Protocol Number: D3461C00009

Official Title: A Multicentre, Randomised, Double-blind, Placebo-Controlled Phase 3 Extension Study to Characterise the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

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Study Statistician [redacted] 27-Apr-22
Date

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Global Product Statistician [redacted]

26 Apr 2022
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AST	Aspartate transaminase
[redacted]	[redacted]
BDR	Blind delivery review
BMI	Body mass index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Clinical research organisation
CSR	Clinical Study Report
CV-EAC	Cardiovascular Event Adjudication Committee
dsDNA	Double-stranded deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDV	Early Discontinuation Visit
[redacted]	[redacted]
GGT	gamma glutamyl transferase
IFN	Interferon
IP	Investigational product
IV	Intravenous
IXRS	Interactive Voice/Web Response System
LOCF	Last observation carried forward
LTE	Long-term extension

Abbreviation or special term	Explanation
MACE	Major adverse cardiovascular events
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
OCS	Oral corticosteroids
[redacted]	[redacted]
PGA	Physician's Global Assessment
[redacted]	[redacted]
[redacted]	[redacted]
Q	Question
Q-Q	Quartile-quartile
Q4W	Every 4 weeks
SAE	Serious adverse event
SD	Standard deviation
[redacted]	[redacted]
TELVC	Treatment-emergent laboratory/vital signs changes
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
[redacted]	[redacted]
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOC	Standard of care
ULN	Upper limit of normal
[redacted]	[redacted]
WHO-DD	World Health Organization Drug Dictionary
WOCF	Worst observation carried forward
[redacted]	[redacted]

AMENDMENT HISTORY

Date	Brief description of change
29 Jul 2019 (v2.0)	• Clarified the definition of treatment groups and added a descriptive figure. • Added the Full Analysis Set – LTE Study analysis set for use in the LTE only summaries. • Removed reference to treatment-emergent Adverse Events (AEs) and added definitions for the categories: AEs during treatment, follow-up and during treatment and follow-up. Added analyses by categories for select AE summaries. • Expanded the definition for duration of exposure to account for specific treatment groups. [redacted] [redacted] [redacted] • Added to the changes from protocol specified analyses to identify clarification for the treatment groups and analysis sets.

Date	Brief description of change
15 Apr 2020 (v3.0)	• Updates which are editorial in nature and do not impact the analyses are not listed. • Section 3.1: Added clarification regarding the analysis of data from subjects who did not participate in the LTE in non-visit-based analyses. • Section 3.1.1: Updated the definition of "Year 1". • Section 4.1.1: Updated the sentence regarding the exclusion of subject [redacted] from analyses. • Section 0: Updated rules in case of multiple readings recorded within a single visit window (unscheduled vs. scheduled visits; antinuclear antibody titres; week 52 data from Phase 3 feeder studies which were imputed using LOCF). • Section 4.1.4: Clarified the use of LOCF. • Section 4.1.4: Clarified the calculation of scores.
17 Mar 2021 (v4.0)	• Section 4.1.1: Added the paragraph regarding the exclusion of site [redacted] from analyses.

Date	Brief description of change
14 Apr 2022 (v5.0)	• Updates which are editorial in nature and do not impact the analyses are not listed. • Added definitions and analyses of COVID-19 events and impact of the COVID-19 pandemic on the analysis. Sections 2.2, 3.1.1, 3.3.5, 4.2.1.1, 4.2.3.1. • Section 4.1.1: Added the paragraph regarding the exclusion of site [redacted] from analyses. • Section 3.2.3.3: Added details regarding faulty reagents issue. • Section 4.1.1, 4.2.1.1: Sensitivity analyses including ALL patients (including the patients excluded), add subjects to be excluded. • Safety: 90% CI replaced by 95% CI • Addition of safety analysis set (section 2.1.3) and safety analysis set – LTE study (section 2.1.4) • Section 3.1.6: Cholesterol to be considered only if the subject fasted for at least 8 hours prior to the assessment. [redacted] • Section 3.3.3: Updated definition of concomitant medication – include medication up to end of study/participation). • Section 3.3.4: Added definition of infusion of IP. • Section 4.1.2: Update of visit windows to cover safety follow-up after week 208. [redacted] • Section 4.2.3.1: Updated wording regarding completion of the phase 3 feeder studies. • Section 5: Add details regarding the interim analysis.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measure:
To characterise the long-term safety and tolerability of intravenous (IV) anifrolumab	Rates of adverse events of special interest (AESIs) and serious adverse events (SAEs)

1.1.2 Secondary objectives (not applicable)

1.1.3 Safety objective

See Section 1.1.1 Primary objective.

[redacted]

1.2 Study design

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled extension study characterising the long-term safety and tolerability of an IV treatment regimen of anifrolumab (300 mg) versus placebo in subjects with moderately to severely active systemic lupus erythematosus (SLE) who completed a Phase 3 study (D3461C00004 or D3461C00005) through the 52-week double-blind treatment period.

Approximately 575 subjects from Studies D3461C00004 or D3461C00005 (also referred to as the feeder studies) who were previously treated with anifrolumab (150 or 300 mg) or placebo for 52 weeks while receiving standard of care (SOC) treatment and who are willing to continue treatment may participate in the long-term extension (LTE) study if all eligibility criteria are met. Subjects will receive either a fixed IV dose of 300 mg anifrolumab every 4 weeks (Q4W) for up to 39 doses (LTE Week 0 to LTE Week 152) or placebo. Investigational product (IP) will be administered as an IV infusion via an infusion pump over a minimum of 30 minutes, Q4W.

In order to ensure that subjects with active SLE who enter the LTE will have adequate treatment of their disease in this 3-year blinded, placebo-controlled extension study, Investigators will be allowed to change the background SOC treatment for SLE during the course of the study. This LTE protocol allows for adding a new oral immunosuppressant or changing background immunosuppressants, as well as for flexible oral corticosteroids (OCS) use, so that subjects may achieve adequate control of their disease on study. However, it is recommended that subjects receive the lowest possible corticosteroid dose.

In the LTE study, treatment assignment will follow an Interactive Voice/Web Response System (IXRS) algorithm as follows:

- Subjects previously treated with anifrolumab 300 mg IV will stay on blinded treatment
- Subjects previously treated with anifrolumab 150 mg will switch to blinded anifrolumab 300 mg
- Subjects previously randomised to placebo will be re-randomised 1:1 to blinded anifrolumab 300 mg or placebo

Therefore, in the LTE study subjects will receive double-blind treatment with either anifrolumab 300 mg or placebo in an approximate ratio of 4:1.

Although the study will initially be completely double-blind (ie, blind for subjects, Investigators/site staff, and Sponsor/designated clinical research organisation [CRO]), at the conclusion of the Phase 3 Studies D3461C00004 or D3461C00005 treatment allocation for all subjects who were previously on active treatment will become known to the Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator and investigational site staff, for select roles at the CRO, and for the subjects. Further details are described in a separate unblinding plan.

In general, the first dose of study drug in the LTE study (LTE Day 1/Visit 1/Week 0) should occur on the same day as the final study visit of the prior study (ie, Week 52); however, special circumstances may warrant a delay in subject randomisation of up to 30 days following the final visit of the prior study (ie, Week 52). Administration of study drug in the LTE study should not occur until all LTE Day 1/Visit 1/Week 0 evaluations are completed.

This LTE study includes:

- **Treatment Period**: A 156-week treatment period with investigational product administered Q4W from LTE Week 0 to LTE Week 152 for a total of 39 doses. During the treatment period, visits will be scheduled for each Q4W administration.
- **At LTE Week 156 (or after the last dose of investigational product)** subjects will continue in the study for another 8 weeks to complete a 12-week safety follow up after the last dose of investigational product (last dose of investigational product will be given at LTE Week 152).

The total study duration will be up to approximately 164 weeks (including a 12-week Follow up Period after administration of the final dose).

Once subjects have completed Studies D3461C00004 or D3461C00005 (through Week 52), signed the informed consent form, and met all study eligibility criteria, they may be included in the LTE study.

In the event a site has not obtained the required approval (e.g., regulatory authority, local ethics committee) by the time a subject is eligible to be randomised in the LTE study, the site may be allowed the time to obtain the approval(s).

If due to regulatory delays or other exceptional circumstances it is likely that LTE Day 1/Visit 1/Week 0 will occur greater than 30 days after the final visit of the prior study, the PRA Medical Monitor must be contacted to confirm that the subject will be permitted to be randomised. The rationale for the delayed start, date of last dose of study drug, and subject compliance in the prior study will be reviewed to determine whether the subject will be permitted to be randomised. In addition, all Day 1/Visit 1/Week 0 visit procedures must be performed.

If dosing occurs on the same day of the final visit of the prior study, it should occur after all LTE Day 1/Visit 1/Week 0 assessments have been completed, the Investigator has determined that the subject can continue dosing, and the subject has been re-randomised.

Interim analyses may be performed based on regulatory or other requirements.

1.3 Number of subjects

No formal comparisons are planned in this study; point estimates and confidence intervals (CIs) will be presented for each treatment group separately. The sample size is not based on statistical considerations, but is defined as all subjects who completed the treatment period in

the Phase 3 feeder Studies D3461C00004 or D3461C00005 (through Week 52) and met all study eligibility criteria. Assuming annual dropout rates of 30%, 30%, and 20% following placebo, anifrolumab 150 mg, and anifrolumab 300 mg, and that 90% of the subjects completing studies D3461C00004 or D3461C00005 enter the LTE, follow-up times of approximately 893, 517, and 1343 subject years for the "Randomised Anifrolumab 300 mg," "Randomised Placebo," and "All Anifrolumab" treatment groups are expected. Given this exposure, the 95% CIs for an AESI for which the observed incidence rate is 10 events in 1000 subject years will be 5.21 to 19.21 for "Randomised Anifrolumab 300 mg," and 4.24 to 23.57 for "Randomised Placebo." For an AESI for which the observed incidence rate is 1 event in 1000 subject years, the 95% CI will be 0.18 to 5.42 for "All Anifrolumab" (0.13 to 7.95 for "Randomised Anifrolumab 300 mg"), and 0.07 to 15.25 for "Randomised Placebo," using the Rothman-Greenland Method (Rothman and Greenland, 1998).

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis set

All subjects enrolled in Studies D3461C00004 or D3461C00005 will be included in the main analysis of the LTE study, even if they do not enter the LTE study. Therefore, the full analysis set will consist of all subjects who were randomised and received at least 1 dose of investigational product in the Phase 3 feeder Studies D3461C00004 or D3461C00005. Subjects will be analysed according to the Intention-To-Treat principle (ie, as randomised). Subjects who withdraw consent to participate in the study will be included up to the date of their study termination.

Any major deviations from randomised treatment in the Phase 3 feeder studies or the LTE study will be listed and considered when interpreting the safety data.

2.1.2 Full analysis set – LTE Study

The full analysis set – LTE Study will consist of all subjects who were randomised and received at least 1 dose of investigational product in the LTE Study. Subjects will be analysed according to the Intention-To-Treat principle (i.e., as randomised). Subjects who withdraw consent to participate in the study will be included up to the date of their study termination.

2.1.3 Safety analysis set

The safety analysis set will comprise all subjects included in the full analysis set but with the treatment assignment based on the actual treatment received for ≥ 50% of doses in the LTE, which may differ from the randomly assigned treatment. If the safety analysis set is equivalent to the full analysis set, then the full analysis set will be used as the population description on the tables. If the safety analysis set is not equivalent to the full analysis set, key safety tables will be rerun using the safety analysis set. Any important deviations from randomised treatment will be listed and considered when interpreting the safety data.

2.1.4 Safety analysis set – LTE Study

The safety analysis set – LTE Study will comprise all subjects included in the full analysis set – LTE Study but with the treatment assignment based on the actual treatment received for ≥ 50% of doses in the LTE, which may differ from the randomly assigned treatment. If the safety analysis set – LTE is equivalent to the full analysis set – LTE, then the full analysis set – LTE will be used as the population description on the tables. If the safety analysis set – LTE is not equivalent to the full analysis set – LTE, key safety tables will be rerun using the safety analysis set – LTE. Any important deviations from randomised treatment will be listed and considered when interpreting the safety data.

[redacted]

2.1.6 Treatment groups for analysis

Summaries will be presented according to the following combined treatment groups. If not mentioned otherwise, data from subjects discontinuing from the investigational product in studies D3461C00004 or D3461C00005, or who elect not to participate in the LTE, will be considered up to the adjusted analysis-defined visit window of Week 52 (ie, up to Day 378).

Primary:

- ***Randomised Anifrolumab 300 mg:*** Subjects randomised to anifrolumab 300 mg in studies D3461C00004 or D3461C00005 using all data from start of feeder study to end of LTE.

