#]AESI considered for the analyses are described in Appendix 3.<br><br>**Pharmacokinetic endpoints**<br>• $C_{trough}$ 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);<br>• ACT-334441 plasma concentration at EOS (i.e., 6 weeks after study treatment discontinuation).<br>**Exploratory disease activity endpoints**<br>• Change in SLEDAI-2K score from baseline to each post-baseline assessment;<br>• Change in Physician's Global Assessment (PGA) score from baseline to each post-baseline assessment;<br>• Change in SLEDAI-2K mucocutaneous and/or muscoskeletal scorings from baseline to each post-baseline assessment.<br>**Quality of life endpoints**<br>• Change in SF-36v2™ Health Survey domain and |

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| | component scores from baseline to EOT.<br>**Exploratory biomarker endpoints**<br>• Change in immunoglobulin serum levels (IgG, IgM, IgA) from baseline to each post-baseline assessment;<br>• Change in ANA and anti-dsDNA antibody titers from baseline to each post-baseline assessment;<br>• 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;<br>• 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.<br>The SAP will be finalized prior to database lock.<br>Baseline is defined as the last assessment prior to initiation of the study treatment.<br>**Analysis sets**<br>Screened Analysis Set: includes all subjects who were screened and received a subject number.<br>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.<br>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.<br>Full Analysis Set (FAS): includes all randomized subjects. Subjects will be analyzed according to their randomized |

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| | treatment.<br><br>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.<br><br>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.<br><br>**Pharmacodynamic variable**<br><br>The change in lymphocyte count from baseline to EOT is defined as:<br><br>• Total lymphocyte count at EOT – total lymphocyte count at baseline<br><br>Last observation carried forward (LOCF; using the Week 4 visit or later) will be used for subjects with a missing EOT assessment.<br><br>**Exploratory disease activity variables**<br><br>The change from baseline in the SLEDAI-2K (modified to exclude leukopenia) score at each visit is calculated as :<br><br>• SLEDAI-2K score at each visit – SLEDAI-2K score at baseline.<br><br>The change from baseline in PGA score and the SLEDAI-2K mucocutaneous and/or muscoskeletal score will be calculated in a similar manner.<br><br>**Overall testing strategy for the pharmacodynamic endpoint**<br><br>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.<br><br>**Pharmacodynamic endpoint analysis**<br><br><u>Null and alternative hypotheses</u><br><br>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%.

Main pharmacodynamic 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 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

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| | correlation matrix $\Sigma_{Dunnett}$.<br><br>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.<br><br>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.<br><br>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.<br><br>This analysis will be performed on the PD analysis set, and a supportive analysis will be performed on the FAS and the PPS.<br><br>**Exploratory efficacy endpoint analysis**<br><br>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.<br><br>Other changes from baseline variables will be analyzed in a similar manner using an ANCOVA.<br><br>All exploratory efficacy endpoints will be analyzed on the FAS and PPS populations. |

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| | No multiplicity adjustments will be made on exploratory efficacy endpoints.<br><br>**Safety endpoints**<br><br>Safety endpoints will be mainly analyzed descriptively by treatment group on the Safety Set.<br><br>**Sample size**<br><br>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 = $2.0 \times 10^9$/L) for placebo and a maximum of 70% for any ACT-334441 dose (mean at Week 12 = $0.6 \times 10^9$/L). The pooled SD is assumed to be $0.45 \times 10^9$/L. This takes into account 10% of subjects being excluded from the PD analysis set.<br><br>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]).<br><br>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**<br><br>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 |

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| | 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.<br><br>**Ophthalmology Safety Board**<br><br>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. |

## 15.2 Discussion and further considerations of the applied statistical methods

### 15.2.1 Clinical laboratory evaluation

**Table 16 Clinical laboratory evaluation: Marked abnormalities in laboratory parameters (adapted from Table 5 from the Clinical Study Protocol)**