- ***Randomised Placebo:*** Subjects randomised to placebo in studies D3461C00004 or D3461C00005 using data from start of feeder study up until switch to anifrolumab 300 mg or to end of LTE for subjects re-randomised to placebo in LTE, respectively.

Supportive:

- ***Placebo Feeder + Placebo LTE:*** Subjects randomised to placebo in Studies D3461C00004 or D3461C00005 and re-randomised to placebo in LTE using all data from start of feeder study to end of LTE. Data from subjects not randomised into the LTE for any reason but that would have been re-randomised to placebo are included in this treatment group up to Week 52. Subjects who are not randomised into the LTE study will be assigned to Placebo or anifrolumab 300 mg via a

separate randomization process in order to determine who would have been re-randomised to placebo.

- ***All Anifrolumab:*** Subjects randomised to anifrolumab in studies D3461C00004 or D3461C00005, regardless of dose, and subjects randomised to placebo in studies D3461C00004 or D3461C00005 and then re-randomised to anifrolumab 300 mg in LTE, using all data from start of feeder study or switch to anifrolumab, respectively, to end of LTE. Baseline data from the feeder study will be included for all subjects.

Additional supportive:

- ***Placebo Feeder + Anifrolumab 300 mg LTE:*** Subjects randomised to placebo in studies D3461C00004 or D3461C00005 and then re-randomised to anifrolumab 300 mg in LTE using data from start of feeder study to end of LTE. Data from subjects not randomised into the LTE for any reason, but that would have been re-randomised to anifrolumab 300 mg are included in this treatment group up to Week 52. Subjects who are not randomised into the LTE study will be assigned to Placebo or anifrolumab 300 mg via a separate randomization process in order to determine who would have been re-randomised to anifrolumab 300 mg.

- ***Anifrolumab 150 mg Feeder + Anifrolumab 300 mg LTE:*** Subjects randomised to anifrolumab 150 mg in Study D3461C00005 and then switched to anifrolumab 300 mg in LTE using data from start of feeder study to end of LTE. Data from subjects discontinuing from the investigational product in study D3461C00005, or who elect not to participate in the LTE are included in this treatment group up to Week 52.

Figure 1 Primary: Combined treatment groups Randomised Anifrolumab 300 mg and Randomised Placebo (main comparison)

Figure 2 **Supportive: Combined treatment groups Placebo Feeder + Placebo LTE and All Anifrolumab**

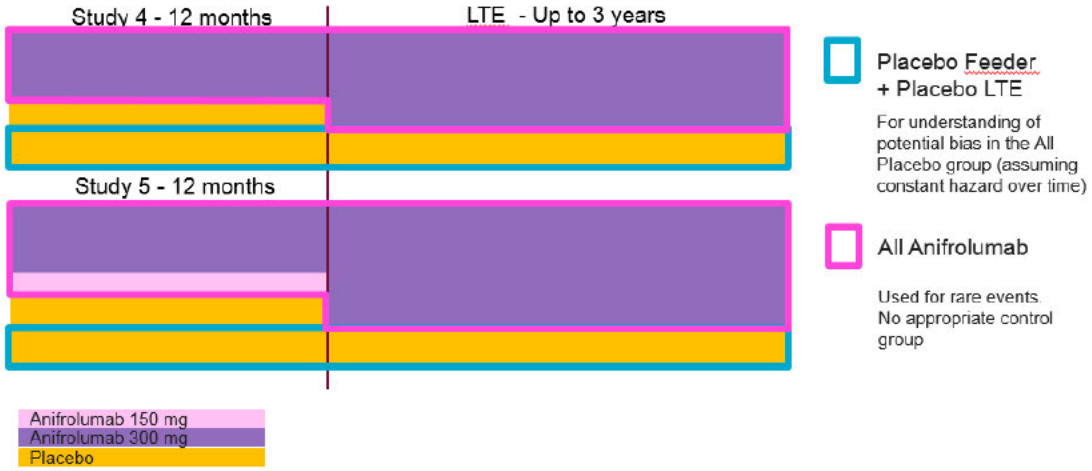
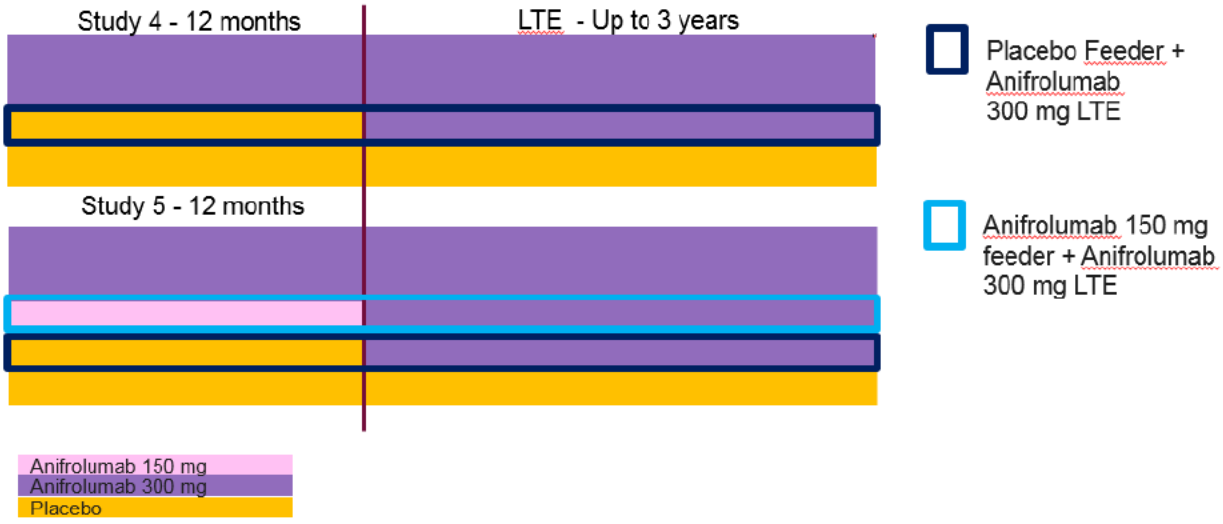


Figure 3 **Additional Supportive: Combined treatment groups Placebo Feeder + Anifrolumab 300 mg LTE and Anifrolumab 150 mg Feeder + Anifrolumab 300 mg LTE**



Additional summaries for data collected during the LTE study only will be presented according to the following supportive LTE treatment groups:

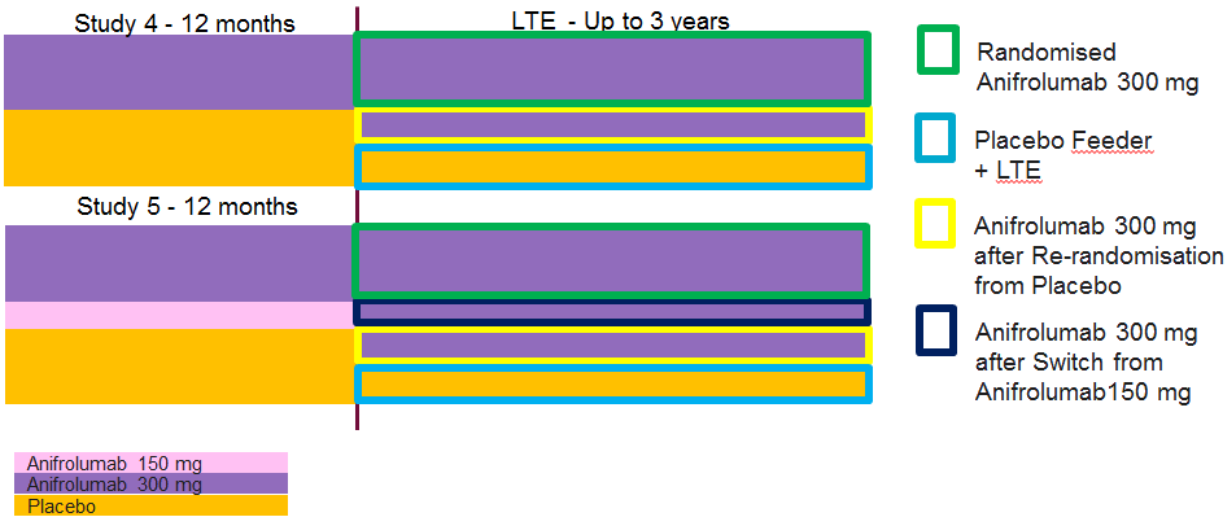
- ***Randomised Anifrolumab 300 mg:*** As described above but using data collected during the LTE study only, ie, reduced to subjects enrolled to the LTE study.

- ***Placebo Feeder + Placebo LTE:*** As described above but using data collected during the LTE study only, ie, reduced to subjects enrolled to the LTE study.

- ***Placebo Feeder + Anifrolumab 300 mg LTE:*** Subjects randomised to placebo in studies D3461C00004 or D3461C00005 and then re-randomised to anifrolumab 300 mg in LTE using data from switch to end of LTE.

- ***Anifrolumab 150 mg Feeder + Anifrolumab 300 mg LTE:*** Subjects randomised to anifrolumab 150 mg in Study D3461C00005 and then switched to anifrolumab 300 mg in LTE using data from switch to end of LTE.

Figure 4 LTE treatment groups



2.2 Protocol deviations

All protocol deviations identified during monitoring of the study will be recorded in the clinical trial management system (CTMS). Important protocol deviations (IPDs) during the LTE study are a subset of protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Protocol deviations will be classified as important or not important by the PRA Medical Monitor as defined in the Protocol Deviation Guidance based on periodic reviews of CTMS deviation reports and blinded delivery reviews (BDR). The Sponsor then reviews the classification and provides the final determination. The list of important protocol deviations will be finalised and documented prior to unblinding the study data.

COVID-19 related protocol deviations should be recorded prefixed by "COVID-19".

Only important protocol deviations (any, COVID-19 related, and not COVID-19 related) will be listed and tabulated in the Clinical Study Report (CSR).

3. PRIMARY AND SECONDARY VARIABLES

If not stated otherwise, not only data collected during the LTE study but also data collected in the Phase 3 feeder Studies D3461C00004 and D3461C00005 will be considered. If not stated otherwise, all references to Day 1 and date of first dose of investigational product, respectively, refer to the respective day in the Phase 3 feeder studies. The date of last dose of investigational product refers to the last dose during the LTE study for subjects who started the LTE study and to the last dose in the Phase 3 feeder studies for subjects not continuing in the LTE study.

Baseline is defined as baseline of the Phase 3 feeder studies, i.e., the last non-missing measurement prior to dose administration on Day 1. If the Day 1 value is missing or is invalid or is collected after administration of investigational product, the latest assessment prior to dose administration on Day 1 will serve as baseline.

If not stated otherwise, change from baseline will be calculated as value at the respective post-baseline time point minus value at baseline.

3.1 Safety variables

The following primary safety data will be collected: AESIs and SAEs.

Other safety variables include adverse events (AEs), vital signs, physical examination, electrocardiograms (ECGs), flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K, haematology, clinical chemistry, and urinalysis.

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements.

If not stated otherwise, on-treatment values are defined as values with an assessment date after the first administration of investigational product and on or before the date of last administration of investigational product + 28 days.

The restriction that "data from subjects discontinuing from the investigational product in studies D3461C00004 or D3461C00005, or who elect not to participate in the LTE, will be considered up to the adjusted analysis-defined visit window of Week 52 (ie, up to Day 378)" (see section 2.1.6) does only apply to visit-based analyses of safety variables.

3.1.1 Adverse events

Adverse events experienced by the subjects will be collected throughout the entire studies and will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event data will be categorised according to their onset date based on the last dose of administration in either the feeder studies or the LTE, whichever is later, as follows:

In general:

- AEs occurring during treatment:
  An AE during treatment is defined as an AE with a date of onset ≥ day of first dose of investigational product and ≤ date of last dose of investigational product + 28 days.
- AEs occurring during follow-up:
  An AE during follow-up is defined as an AE with a date of onset > date of last dose of investigational product + 28 days and ≤ date of last dose of investigational product + 84 days.
- AEs occurring during treatment and follow-up:
  An AE during treatment and follow-up is defined as an AE with a date of onset ≥ day of first dose of investigational product and ≤ date of last dose of investigational product + 84 days

The following are exceptions:

- For subjects in the "Randomised Placebo" treatment group with a switch to anifrolumab 300 mg in the LTE study, AEs with a date of onset ≥ day of first dose of investigational product in the LTE study will not be considered in the categories above, except for those with an onset on the day of first dose of investigational product in the LTE that are recorded in the Phase 3 feeder studies.
- For subjects in the "All Anifrolumab" treatment group who were randomised to placebo in the Phase 3 feeder studies, AEs with a date of onset < day of first dose of investigational product in the LTE study and those with an onset on the day of first dose of investigational product in the LTE that are recorded in the Phase 3 feeder studies will not be considered in the categories above.

In general, an AE during LTE is defined as an AE in the categories above with a date of onset ≥ day of first dose of investigational product in the LTE study. AEs with onset on the day of first dose of investigational product in the LTE, but which were recorded in the Phase 3 feeder studies will not be considered as occurring during the LTE.

If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, it will be considered an AE in the categories above. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, it will be considered an AE in the categories above. If the missing or partial start date does not allow an assignment of the event as during the Phase 3 feeder studies or the LTE study, the AE will be assigned to the study in which it was documented.

Adverse events of special interest are marked as such in the electronic Case Report Form (eCRF).

Major acute cardiovascular events (MACEs) will be determined according to the assessments of the Cardiovascular Event Adjudication Committee (CV-EAC).

An infusion-related reaction (as assessed by the investigator) is defined as an AE with a preferred term of "Infusion related reaction".

An infection is defined as an AE within the MedDRA system organ class infections and infestations.

Opportunistic infections are those marked in the eCRF as assessed by the investigator as opportunistic and non-opportunistic infections are all infections not marked as opportunistic by the investigator.

Hypersensitivity is defined as adverse events with MedDRA preferred term (PT) = "Hypersensitivity" and Lower level term (LLT) = "Hypersensitivity reaction".

Herpes zoster is further classified according to the information given on the Herpes zoster log as follows:

Category	Rash [Y/N]	Episode status of HZ Event [localized/ disseminated]	Specify Disseminated [cutaneous/ systemic]	Any organ involvement [Y/N]
Cutaneous (localised) herpes zoster	Y	Localized	[no rule]	N
Cutaneous disseminated herpes zoster	Y	Disseminated	Cutaneous	[no rule]
Visceral disseminated herpes zoster	[no rule]	Disseminated	Systemic	[no rule]

A COVID-19 related adverse event is defined as an AE with one of the following preferred terms: “Asymptomatic COVID-19”, “Congenital COVID-19”, “Coronavirus infection”, “Coronavirus pneumonia”, “Coronavirus test positive”, “COVID-19”, “COVID-19 pneumonia”, “Post-acute COVID-19 syndrome”, “SARS-CoV-2 antibody test positive”, “SARS-CoV-2 carrier”, “SARS-CoV-2 sepsis”, “SARS-CoV-2 test false negative”, “SARS-CoV-2 test positive”, “SARS-CoV-2 viraemia”, “Suspected COVID-19”, “Vaccine derived SARS-CoV-2 infection”.

Adverse events with missing intensity will be assumed to be severe. Events with missing relationship to study medication per the investigator will be assumed to be related. If no information about seriousness is available, the AE will be considered serious.

AEs and AEs leading to discontinuation of investigational product during treatment and follow-up will also be presented by time intervals of the first onset of the event. For this analysis, repeated events with the same preferred term will not be considered (i.e., if a subject has more than one event with the same preferred term, only the event with the earliest date of onset will be used). The following time intervals are defined for AEs during treatment and follow-up:

- Year 1:
  AEs with date of onset ≥ date of first administration of investigational product and either < maximum of date of re-randomisation in LTE study and date of administration of IP in LTE study or from subjects who are not randomised into the LTE study (ie, all AEs documented in the Phase 3 feeder Studies D3461C00004 and D3461C00005 are considered AEs in Year 1). If the AE has an onset on the day of first dose of investigational product in the LTE and is recorded in the Phase 3 feeder studies, it will be considered during year 1.
- Year 2:
  AEs with date of onset ≥ date of first administration of investigational product in LTE study and < date of first administration of investigational product in LTE study plus 364 days
- Year 3:
  AEs with date of onset ≥ date of first administration of investigational product in LTE study plus 364 days and < date of first administration of investigational product in LTE study plus 728 days
- Year 4:
  AEs with date of onset ≥ date of first administration of investigational product in LTE study plus 728 days and < date of first administration of investigational product in LTE study plus 1092 days
- After year 4:
  AEs with date of onset ≥ date of first administration of investigational product in LTE study plus 1092 days

If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, it will be assigned to the "Year 1" time interval. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, it will be assigned to the earliest time interval given the available date information. If the missing or partial start date does not allow an assignment of the event as during the Phase 3 feeder studies or the LTE study, the AE will be assigned to "Year 1" if documented in one of the Phase 3 feeder studies or to "Year 2" if documented in the LTE.

The event rate per 100 subject years is defined as the number of subjects with an event divided by the sum of exposure time in days in the respective time period for all subjects in the analysis set multiplied by 365.25 days/year multiplied by 100. The exposure in a time period for each subject will be calculated as end of period – start of period + 1 (e.g., as the earlier of either (date of last dose of investigational product + 84 days, or date of study discontinuation) - date of first dose of investigational product + 1 day for the summary of all AEs during treatment and follow-up; for AEs during treatment, the same definition will apply, with the exception of last dose of investigational product + 28 days will be used). For analyses based on LTE data only (e.g. AE rates for subjects switching from Placebo to 300 mg anifrolumab in the "All Anifrolumab" treatment group), the first administration of investigational product during the LTE will be considered as the start of the overall period. For analyses based on feeder study data only (e.g. AE rates for subjects switching from Placebo to 300 mg anifrolumab in the "All Randomised Placebo" treatment group), the end of the overall period will be defined as the first administration of investigational product in the LTE -1 day. If a subject discontinued during a period or had the last follow-up visit earlier than expected, the date of study discontinuation/end of study will be used as end of the respective period.

For AESIs, SAEs, and COVID-19 related analyses of AEs, additional analyses based on an alternative event rate per 100 subject years will be derived as the number of subjects with the respective AE divided by the sum of time at risk in days for all subjects in the analysis set multiplied by 36,525. The time at risk is defined as time (including start and end date) from start of period (e.g., date of first administration of investigational product for all AEs) to the date of first event, death, withdrawal of consent, or end of period, whatever comes first. The same considerations for analyses based on LTE/feeder phase 3 data only as defined above will apply for alternative event rates.

The time to first onset of a specific AESI category will be derived as date of first onset of any AE in the respective category – date of first administration of investigational product + 1. For time to event analyses based on LTE data only (e.g. for subjects switching from Placebo to 300 mg anifrolumab in the "All Anifrolumab" treatment group), the first administration of investigational product during the LTE will be used in the above. AEs with an onset date before the date of first administration of investigational product and AEs with an onset after 84 days after the date of last administration of investigational product will not be considered for the time to first onset of AESI. If a subject has no AESI in a specific category, the time to first onset will be censored at the date of last administration of investigational product + 84 days. For time to event analyses based on feeder study data only (e.g. for subjects switching from Placebo to 300 mg anifrolumab in the "All Randomised Placebo" treatment group), the

minimum of last administration of investigational product in the feeder study +84 days and first administration of investigational product in the LTE -1 day will be used in the above. If a subject discontinued the study or had the last follow-up visit earlier than expected, the date of study discontinuation/end of study will be used as the censoring date.

For time to event analyses and calculation of alternative event rates only, the following rules will be applied for imputing (partially) missing onset dates prior to analysis: If an AE has a (partially) missing onset date, it will be imputed with the earliest possible date on or after the day of first administration of investigational product given the available start and stop date information. If the available start or stop date information indicate that the AE started prior to first administration of investigational product, no imputation of the start date will be done.

For the by timepoint analysis of anaphylaxis, hypersensitivity, and infusion related reactions, an AE at a visit is defined as an AE with a date of onset ≥ day of administration of investigational product at the respective visit and ≤ date of administration of investigational product at the following visit (or ≤ date of last dose of investigational product + 84 days for the last visit with investigational product). Analogous to assignment of AEs to time intervals, AEs with (partially) missing date will be assigned to the earliest possible visit giving the available start and stop date information, in the study (feeder phase 3 or LTE) they were recorded in.

3.1.1.1 Other significant adverse events

During the evaluation of the AE data, a PRA medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Astra Zeneca Global Patient Safety Physician, be considered other significant AEs and reported as such in the CSR.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

3.1.2 Vital signs

The following variables will be explored:

- Pulse (beats per minute)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Respiration rate (breaths per minute)
- Body temperature (°C)

Changes from baseline will be calculated for post-baseline assessments with a corresponding baseline observation.

Where applicable, absolute values will be compared to the reference ranges [redacted] and classified as low (below range), normal (within range or on limits), or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Post-baseline values will be classified as treatment-emergent laboratory/vital signs changes (TELVC) according to reference ranges [redacted]

For infusion visits, only measurements before the start of investigational product infusion will be considered for by-visit presentations. In the case of multiple measurements before the start of investigational product, the first measurement will be used for by-visit presentations, but all measurements will be considered for the TELVC classification.

3.1.3 Physical examination

Weight (kg) will be explored using the mean change from baseline longitudinally over time.

3.1.4 ECGs

The outcome of the overall evaluation of 12-lead ECG measurements by the central reading will be assessed as normal or abnormal. It is the investigator's judgment whether the findings/results on the central ECG laboratory report are clinically relevant or not. The combination of both judgments leads to the following categories used for analysis:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

If the overall evaluation by the investigator and the central ECG report don't match, the investigator's judgement will be used. In case of repeated measurements (triplicates) at a visit, the worst category at the respective visit will be used for the analysis, with "abnormal, clinically significant" defined as worse than "abnormal, not clinically significant," which in turn is worse than "normal."

Changes from baseline of the following variables will be explored:

- Heart rate (beats per minute)
- QRS duration (ms)
- PR interval (ms)
- RR interval (ms)
- QT (ms)
- QTcB (ms)
- QTcF (ms)

Potentially Clinically Significant post-baseline values or changes from baseline [redacted]. For some parameters, more than one criterion is given. The proportion of subjects meeting each criterion will be explored.

In case of repeated measurements (triplicates) at a visit, the mean of all non-missing values at the respective visit will be used for the analyses of the continuous ECG variables and the determination of Potentially Clinically Significant values.

3.1.5 Modified SELENA Flare Index based flares

A modification of the classic SELENA Flare Index using the SLEDAI-2K will be used as a safety outcome to characterise flares. The modified SELENA Flare Index-Based Flare Assessment Scale has 2 sets of definitions:

Mild/moderate flare

A mild/moderate flare is defined if at least one of the following criteria are met:

- Increase from previous visit in SLEDAI-2K of ≥3 points but less than 7 points
- At least 1 new or worse manifestation in
  - Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus
  - Nasopharyngeal ulcers
  - Pleuritic
  - Pericarditis
  - Arthritis
  - Fever (SLE)
- Increase from previous visit in PGA of ≥1 but PGA value of ≤2.5 points

Severe flare

A severe flare is defined if at least one of the following criteria are met:

- Increase from previous visit in SLEDAI-2K of ≥7 points
- At least 1 new or worse manifestation in
  - Central nervous system SLE
  - Vasculitis
  - Nephritis
  - Myositis
  - Haemolytic anaemia
    defined as haemoglobin <70 g/L or decrease in haemoglobin >30 g/L with positive Coombs AND at least 1 of the following: decreased haptoglobin, increased total bilirubin not due to Gilbert's disease, increased reticulocyte count
- Hospitalization due to SLE disease activity
- Increase from previous visit in PGA to a value >2.5 points

The flare rate per subject year will be calculated separately for mild/moderate flares and severe flares as well as overall. The flare rate per subject year is defined as the number of subjects with a respective flare divided by the sum of exposure time in days (i.e., date of last dose of investigational product + 28 days - day of first dose of investigational product + 1 day) for all subjects in the analysis set multiplied by 365.25 days/year.

For analyses based on LTE data only (e.g. for subjects switching from Placebo to 300 mg anifrolumab in the "All Anifrolumab" treatment group), the first administration of investigational product during the LTE will be considered in the above. For analyses based on feeder study data only (e.g. for subjects switching from Placebo to 300 mg anifrolumab in the "All Randomised Placebo" treatment group), the minimum of last administration of investigational product in the feeder study + 28 days and first administration of investigational product in the LTE -1 day will be used in the above. If a subject discontinued the study or had the last follow-up visit earlier than expected, the date of study discontinuation/end of study will be used as the censoring date.

3.1.6 Laboratory variables

The parameters haematology, serum chemistry, urinalysis (outlined in Table 5 in Section 5.2.9 of the clinical study protocol), and fasting lipid profile (high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) will be explored.

Glucose (serum chemistry), cholesterol (serum chemistry), high density lipoprotein cholesterol (fasting lipid profile), low density lipoprotein cholesterol (fasting lipid profile), and triglycerides (fasting lipid profile) will only be considered in tables and figures if the subject fasted for at least 8 hours prior to the assessment.

Laboratory data will be reported in SI units. Changes from baseline in haematology, clinical chemistry, and lipid profile variables will be calculated.