| Category | Test Code | Test Name | Standard Unit | Sex | LLL | LL | LO | HI | HH | HHH |
|---|---|---|---|---|---|---|---|---|---|---|
| CHEMISTRY | ALB | Albumin | g/L | | < 20 | < 30 | 35 | 52 | 71 | NA |
| CHEMISTRY | ALP | Alkaline Phosphatase | U/L | F | NA | NA | 42 | 98 | > 2.5 ULN | > 5 ULN |
| CHEMISTRY | ALP | Alkaline Phosphatase | U/L | M | NA | NA | 53 | 129 | > 2.5 ULN | > 5 ULN |
| CHEMISTRY | ALT | Alanine Aminotransferase | U/L | F | NA | NA | 0 | 33 | ≥ 3 ULN | ≥ 5 ULN |
| CHEMISTRY | ALT | Alanine Aminotransferase | U/L | M | NA | NA | 0 | 44 | ≥ 3 ULN | ≥ 5 ULN |
| CHEMISTRY | AST | Aspartate Aminotransferase | U/L | F | NA | NA | 14 | 34 | ≥ 3 ULN | ≥ 5 ULN |
| CHEMISTRY | AST | Aspartate Aminotransferase | U/L | M | NA | NA | 14 | 39 | ≥ 3 ULN | ≥ 5 ULN |

| Category | Test Code | Test Name | Standard Unit | Sex | LLL | LL | LO | HI | HH | HHH |
|---|---|---|---|---|---|---|---|---|---|---|
| CHEMISTRY | BILI | Bilirubin | umol/L | | NA | NA | 5.1 | 20.5 | ≥ 2 ULN | ≥ 5 ULN |
| CHEMISTRY | BUN | Blood Urea Nitrogen | mmol/L | | NA | NA | 3.2 | 8 2 | 20.5 | 41.0 |
| CHEMISTRY | CA | Calcium | mmol/L | | < 1.75 | < 2.0 | 2.15 | 2 55 | > 2.9 | > 3.1 |
| CHEMISTRY | CHOL | Cholesterol | mmol/L | | NA | NA | 0 | 5 2 | > 7.75 | > 12.92 |
| CHEMISTRY | CL | Chloride | mmol/L | | NA | 74 | 99 | 109 | 131 | NA |
| CHEMISTRY | CREAT | Creatinine | umol/L | F | NA | NA | 44 | 97 | > 1.5 ULN or > 1 5 × baseline | > 3 ULN or > 3 × baseline |
| CHEMISTRY | CREAT | Creatinine | umol/L | M | NA | NA | 62 | 115 | > 1.5 ULN or > 1 5 × baseline | > 3 ULN or > 3 × baseline |
| CHEMISTRY | GRFE | Creatinine Clearance | mL/min/1.73 m2 | | <30 | <60 | 60 | NA. | NA | NA |
| CHEMISTRY | GLUC | Glucose | mmol/L | | < 2.2 | < 3.0 | 3.3 | 5 5 | > 8.9 | > 13.9 |
| CHEMISTRY | K | Potassium | mmol/L | | < 3.0 | < 3.2 | 3.5 | 5 1 | > 5.5 | > 6.0 |
| CHEMISTRY | LDH | Lactate Dehydrogenase | U/L | | NA | NA | 120 | 246 | >=524 | NA |
| CHEMISTRY | PROT | Protein | g/L | | NA | 39 | 64 | 83 | 101 | NA |
| CHEMISTRY | SODIUM | Sodium | mmol/L | | < 130 | NA | 136 | 145 | > 150 | > 155 |
| CHEMISTRY | TRIG | Triglycerides | mmol/L | | NA | NA | 0 | 1.68 | > 3.42 | > 11.4 |
| CHEMISTRY | URATE | Urate | umol/L | F | NA | NA | 137 | 393 | > 590 | > 720 |
| CHEMISTRY | URATE | Urate | umol/L | M | NA | NA | 262 | 452 | > 590 | > 720 |
| COAGULATION | APTT | Activated Partial Thromboplastin Time | sec | | NA | 14.0 | 24 | 37 | > 1.5 - 2 5 × ULN | > 2.5 × ULN |

| Category | Test Code | Test Name | Standard Unit | Sex | LLL | LL | LO | HI | HH | HHH |
|---|---|---|---|---|---|---|---|---|---|---|
| COAGULATION | FIBRINO | Fibrinogen | g/L | | < 0.25 LLN or < 75% decrease from baseline or absolute value < 0.5 | < 0.75 - 0.5 LLN or 25 - < 50% decrease from baseline | 2.1 | 4.7 | 6.0 | NA |
| COAGULATION | INR | Prothrombin Intl. Normalized Ratio | Fraction of 1 | | NA | NA | 0.8 | 1 2 | ≥ 1.5 ULN | ≥ 2.5 ULN |
| COAGULATION | PT | Prothrombin Time | sec | | NA | NA | 9.4 | 13 | NA | 100.1 |
| HEMATOLOGY | EOS | Eosinophils | 10e9/L | | NA | NA | 0 | 0 5 | > 5.0 | ND |
| HEMATOLOGY | HCT | Hematocrit | L/L | F | < 20 | < 28 | 0.364 | 0.489 | > 55 | > 65 |
| HEMATOLOGY | HCT | Hematocrit | L/L | M | < 20 | < 32 | 0.416 | 0 541 | > 60 | > 65 |
| HEMATOLOGY | HGB | Hemoglobin | g/L | F | < 80 g/L | < 100 g/L | 115 | 160 | Increase in > 20 g/L above ULN or Increase in > 20 g/L above baseline (if baseline is above ULN) | Increase in > 40 g/L above ULN or Increase in >40g/L above baseline (if baseline is above ULN) |

| Category | Test Code | Test Name | Standard Unit | Sex | LLL | LL | LO | HI | HH | HHH |
|---|---|---|---|---|---|---|---|---|---|---|
| HEMATOLOGY | HGB | Hemoglobin | g/L | M | < 80 | < 100 | 130 | 175 | Increase in > 20 g/L above ULN or Increase in > 20 g/L above baseline (if baseline is above ULN) | Increase in > 40 g/L above ULN or Increase in > above baseline (if baseline is above ULN) |
| HEMATOLOGY | NEUT | Neutrophils | 10e9/L | | < 1.0 | < 1.5 | 1.8 | 7.7 | 15.4 | NA |
| HEMATOLOGY | PLAT | Platelets | 10e9/L | | < 50.0 | < 75 | 130 | 400 | > 600 | > 999 |
| HEMATOLOGY | RBC | Erythrocytes | 10e12/L | | NA | NA | 3.8 | 5 2 | NA | NA |
| HEMATOLOGY | RBC | Erythrocytes | 10e12/L | M | NA | NA | 4.5 | 5 9 | NA | NA |
| HEMATOLOGY | WBC | Leukocytes | 10e9/L | F | < 1.9 | NA | 4.5 | 11.0 | > 20.0 | > 100.0 |
| HEMATOLOGY | LYM | Lymphocytes | 10e9/L | | < 0.2 | NA | 1.00 | 4.80 | > 4.0 | ≥ 8 |
| URINALYSIS | PROT | Protein | mg/L | | NA | NA | 10 | 140 | 1000 | 3500 |
| URINALYSIS | PROTCRT | Protein/Creatinine | g/mol | | NA | NA | 1.1 | 12.1 | >100 | >300 |
| URINALYSIS | PROTCRT | Protein/Creatinine | g/mol | | NA | NA | 1.7 | 7.7 | >100 | >300 |

### 15.2.2 Definitions of AEs of special interest, S1P1 compounds (09-Sep-2016)

The definitions for adverse events of special interest are based on systematic approach using Standardized MedDRA Queries (SMQ). The additional relevant term can be added to the search or deleted appropriately providing the rationale for the change. The current proposal is based on MedDRA version 19.0. The following safety areas are addressed by the pre-defined adverse events of special interest:

- **Effect on heart rate and rhythm AESI (including hypotension)**

Effect on heart rate and rhythm AESI are identified by the preferred terms in the following SMQ: **Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ).** In addition, to the preferred terms included in Bradyarrhythmias (including conduction defects and disorders of sinus node function (SMQ)), the following preferred terms will be added to the search for AEs addressing effects on heart rate and rhythm: “BRADYCARDIA”, “ELECTROCARDIOGRAM RR INTERVAL PROLONGED”, “HEART RATE DECREASED”, “CHRONOTROPIC INCOMPETENCE”, “PRESYNCOPE”, “SYNCOPE” and “LOSS OF CONSCIOUSNESS”.
The following preferred terms will be added to the search for AEs addressing hypotension: “BLOOD PRESSURE DECREASED”, “BLOOD PRESSURE DIASTOLIC DECREASED”, “BLOOD PRESSURE ORTHOSTATIC DECREASED”,”BLOOD PRESSURE SYSTOLIC DECREASED”, “DIASTOLIC HYPOTENSION”, “MEAN ARTERIAL PRESSURE DECREASED”, “ORTHOSTATIC HYPOTENSION”, “PROCEDURAL HYPOTENSION”, “HYPOTENSION”, “CIRCULATORY COLLAPSE”, “BLOOD PRESSURE FLUCTUATION”, “LABILE BLOOD PRESSURE” and “BLOOD PRESSURE AMBULATORY DECREASED”.