Absolute values will be compared to the reference range [redacted] and classified as low (below range), normal (within range or on limits), or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Treatment-emergent laboratory/vital signs changes will be defined for post-baseline values according to the reference ranges [redacted]

Urinalysis data will be categorised as negative (0), trace, positive (+), or strongly positive (++, +++, or >+++) at each time-point. Treatment-emergent changes will also be assessed. Treatment-emergent changes of urinalysis data are defined as

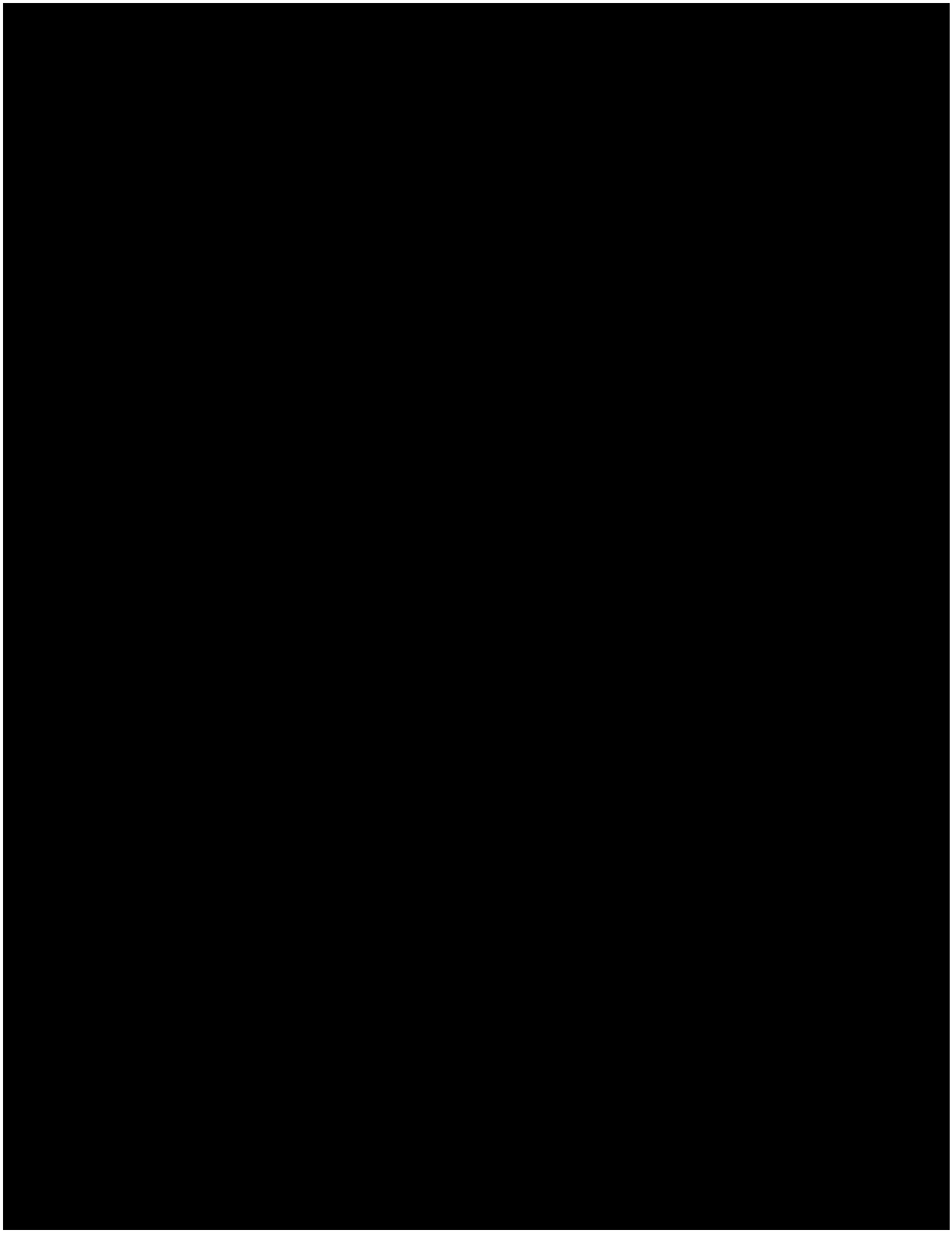
- Negative/Trace/+ at baseline to ++, +++, ++++ at any post-baseline value OR
- Increase from baseline of at least ++ at any post-baseline value.

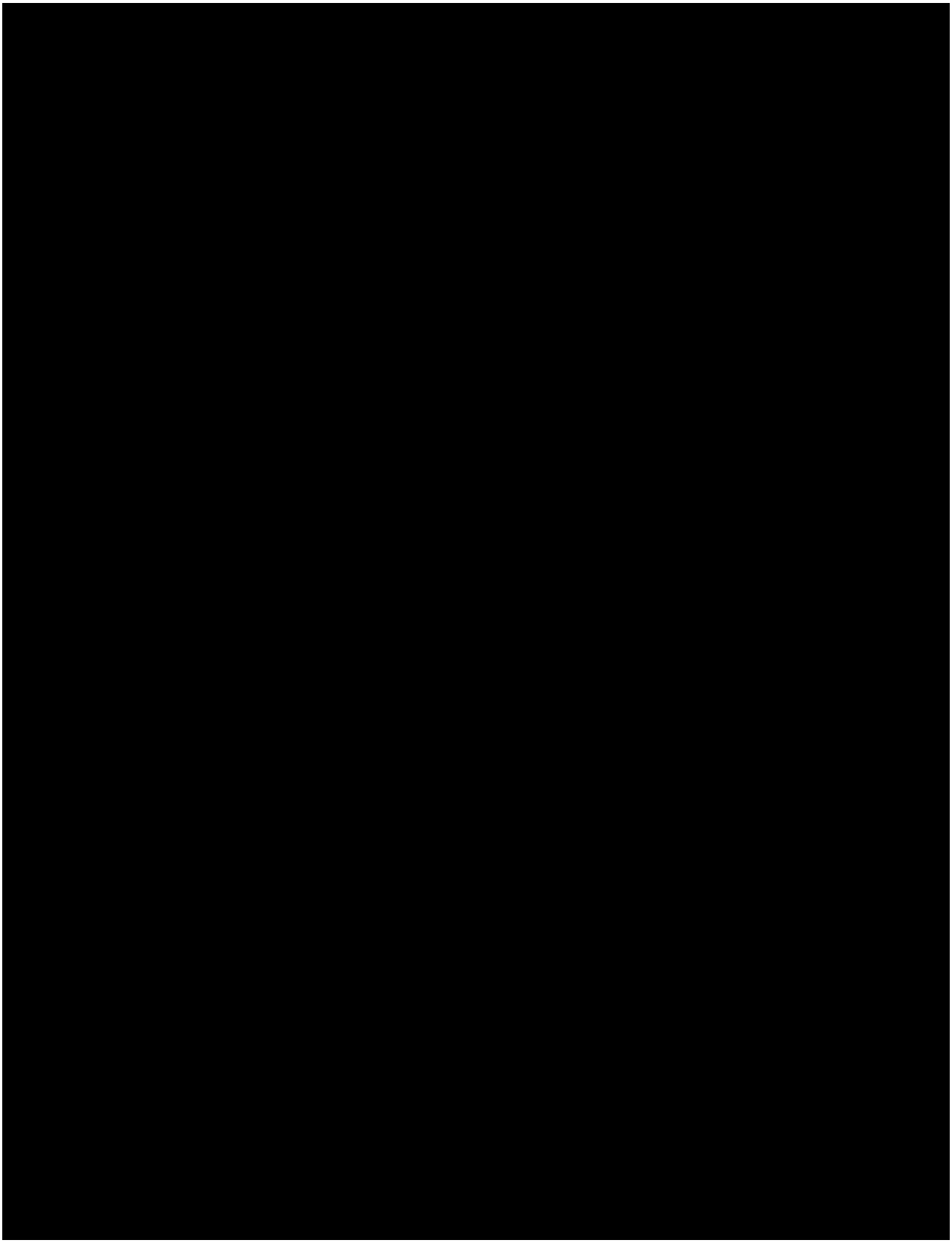
For the liver function tests: aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT), and total bilirubin, the multiple of

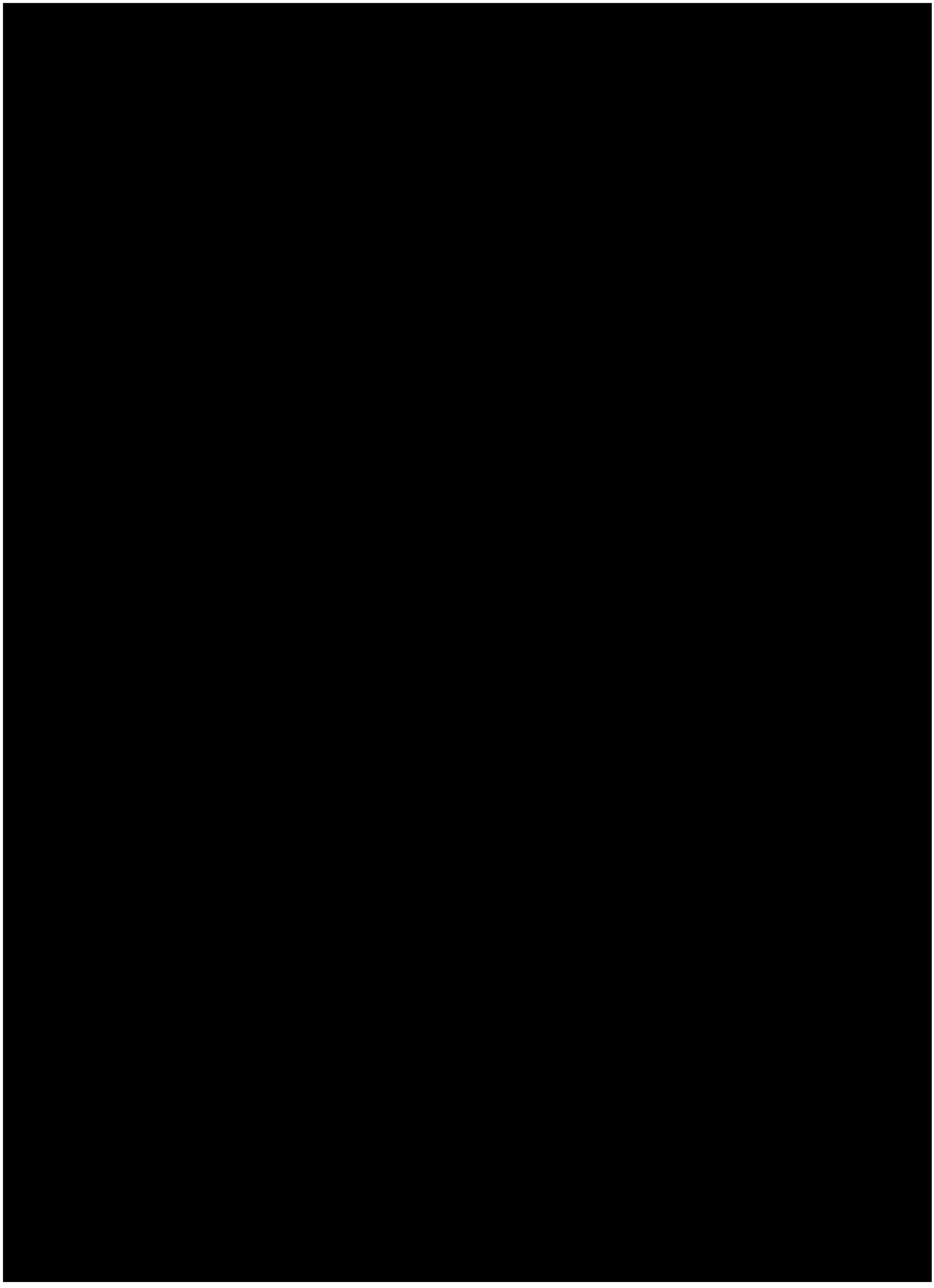
the upper limit of the normal (ULN) range [redacted] will be calculated for each data point. Multiple = Value / ULN, ie, if the ALT value was 72 IU/L (ULN = 36) then the multiple would be 2. Subjects meeting both of the following biochemical criteria for Hy's law (potential Hy's Law) at any point during the study (not necessarily at the same time) will be flagged:

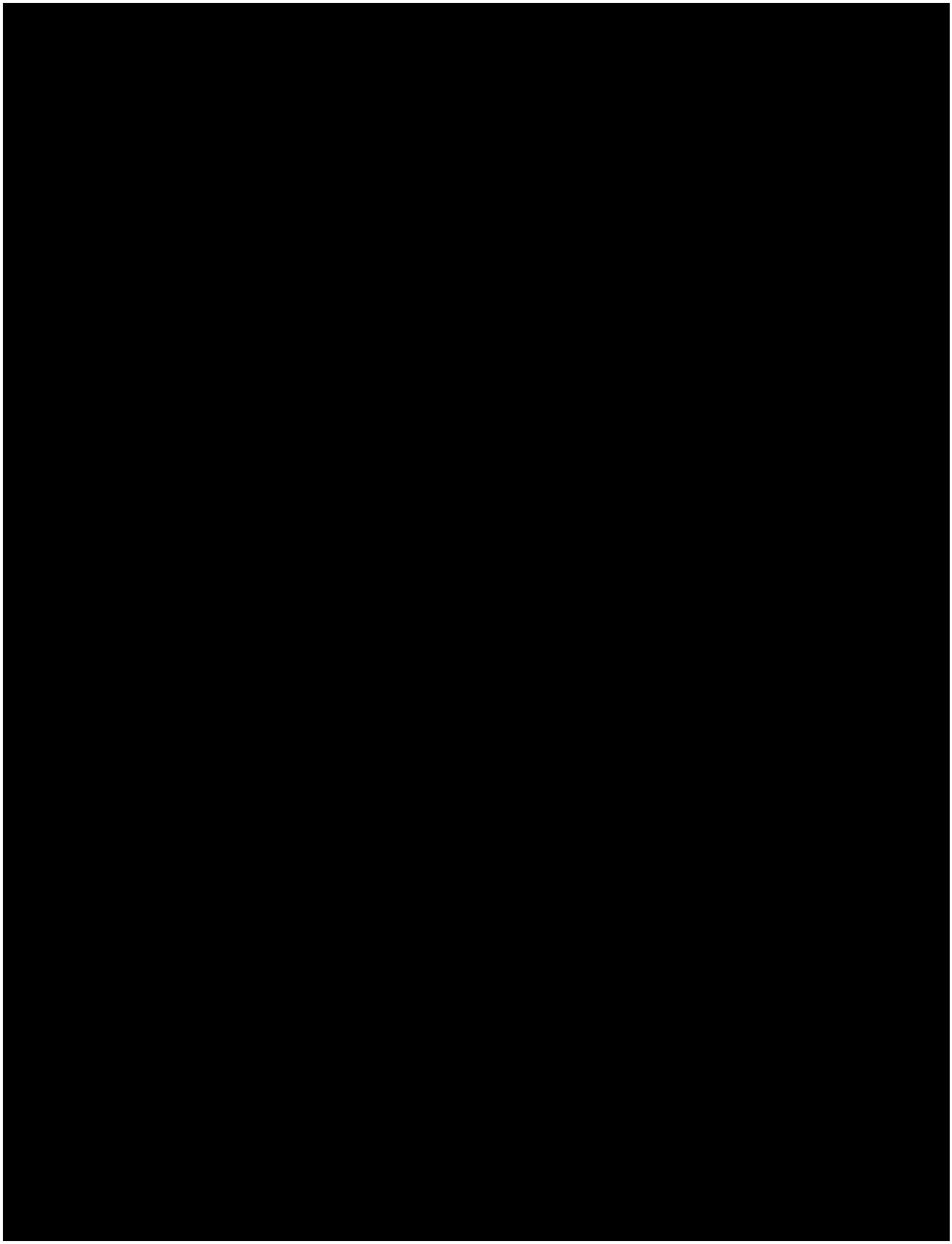
- AST ≥3x ULN and/or ALT ≥3x ULN
- Total bilirubin ≥2xULN

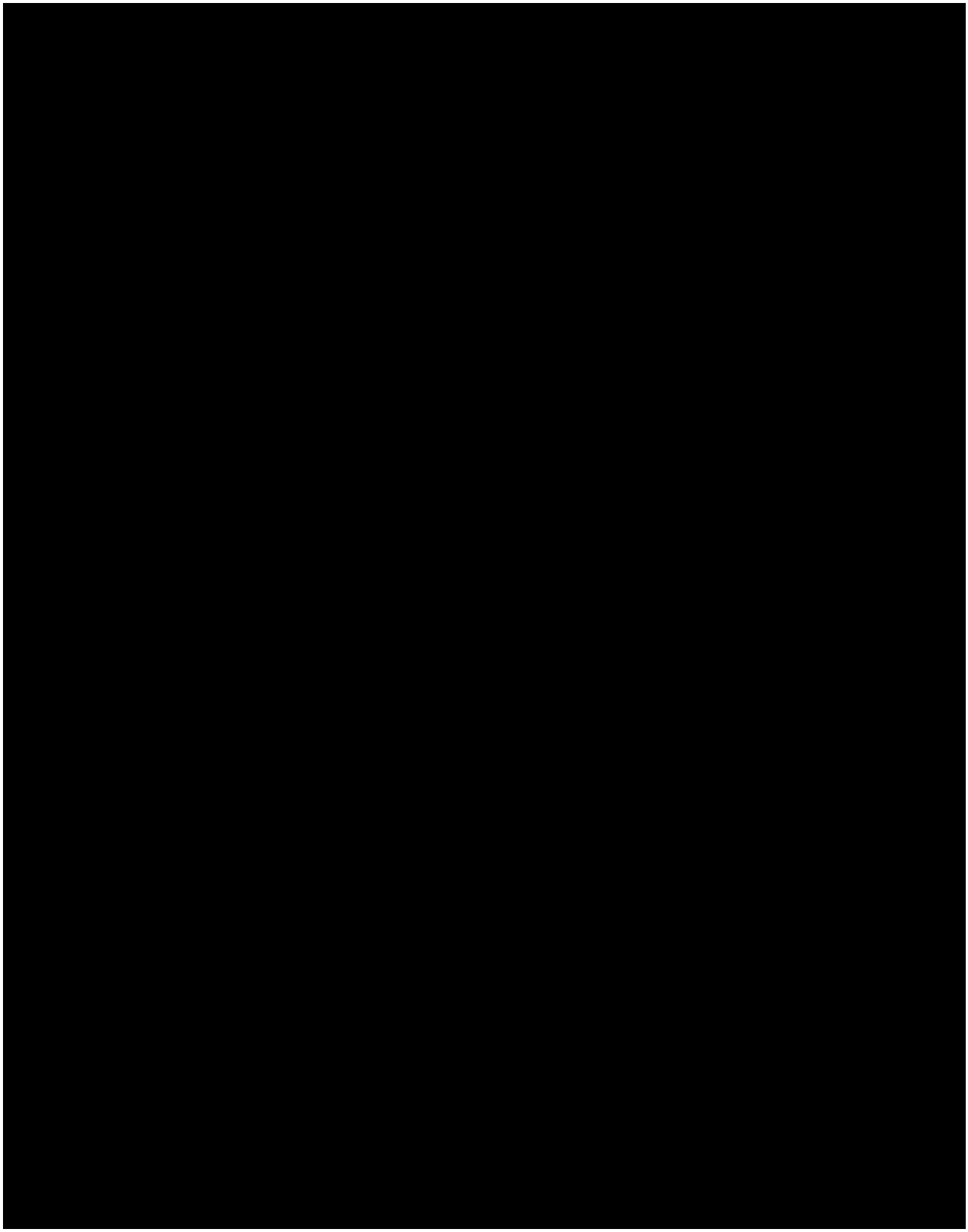
[redacted]