- **Cardiovascular AESI**

Cardiovascular AESI are identified by any preferred term in the following SMQs: **Ischemic heart disease (SMQ)** or **Cardiomyopathy (SMQ) or Cardiac failure (SMQ)** excluding the preferred term “DYSPNOEA” .

- **Hypertension AESI**

Hypertension AESI are identified by the preferred terms in the following SMQ: **Hypertension (SMQ)**

- **Hepatobiliary disorders / Liver enzyme abnormality AESI**

Hepatobiliary disorders/ Liver enzyme abnormality AESI are identified by the preferred terms in the following SMQ: **Drug related hepatic disorders - comprehensive search (SMQ)** This SMQ is included in the SMQ Hepatic disorder (SMQ) but only the preferred terms included in Drug related hepatic disorders - comprehensive search (SMQ) are included to identify hepatobiliary disorders / Liver enzyme abnormality AESI.

- **Pulmonary AESI**

These AEs are identified by the preferred terms the in the following SMQs: **Asthma/bronchospasm (SMQ)** or **Interstitial lung disease (SMQ).** The preferred terms "DYSPNOEA AT REST", "DYSPNOEA" and "DYSPNOEA EXERTIONAL" are added to the search pre-defined by SMQs Asthma/bronchospasm or Interstitial lung disease. SMQs related to respiratory system do not cover the preferred terms on investigations (i.e., AEs based on PFT or chest X Ray or CT scan). Therefore, any preferred term from the MedDRA System Organ Class (SOC) 'Investigations' identified by the following high level terms (HLT) are added to the search: '**Respiratory tract and thoracic histopathology procedures' (HLT)** or '**Respiratory tract and thoracic imaging procedures' (HLT)** and **'Respiratory and pulmonary function diagnostic procedures**' **(HLT)** with the exception of the following preferred terms: 'CAPNOGRAM NORMAL', 'END-TIDAL CO2 NORMAL', 'EXPIRATORY RESERVE VOLUME NORMAL', 'FORCED EXPIRATORY VOLUME NORMAL', 'FORCED VITAL CAPACITY NORMAL', 'FUNCTIONAL RESIDUAL CAPACITY NORMAL', 'INSPIRATORY CAPACITY NORMAL', 'MAXIMAL VOLUNTARY VENTILATION NORMAL', 'PEAK EXPIRATORY FLOW RATE NORMAL', 'PULMONARY FUNCTION CHALLENGE TEST NORMAL', 'PULMONARY FUNCTION TEST NORMAL', 'RHINOMANOMETRY NORMAL', 'SPIROMETRY NORMAL', 'TOTAL LUNG CAPACITY NORMAL', 'VITAL CAPACITY NORMAL'.

- **Macular edema AESI**

Macular edema AESI are identified by the following preferred terms: "MACULAR OEDEMA", "MACULAR HOLE", "MACULAR PSEUDOHOLE", "MACULAR RUPTURE", "MACULAR CYST", "RETINAL OEDEMA", "DIABETIC RETINAL OEDEMA", "CYSTOID MACULAR OEDEMA", "PAPILLOEDEMA", and "PSEUDOPAPILLOEDEMA".

- **Infection AESI**

Infection AESI are identified by the adverse events belonging to the SOC (System Organ Class) **Infections and Infestations (SOC)**, only if reported as **serious or severe**.

- **Herpetic infection AESI**

Herpetic infection AESI are identified by the preferred terms in the following high level terms: **Herpes viral infections (HLT)** and the following preferred term will be added to the search for AEs addressing varicella zoster infection: "ENCEPHALITIS POST VARICELLA", "HERPES GESTATIONIS", "HERPES SIMPLEX TEST POSITIVE", "HUMAN HERPES VIRUS 6 SEROLOGY POSITIVE", and "HUMAN HERPES VIRUS 8 TEST POSITIVE".

- **Skin malignancy AESI**

Skin malignancy AESI are identified by the preferred terms in the following SMQs: **Skin neoplasmsm malignant and unspecified (SMQ)** or **Skin premalignant disorders (SMQ).**

- **Non-skin malignancy AESI**

Non-skin malignancy AESI are identified by the preferred terms in the following SMQ: **Malignant tumours** excluding the preferred terms included in the following SMQs: **Skin neoplasms, malignant and unspecified (SMQ)** or **Skin premalignant disorders (SMQ).**

- **Stroke AESI**

Stroke AESI are identified by any preferred term in the following SMQ: **Central nervous system haemorrhages and cerebrovascular conditions (SMQ).** This SMQ consists of 3 following SMQs: Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic cerebrovascular conditions (SMQ) and Ischaemic cerebrovascular conditions (SMQ).