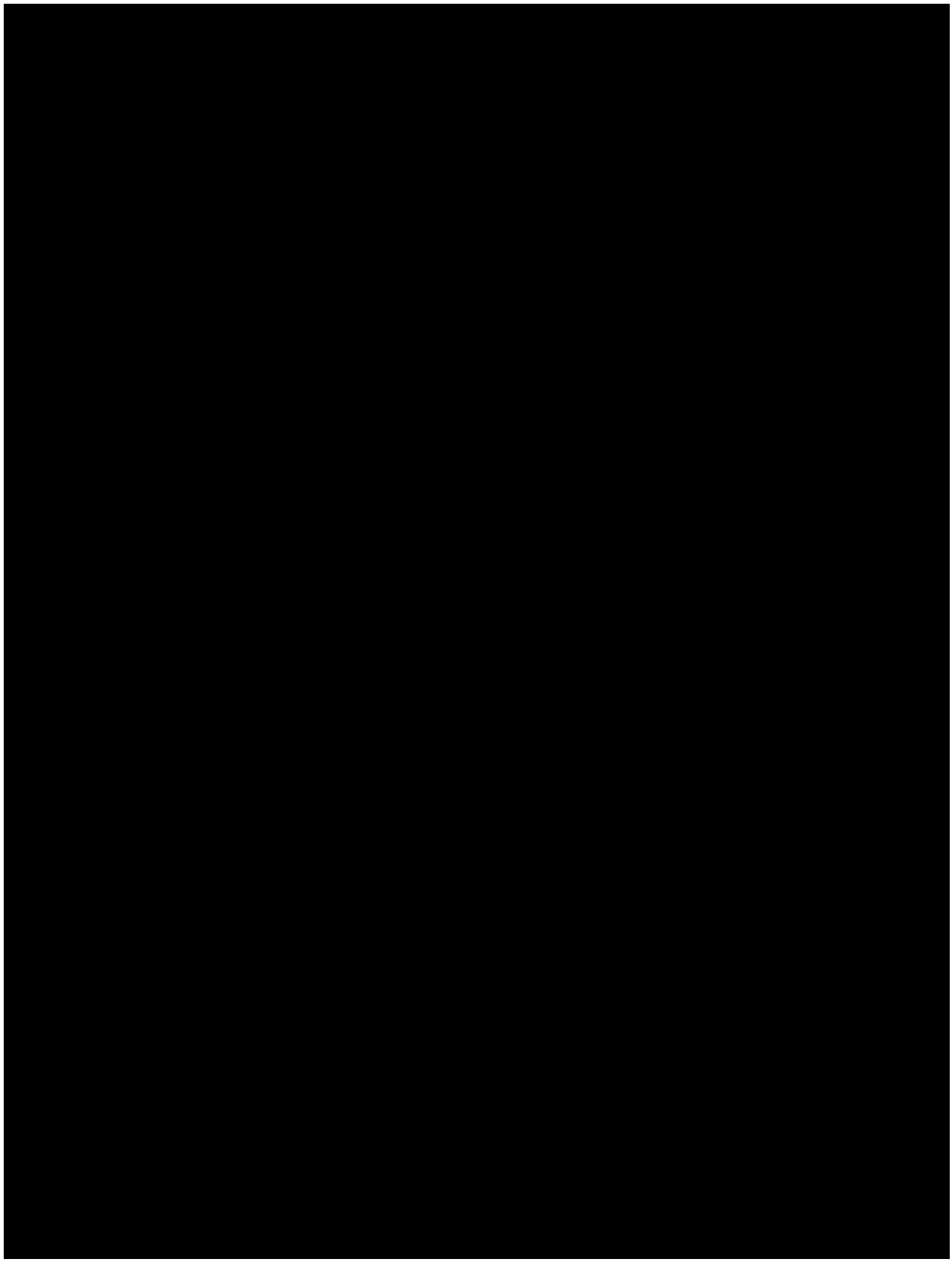


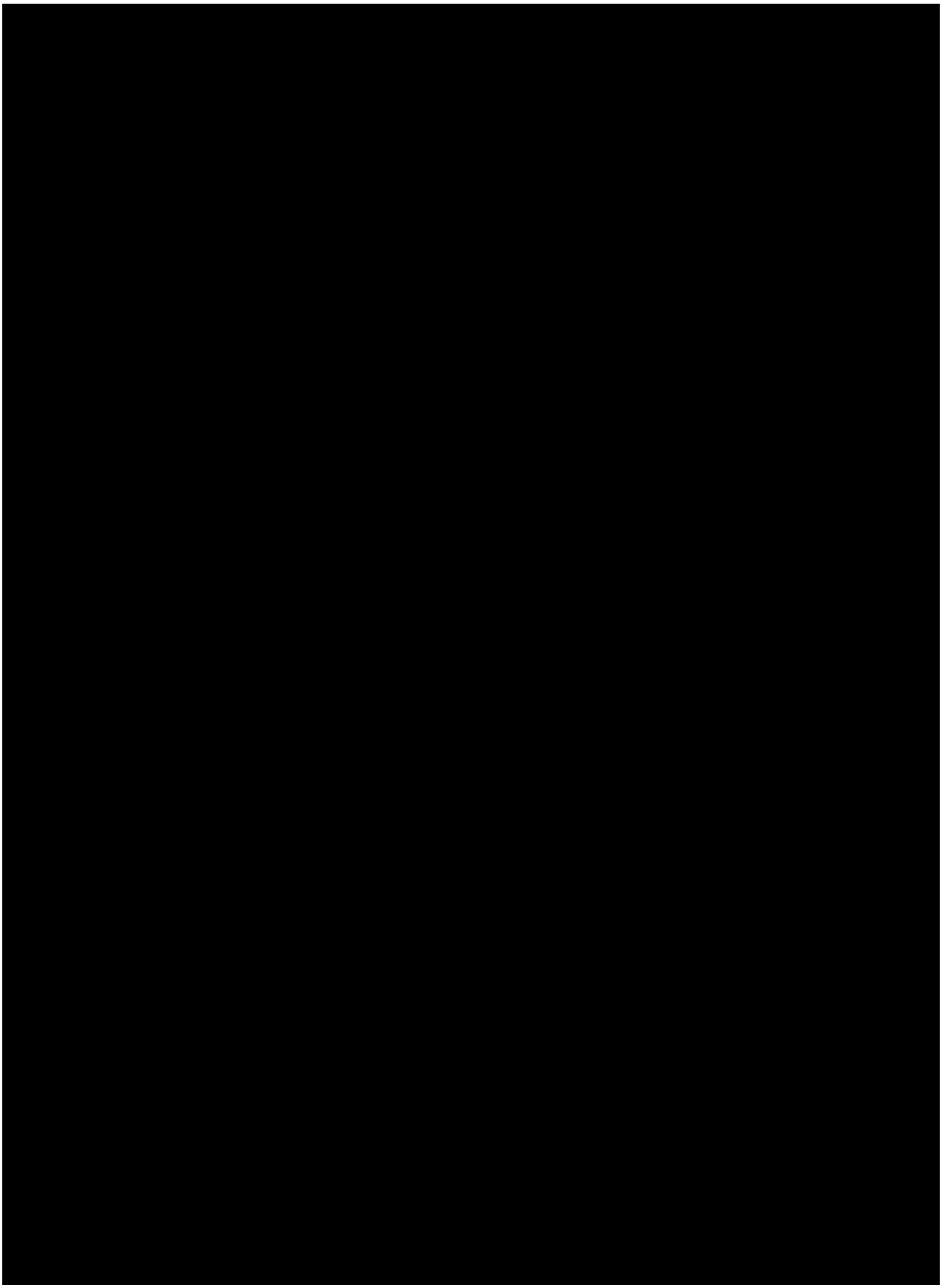












[redacted]

3.3 Assessment of study population

3.3.1 Demographic and baseline characteristic variables

Demographic characteristics (including geographic region, age, gender, ethnicity, and race) and baseline characteristics (including height, weight, body mass index [BMI], and disease characteristics) from the Phase 3 feeder studies will be used.

[redacted]

3.3.2 Medical history

Medical histories will be coded using the latest MedDRA version. Medical history as recorded in the phase 3 feeder studies will be explored separately for past and current conditions as given in the eCRF.

3.3.3 Prior and concomitant medications

All medications will be coded using the latest version of World Health Organization Drug Dictionary (WHO-DD).

Any medications taken by the subject prior to the first dose date of investigational product in the phase 3 feeder studies will be considered prior medication. Any medication taken by the subject at any time between the date of the first dose (including the date of the first dose) of investigational product up to end of study/participation, inclusive, will be considered concomitant medication. Any medication started prior to the first dose of investigational product of the phase 3 feeder studies and ended/ was ongoing after the first dose up to end of study/participation will be considered as both prior and concomitant medication. In case of missing or partial dates, the imputation rules [redacted] will be applied to classify medication as prior and/or concomitant, as appropriate.

Disease related treatments at baseline and during the LTE study will be explored every 3 months (ie, at baseline and weeks 52, 64, 76, 88, 104, 116, 128, 140, 156, 168, 180, 192, and 208). Disease related treatments at a specific visit are defined as all medications with therapy reason containing "disease under study" with an intake at the date of the respective visit. For baseline and Week 52 visits, the timepoints as derived in the feeder studies will be used. For all other timepoints, the scheduled day will be used. If a subject discontinued in a visit window before the scheduled day, the date of discontinuation will be used instead. The medications will be presented in the following categories:

- Anti-malarial
  defined as medications with an ATC code level 4 of P01BA (aminoquinolones) and P01AX (Other agents against amoebiasis and other protozoal diseases)
  - Any anti-malarial
  - Anti-malarial only
  - Anti-malarial in combination with OCS and/or immunosuppressants
- Azathioprine
  defined as medications with a preferred term of azathioprine or azathioprine sodium
- Methotrexate
  defined as medications with a preferred term of methotrexate or methotrexate sodium
- Mycophenolate
  defined as medications with a preferred term of mycophenolate mofetil or mycophenolate sodium or mycophenolic acid
- Mizoribine
  defined as medications with a preferred term of mizoribine
- OCS
  - Any OCS
  - OCS only
  - OCS in combination with immunosuppressants and/or anti-malarial
  - Time on corticosteroids up to randomisation
- NSAID
  defined as medication with an ATC code level 4 of M01AB, M01AC, M01AE, M01AG, M01AH, or M01AX except preferred terms SULFASALAZINE, and RABBIT VACCINIA EXTRACT
- Other SLE medication
  defined as SLE medications not covered within the above categories

Starting with Week 52, the change of medication use versus baseline will be explored for each of the above medication categories as follows:

- Added
  defined as intake of at least 1 medication of the respective category at the respective visit but no intake of any medication in the respective category at baseline
- No change
  defined as either intake of at least 1 medication of the respective category at the respective visit and baseline or no intake of any medication in the respective category at the respective visit and baseline
- Discontinued
  defined as no intake of any medication of the respective category at the respective visit but intake of at least 1 medication in the respective category at baseline

3.3.4 Exposure of investigational product

An infusion of IP is defined as follows:

- Start time and end time of study drug infusion are not missing and start time and end time are not equal, and
- Volume of infusion bag prior to infusion start is greater than volume of infusion bag at the end of infusion or investigator confirmed that study drug was administrated according to protocol.

The duration of exposure to the investigational product per subject is defined as the number of days between the start and the end dates of investigational product plus the dosing frequency time:

For the subjects randomised to Placebo in the feeder study who switch to Anifrolumab, the following definition applies, to account for exposure time of the feeder study (placebo) up until the day before their first dose of Anifrolumab in the LTE study:

Duration of exposure (days) = ([first dose date in LTE-1]) – first dosing date in feeder study + 1,

For the All Anifrolumab group the following definition applies, to account only for their exposure time of Anifrolumab:

Duration of exposure (days) = (Last Anifrolumab dosing date + 28 days) – first Anifrolumab dosing date + 1,

For all other subjects, duration of exposure is defined as:

Duration of exposure (days) = (Last dosing date + 28 days) – first dosing date + 1.

Duration of LTE exposure is consequently defined as

Duration of LTE exposure (days) = (Last dosing date of LTE study + 28 days) – first dosing date of LTE study+ 1.

The total subject years of exposure is the sum of duration of exposure (days) of all subjects in the respective treatment group divided by 365.25 (days/year).

The total number of infusions and infusions during LTE will be counted per subject.

The time to discontinuation of investigational product is the same as the duration of exposure.

3.3.5 Subject Disposition

If a subject permanently and prematurely discontinued the treatment with IP in the LTE study due to the COVID-19 pandemic, identified by the keywords “COVID”, “pandemic” or “corona” in specification of other reason, then the reason for discontinuation of IP in the LTE study is set to “Due to COVID-19 pandemic”.

If a subject withdrew from the LTE study prematurely, the reason for withdrawal is “Other” and the patient’s final status was impacted by the pandemic then the reason for withdrawal from the LTE study is set to “Due to COVID-19 pandemic”.

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Data excluded from analysis

In the rare event that a site needs to be closed during the course of the study for quality reasons (e.g., suspicion of fraud, non-compliance), all subjects of this site will be excluded from all analyses and summaries. In this situation, the SAP will be amended prior to database lock and details will be added documenting decisions about site closure and data handling (including details of important data to be presented in separate listings).

On 10-Feb-2017, the decision was made to close site [redacted] of Study D3461C00004 due to sustained noncompliance with protocol procedures and specifications. This included but was not limited to: failure to follow protocol stipulated inclusion/exclusion criteria, failure to maintain proper documentation in patient source files, and failure to maintain proper principal investigator oversight. The Site, FDA, and IRB have been notified of this site’s closure.

On 12-Jan-2018, the decision was made to close site [redacted] (in the LTE study as well as in Study D3461C00005) due to sustained noncompliance with protocol procedures and specifications. This included but was not limited to: lack of adherence to the blinding plan and delegation log by the unblinded pharmacist, and lack of adherence by the site study

coordinator and unblinded pharmacist to their roles and responsibilities for accountability of investigational product including reconstitution and preparation, leading to potential risk of unblinding study data. The Site, FDA, and IRB have been notified of this site's closure.

On 15-Mar-2021, the decision was made by AstraZeneca to exclude data from site [redacted] in the LTE study due to non-compliance to ICH E6 (R2) GCP section 8.1 addendum "The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data."

On 23 Nov 2021, the decision was made by AstraZeneca to exclude all data from site [redacted] in the LTE study since PRA ICON team decided that as the source documentation was destroyed /cannot be recovered as a result of a flood on site.

Therefore, the 20 randomised subjects [redacted]) at these sites and data of subject [redacted] who switched to site [redacted] after completion of study D3461C00004, will be considered only in repeats of key tables (sensitivity analysis) and key listings (presenting the excluded subjects only) but excluded from all other tables, figures and listings.

Sensitivity analyses are specified in Sections 4.2.1.1 and 4.2.2.1.

4.1.2 Visit windows

For visit-based analyses, the variables will be summarised based on the scheduled days with adjusted analysis-defined visit windows. If not stated otherwise, for the Phase 3 feeder studies, only Baseline, Week 24, and Week 52 will be presented in visit-based summaries. The adjusted analysis-defined windows are summarised below:

Table 2 Visit windows

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline / Day 1	1	Study Day ≤1
Week 24	169	155≤ Study Day ≤182
Week 52	365	351≤ Study Day ≤378 and LTE Study Day 1
Gap[a]	N/A	379≤ Study Day ≤ LTE Study Day 1
Week 56	29 in LTE study	2≤ LTE Study Day ≤42
Week 60	57 in LTE study	43≤ LTE Study Day ≤70
Week 64	85 in LTE study	71≤ LTE Study Days ≤98
…	…	…
Continue in 4-week intervals	Continue in 28-day intervals	Continue in 28-day intervals
…	…	…
Variables to be assessed/measured during follow-up		
Week 208	1092 in LTE study	1079≤ LTE Study Days ≤1106
Week 212 (8 weeks post-final dose)	1120 in LTE study	1107≤ LTE Study Days ≤1134
Week 216 (12 weeks post-final dose)	1148 in LTE study	1135≤ LTE Study Days
Variables not to be assessed/measured during follow-up		
Week 208	1092 in LTE study	1079≤ LTE Study Day

a. This visit window covers longer than expected gaps between the feeder study and the first dose date in the LTE. This visit window will only be used in listings.

For assignment of data to time points using the visit windows, study day will be defined as (Date of assessment – date of first administration of investigational product) +1. Using this definition, the day of first dose of investigational product will be Day 1 and the scheduled visit date of Week 24 will be study day 169 (=168+1), for example. Data captured in the Phase 3 feeder study falling in a visit window after Week 52 [redacted] captured in the Phase 3 feeder study falling in Week 52 visit window will not be considered for by-visit summaries. LTE Study Day is defined accordingly as (Date of assessment – date of first administration of investigational product in LTE study) +1. Data assessed at LTE Study Day 1 will be assigned to Week 52 visit window. Data captured in the LTE study after LTE Study Day 1 falling into a visit window before Week 56 will not be considered for by-visit summaries.

If multiple readings are recorded within a single visit window, the following rules will be followed:

- If there are 2 or more observations within the same visit window, then the non-missing one closest to the scheduled visit will be used in the analysis.
- If 2 observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If 2 observations are collected on the same day, then the non-missing one with the earlier collection time will be included in the analysis. For observations in the Week 52 visit window, the observation captured in the Phase 3 feeder study is assumed to be earlier than the observation captured in the LTE study even if the collection time is missing or indicating otherwise.
- If 2 observations are collected on the same day and time (if applicable), are captured in the same study and one is reported as done on a scheduled visit and the other as done on an unscheduled visit in the vendor data, then the non-missing one reported as done on a scheduled visit will be included in the analysis.
- If 2 or more antinuclear antibody titre observations are collected on the same day and time, are captured in the same study and at the same visit in the vendor data, then the non-missing one with highest value will be used in the analysis. The following order applies, from lowest to highest: 1:40, 1:80, 1:160, 1:320, 1:640, 1:1280, 1:2560, >1:2560.

If missing week 52 data from a Phase 3 feeder studies have been imputed using last observation carried forward (LOCF; see section 4.1.4) then these data will be considered as non-missing for the rules above. Additionally it will be assumed that the data are closest to the scheduled visit, i.e. the imputed data will always be preferred.

If a visit window does not contain any observations, then the data will remain missing.

For overall analyses not based on any particular study visit, all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified.

4.1.3 Presentation of results

All analyses will use SAS® version 9.3 or higher.

If not stated otherwise, summary tables will be presented according to the data used:

- Tables using combined data from feeder studies (i.e., studies D3461C00004 and D3461C00005) and LTE study will be presented by combined treatment group as defined in Section 2.1.6 (randomised anifrolumab 300 mg, randomised placebo, placebo feeder + placebo LTE, and all anifrolumab). For some tables, if mentioned explicitly, the additional supportive treatment groups placebo feeder + anifrolumab

300 mg LTE, and anifrolumab 150 mg feeder + anifrolumab 300 mg LTE will also be presented.

- Tables using data of the LTE study only will be presented by LTE treatment group as defined in Section 2.1.6 (randomised anifrolumab 300 mg, placebo feeder + placebo LTE, placebo feeder + anifrolumab 300 mg LTE, and anifrolumab 150 mg feeder + anifrolumab 300 mg LTE,)

For by-visit presentations, only baseline, Week 24, and Week 52 will be presented for the Phase 3 feeder studies. If not stated otherwise, results of a specific treatment group and visit will be suppressed if the summary is based on data of less than 25 subjects. For all other presentations, all available data for each analysis set will be used in the analyses. Data collected during the LTE study (including derived variables and baseline from the Phase 3 feeder studies) will be presented in listings sorted by LTE treatment group and subject number. A separate document will be produced containing the template table, listing, and figure shells.

Unless otherwise noted, categorical data will be presented using counts and percentages with the denominator for percentages being the number of subjects in the analysis set by treatment group. Percentages will be rounded to 1 decimal place; except 100% which will be displayed without any decimal places. Percentages will not be displayed for zero counts.

Unless otherwise noted, continuous variables will be summarised using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data; the mean, median, and quartiles to a further decimal place; and the SD to 2 additional decimal places. CV% [redacted] will be presented with 1 decimal place.

Due to the limitation of the Rothman and Greenland method for 0 outcomes, the exact Poisson confidence intervals for event rates will be calculated.

Lower bound = $e^{\left[\ln(rate) - Z_{1-\frac{\alpha}{2}}\frac{1}{\sqrt{number\ of\ events}}\right]}$

Upper bound = $e^{\left[\ln(rate) + Z_{1-\frac{\alpha}{2}}\frac{1}{\sqrt{number\ of\ events}}\right]}$

The corresponding confidence intervals to those used in the sample size estimation, but using the exact Poisson are as follows:

> Assuming follow-up times of approximately 893, 517, and 1343 subject years for the "Randomised Anifrolumab 300 mg," "Randomised Placebo," and "All Anifrolumab" treatment groups are expected. Given this exposure, the 95% CIs for an AESI for which the observed incidence rate is 10 events in 1000 subject years will be 4.56 to 19.03 for "Randomised Anifrolumab 300 mg," and 3.32 to 23.03 for "Randomised Placebo." For an AESI for which the observed incidence rate is 1 event in 1000 subject years, the 95% CI will be 0.0173 to 6.03 for "Randomised Anifrolumab

300 mg," arm; 0.001 to 9.10 in the "Randomised Placebo," arm ; and 0.056 to 4.58 in the "All Anifrolumab" arm.

4.1.4 Missing Data

For data captured in the Phase 3 feeder studies the same imputation of missing values using LOCF will be done as in the respective feeder study. No LOCF will be done for data captured in the LTE.

For data captured in the Phase 3 feeder studies the effect of missing items on a score will be handled in the same way as in the respective feeder study. For data captured in the LTE, unless otherwise defined, scores that are derived from summing up items will be considered missing if any of the items are missing.

[redacted]

Missing safety data will generally not be imputed. However, safety assessment values of the form of <x (i.e., below the lower limit of quantification (LLOQ)) or >x (i.e., above the upper limit of quantification) will be imputed as x in the calculation of summary statistics but displayed as <x or >x in the listings.

Anifrolumab serum concentrations reported as below the LLOQ will be imputed with LLOQ/2 for analysis. [redacted]

Details about imputation of partial or missing dates [redacted]

4.2 Analysis methods

Where applicable, the analyses will include data from randomisation in the Phase 3 feeder studies until the end of the LTE study, regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence.

4.2.1 Analysis of the primary variables (safety variables)

If not stated otherwise, safety variables will be summarised by combined treatment group for the full analysis set.

The primary assessment will be the comparison between the treatment groups "Randomised Anifrolumab 300 mg" and "Randomised Placebo". The "All Anifrolumab" treatment group will be used to assess rare events.

4.2.1.1 Adverse events

Even not stated explicitly, all summaries described below will be based on AEs during treatment and follow-up.

An overall summary of subjects with at least 1 AE in the following categories will be presented as event rates per 100 subject years. This summary will also be presented for the additional supportive treatment groups placebo feeder + anifrolumab 300 mg LTE, and anifrolumab 150 mg feeder + anifrolumab 300 mg LTE. This summary will also be presented for the LTE Study only.

- Any AE
- Any AE with outcome = death
- Any SAE (including events with outcome = death)
- Any AE leading to discontinuation of investigational product
- Any AE related to investigational product
- Any AE of severe intensity
- Any AESI
  - Any AESI of non-opportunistic serious infections
  - Any AESI of opportunistic infections
  - Any AESI of anaphylaxis
  - Any AESI of malignancy
  - Any AESI of herpes zoster
  - Any AESI of tuberculosis
  - Any AESI of influenza
  - Any AESI of vasculitis (non SLE)
  - Any AESI of major acute cardiovascular events
- Any other significant AE

The overall summary above will be repeated for the sub-periods prior to the COVID-19 pandemic (events prior to 11-Mar-2020) and during the COVID-19 pandemic (events on or after the COVID-19 pandemic; only subjects remaining in the study on 11-Mar-2020 will be included). These summaries will be presented for the LTE study only. Alternative event rates and event rates will be computed. As sensitivity analysis the overall summary will be repeated including subjects excluded from analysis (see Section 4.1.1).

An overall summary of subjects with at least one COVID-19 related AE in the following categories will be presented as alternative event rates per 100 subject years. This summary will be presented for the LTE Study only. Only subjects remaining in the study on 11-Mar-2020 will be included.

- Any COVID-19 related AE

- Any COVID-19 related AE with outcome = death
- Any COVID-19 related SAE (including events with outcome = death)
- Any COVID-19 related AE leading to discontinuation of investigational product
- Any COVID-19 related AE related to investigational product
- Any COVID-19 related AE of severe intensity

The event rate per 100 subject years including 95% CIs will be summarised for the following categories. Summaries of AESIs will be presented by AESI category (non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, tuberculosis, influenza, vasculitis [non SLE], and major acute cardiovascular events) and preferred term. Summaries for SAEs will be presented by MedDRA system organ class and preferred term.

- Any AESI
- Any AESI by time interval for the first onset of event – alternative event rates
- Any AE leading to discontinuation of IP by time interval for the first onset of event – alternative event rates (combined feeder & LTE study, by preferred term)
- Any AESI – alternative event rates
- Any SAE (including events with outcome = death) (during treatment and during follow-up separately. No event rate for during follow-up will be presented)
- Any SAE (including events with outcome = death) by time interval for the first onset of event – alternative event rates

The event rate per 100 subject years will be summarised by MedDRA system organ class and preferred term for the following AE categories.

- Any AE (during treatment and during follow-up separately. No event rate for during follow-up will be presented)
- Any AE by descending preferred term (during treatment, and during the LTE treatment)
- Any AE with outcome = death
- Any SAE by descending preferred term (including events with outcome = death) (during treatment, and during the LTE treatment)
- Any AE leading to discontinuation of investigational product
- Any AE by relationship to investigational product (yes, no)
  (multiple occurrences of an AE in 1 subjects will only be counted once as related if at least one AE is related and as not related if all occurrences are not related)
- Any AE by maximum intensity (mild, moderate, severe)
  (i.e., multiple occurrences of an AE in 1 subjects will only be counted once with the maximum intensity in this AE)
- Any other significant AE

The alternative event rate per 100 subject years will be summarised by MedDRA preferred term for the following AE categories.

- Any COVID-19 related AE (for the LTE Study only, only subjects remaining in the study on 11-Mar-2020 will be included)
- Any SAE prior to the COVID-19 pandemic (for the LTE Study only)
- Any SAE during the COVID-19 pandemic (for the LTE Study only, only subjects remaining in the study on 11-Mar-2020 will be included)

Cardiovascular outcome events as determined by the CV-EAC will be presented separately, summarising the number of AEs submitted for adjudication and the outcomes of the adjudication including MACE classification. Site reported cardiovascular AEs, cardiovascular SAEs, and their corresponding adjudicated outcomes will be listed.

The time to first onset of an AE in an AESI category will be presented separately for each AESI category as a Kaplan-Meier plot annotated with the number of subjects at risk every 6 months.

Furthermore, the alternative event rates per 100 subject years for the first onset of herpes zoster will be summarized for events overall and by time intervals). The following subcategories will also be considered in this summary: SAE (including events with outcome of death), AE leading to discontinuation, and AE by maximum intensity (mild, moderate, and severe). This summary will also be presented for the additional supportive treatment groups placebo feeder + anifrolumab 300 mg LTE, and anifrolumab 150 mg feeder + anifrolumab 300 mg LTE.

Furthermore, AESIs (by event type and preferred term), SAEs (during treatment and during follow-up separately, by system organ class and preferred term) during LTE will be summarised by LTE treatment group. Summaries of deaths, AESIs by time interval and SAEs by time interval will also be presented for the additional supportive treatment groups placebo feeder + anifrolumab 300 mg LTE, and anifrolumab 150 mg feeder + anifrolumab 300 mg LTE.

The event rate per 100 subject years and number and percentage of subjects with at least one anaphylaxis, hypersensitivity, and infusion-related reaction (investigator), respectively, will be summarised overall as well as for the following respective subcategories: SAE (including events with outcome of death), AE leading to discontinuation, and AE by maximum intensity (mild, moderate, and severe). Furthermore, these AE categories will be presented graphically over time as percentage of subjects with a respective AE at a respective visit according to the definition as given in Section 3.1.1. These summaries will also be presented for the additional supportive treatment groups placebo feeder + anifrolumab 300 mg LTE, and anifrolumab 150 mg feeder + anifrolumab 300 mg LTE.

Infections, opportunistic infections, and non-opportunistic infections will be summarised with the same subcategories as given above. This summary will also be presented for the additional

supportive treatment groups placebo feeder + anifrolumab 300 mg LTE, and anifrolumab 150 mg feeder + anifrolumab 300 mg LTE.

Key subject information for subjects with an AE with outcome of death, subjects with serious AEs, subjects with an AE leading to discontinuation of investigational product, subjects with AESIs, subjects with a cardiovascular event, and subjects with a COVID-19 related AE, respectively, will be provided.

4.2.1.2 Vital signs

Observed values and changes from baseline of pulse, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature, respectively, will be summarised by visit. The summary statistics presented will be minimum, 1st quartile, median, 3rd quartile, maximum, mean, and SD.

For each parameter with available criteria, the number and percentage of subjects with TELVC values will be summarised by year (using the same time windows as defined for AEs in Section 3.1.1 but Year 4 ending at Week 208 [LTE Visit 40/EDV] and not presenting the category 'after Year 4'). Additionally, the number and percentage of subjects with at least 1 TELVC value will be presented. Percentages will be based on subjects with a measurement at baseline and at least 1 subsequent measurement of the variable (in the respective period).

For each parameter, the number and percentage of subjects with values below, within, or above the corresponding normal range will be presented as shift tables from baseline to maximum and minimum post-baseline value, respectively.

4.2.1.3 Physical examination

Observed values and changes from baseline of body weight will be summarised by visit. The summary statistics presented will be minimum, 1st quartile, median, 3rd quartile, maximum, mean, and SD.

4.2.1.4 ECGs

The number and percentage of subjects with normal; abnormal, not clinically significant; and abnormal, clinically significant ECG results will be presented as a shift table from baseline to last on-treatment value.

Observed values and changes from baseline of ECG values will be summarised by parameter and visit using descriptive statistics. The summary statistics presented will be minimum, 1st quartile, median, 3rd quartile, maximum, mean, and SD.

For each ECG parameter with available criteria, the number and percentage of subjects with Potentially Clinically Significant post-baseline values and Potentially Clinically Significant changes from baseline, respectively, will be presented by parameter and criterion.

4.2.1.5 Flares based on Modified SELENA Flare Index

The flare rate per subject year will be presented for mild/moderate flares, severe flares, and any flares.

4.2.1.6 Laboratory variables

Observed values and changes from baseline of laboratory data for haematology, clinical chemistry, and fasting lipid profile will be summarised by visit. The summary statistics presented will be minimum, 1st quartile, median, 3rd quartile, maximum, mean, and SD.