- **Seizure AESI**

Seizure AESI are identified by any preferred term in the following SMQ: **Convulsions (SMQ).**

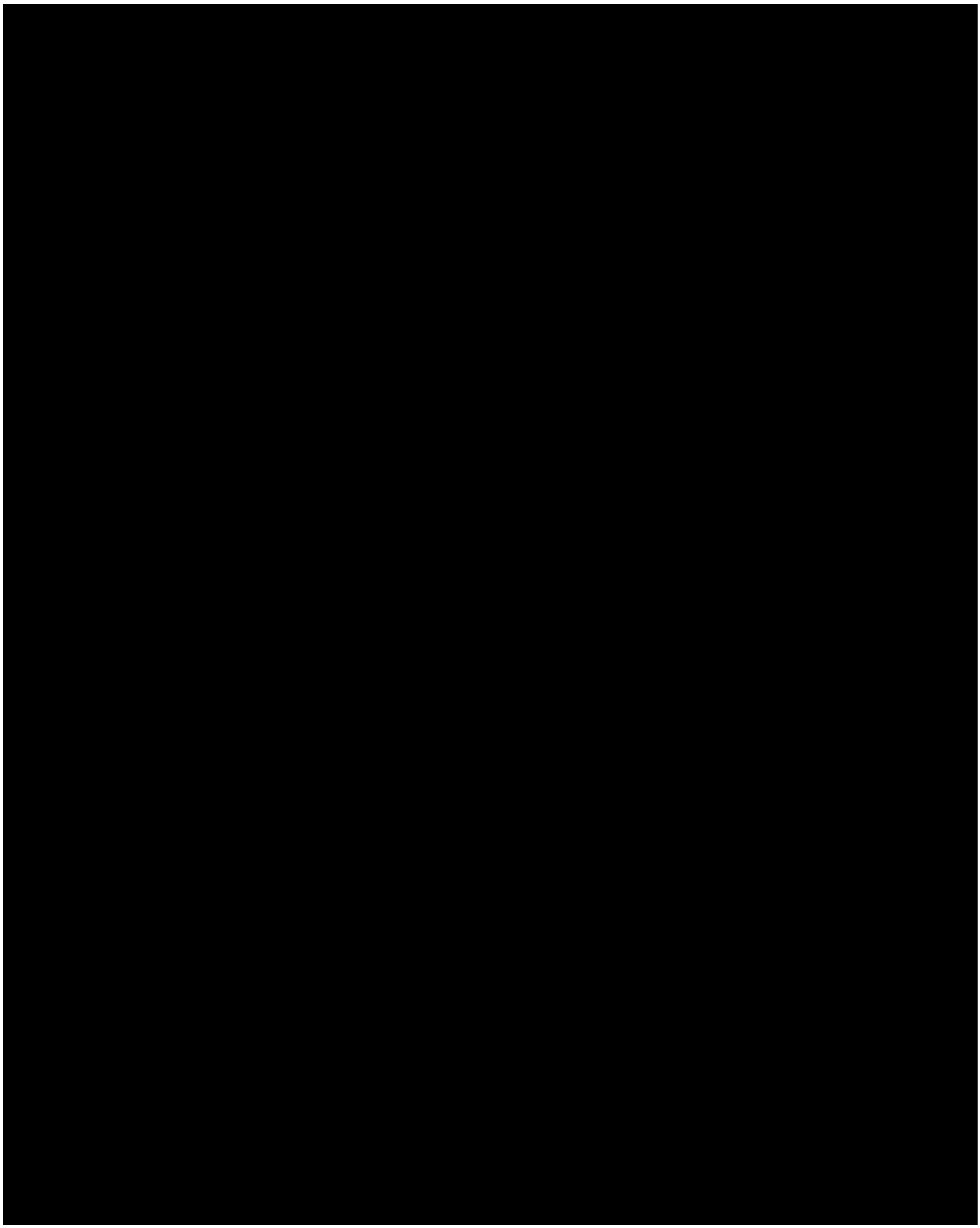
### 15.2.3 SF-36 scoring

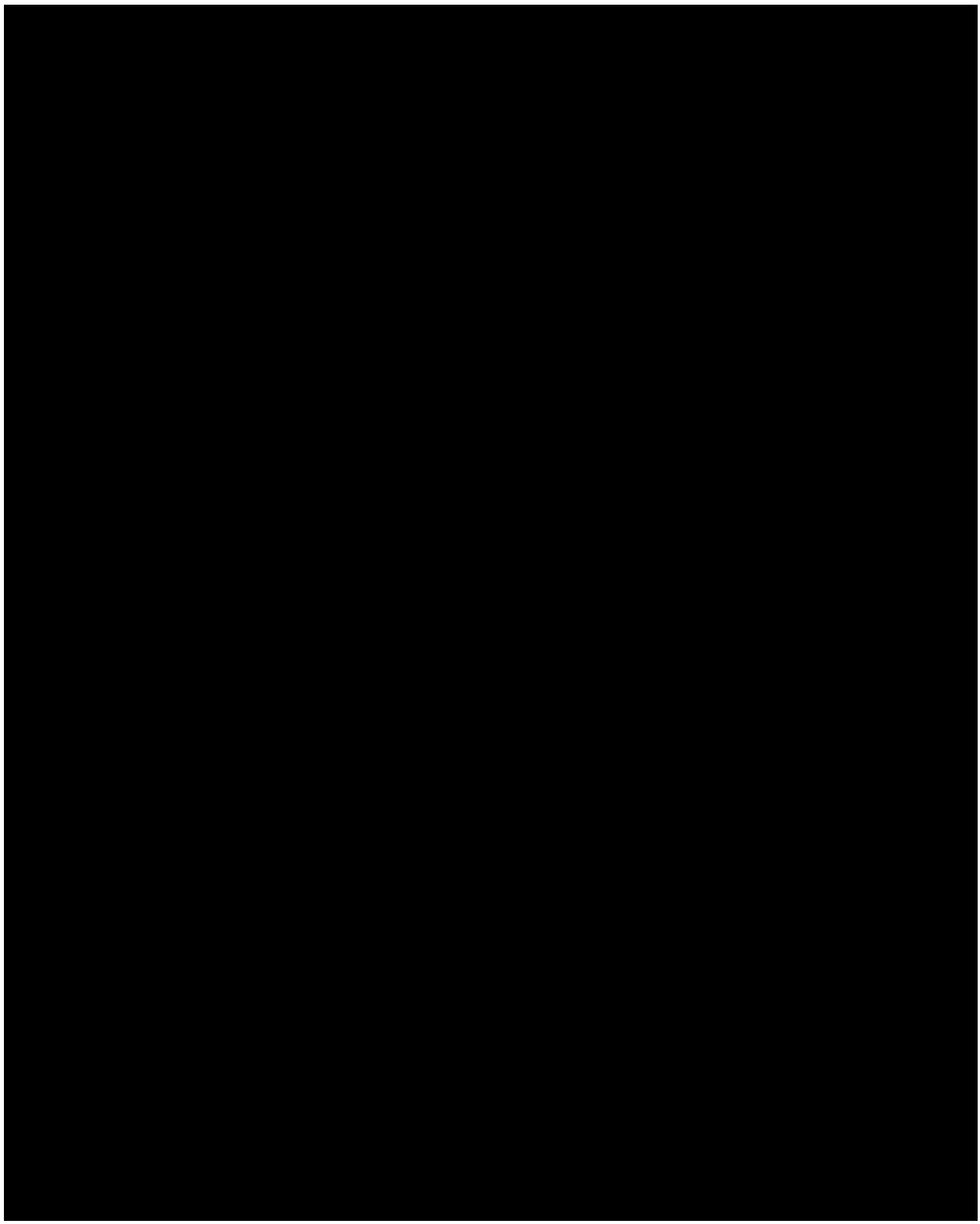
Recoding items

Scores for each question response are indicated on the questionnaire [redacted]

[redacted]

[redacted]





[redacted]

Missing data

For an individual domain where 50% or more of the item questions are non-missing, the average of the non-missing items for that subject in that domain is calculated. This average is then be used to impute the remaining missing item questions of that domain. Note imputation should be based on the final domain score after recalibration / reverse scores of precoded scores. If more than 50% of item questions are missing the domain is recorded as missing. Aggregated scores are computed after the imputation rule has been applied to the component domains, but are set to missing if any domain is missing. Subjects with missing aggregate scores are excluded from analyses and summary statistics.

## 15.3 Document history

| Version | Effective Date | Reason |
|---|---|---|
| 1.0 | 20 April 2017 | New |