Shift plots (scatter plots) presenting baseline values versus minimum post-baseline values (neutrophils, lymphocytes, monocytes, and haemoglobin only) and maximum post-baseline values (creatinine, creatinine kinase, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, bilirubin), respectively, will be provided. A diagonal reference line indicating no change and horizontal and vertical reference lines indicating the limits of the reference ranges will also be displayed on the shift plots.

If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at specific visits, then shift plots of these data may also be produced. This will be discussed and agreed upon during the BDR meeting.

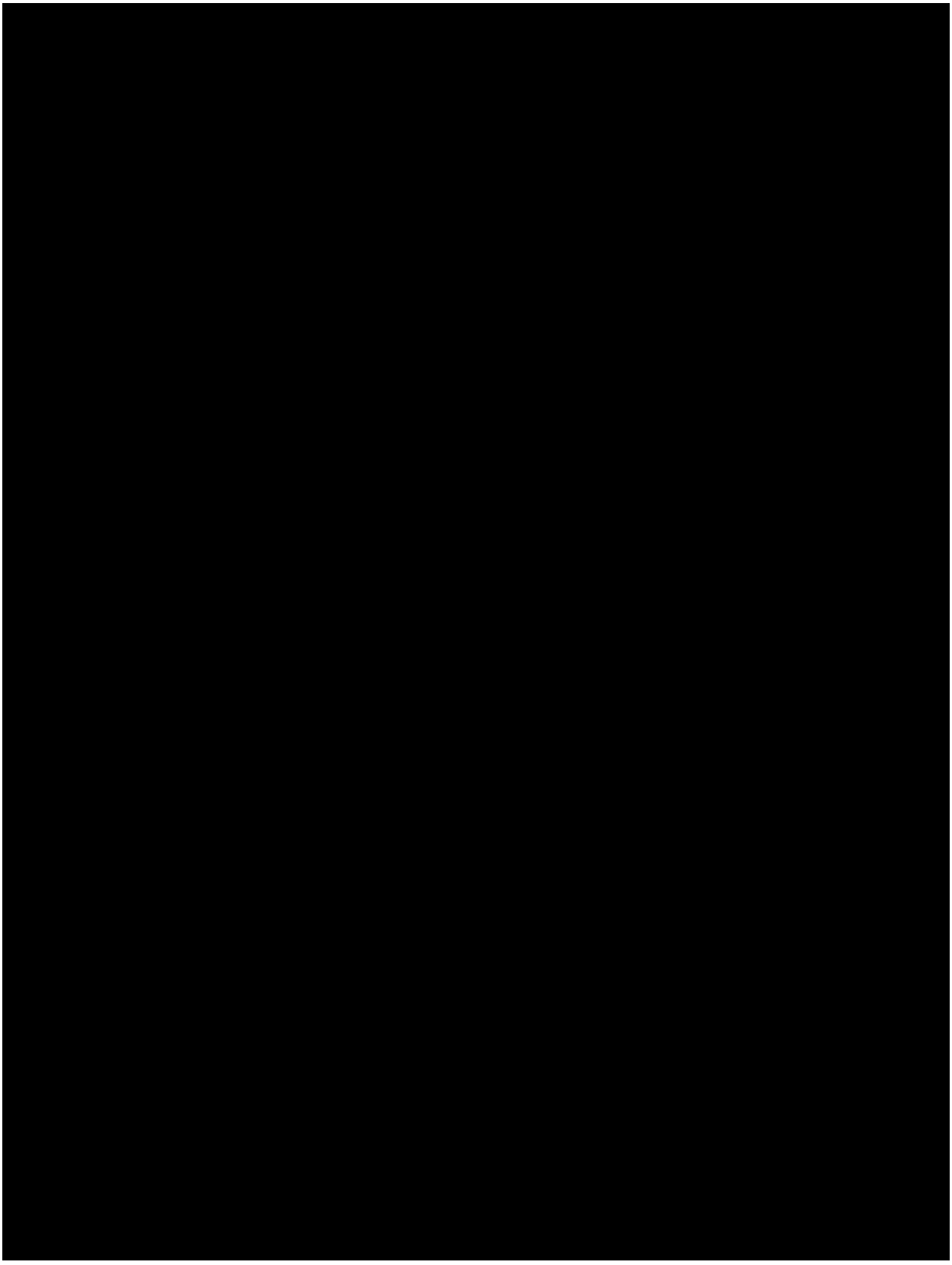
For each laboratory parameter with available criteria, the number and percentage of subjects with TELVC values will be summarised by visit. Additionally, the number and percentage of subjects with at least 1 TELVC value will be presented. Percentages will be based on subjects with a measurement at baseline and at least 1 subsequent measurement of the variable (at the respective visit).

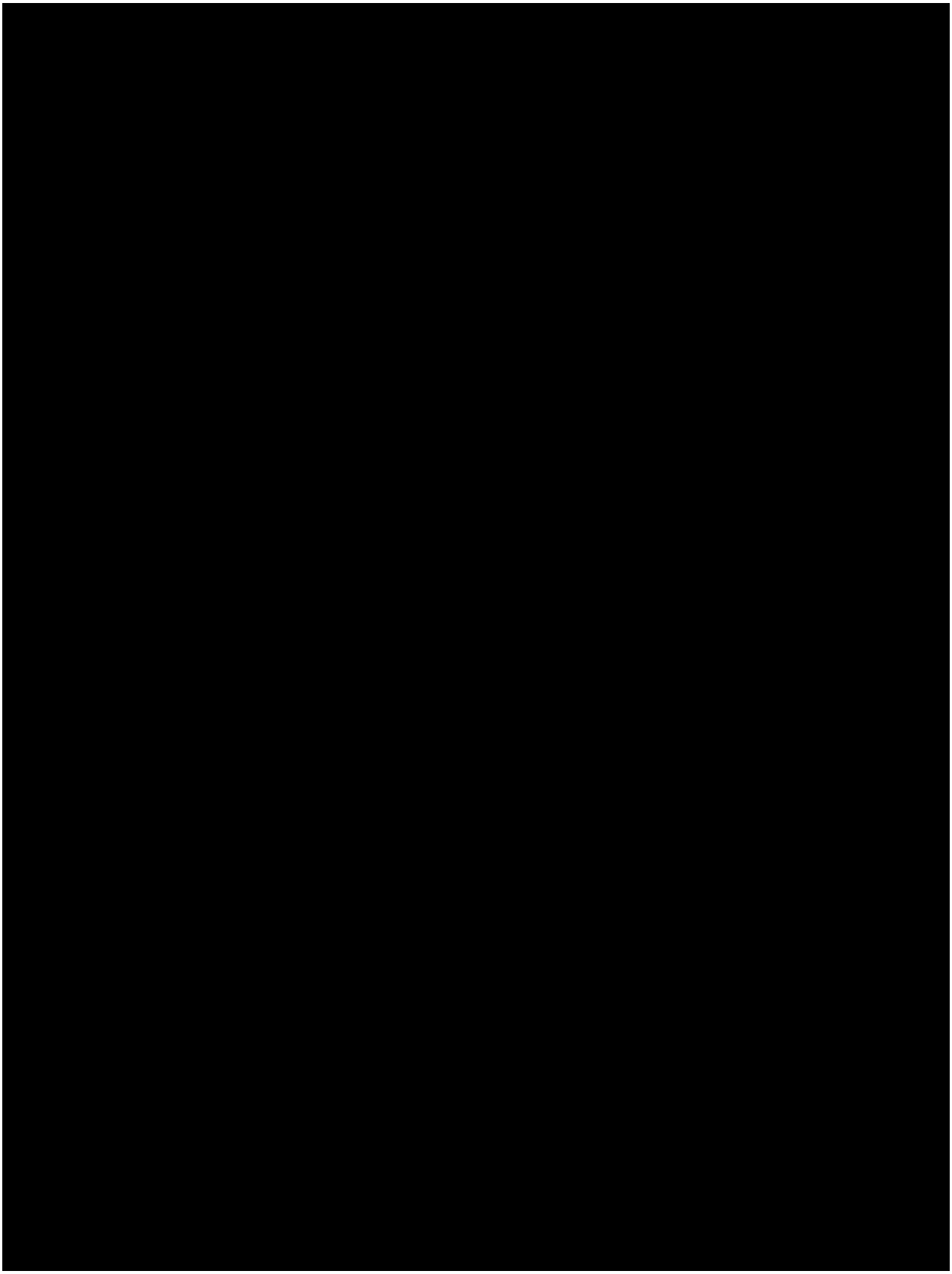
The number and percentage of subjects with laboratory values below, within, or above the corresponding reference ranges [redacted] will be presented as shift tables from baseline to maximum and minimum on-treatment value, respectively.

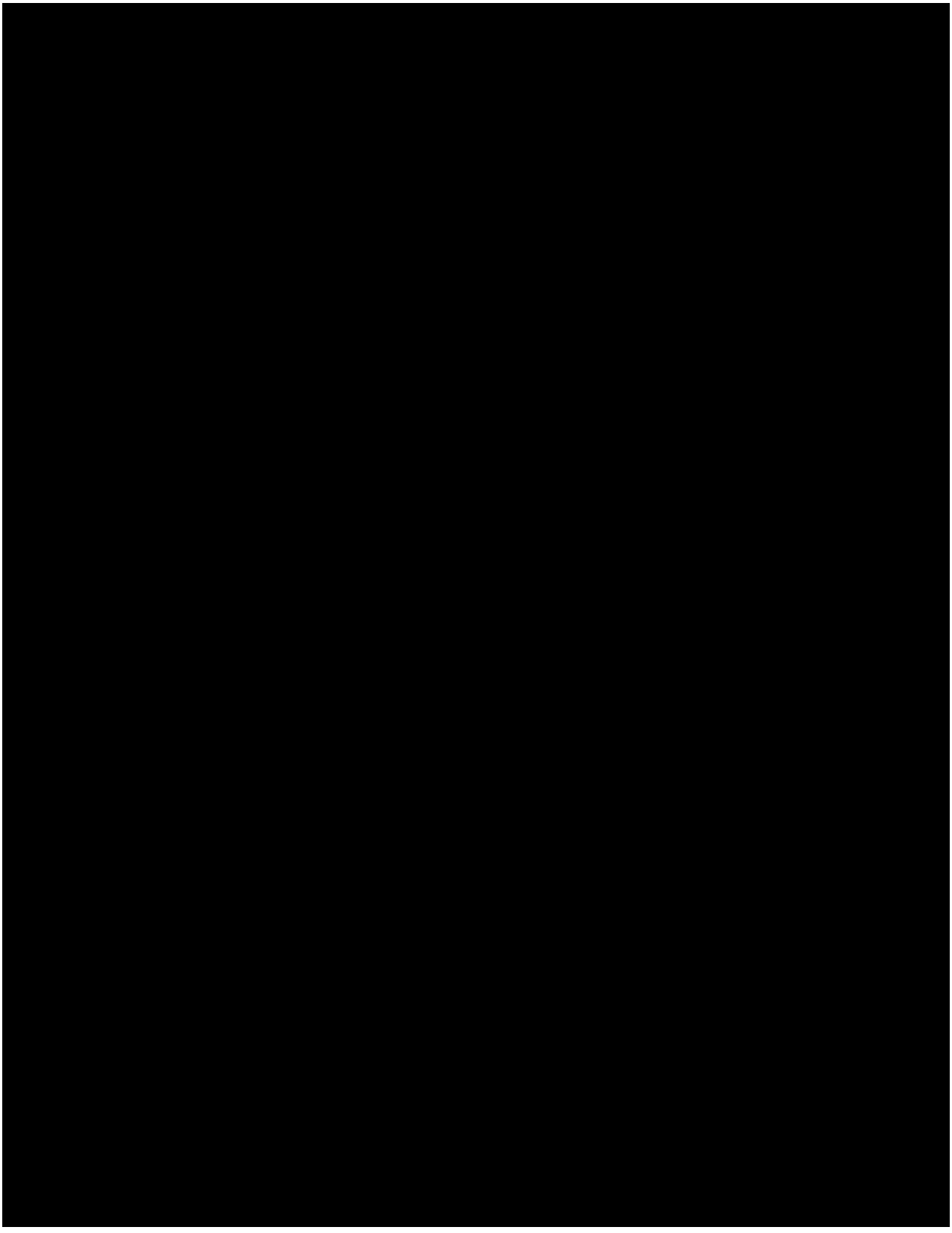
Urinalysis will be summarised as shift tables from baseline to the last on-treatment value for each parameter. Furthermore, the number and percentage of subjects with treatment-emergent changes will be summarised by parameter. Percentages for the summary of treatment-emergent changes will be based on subjects with a measurement at baseline and at least 1 subsequent measurement of the variable.

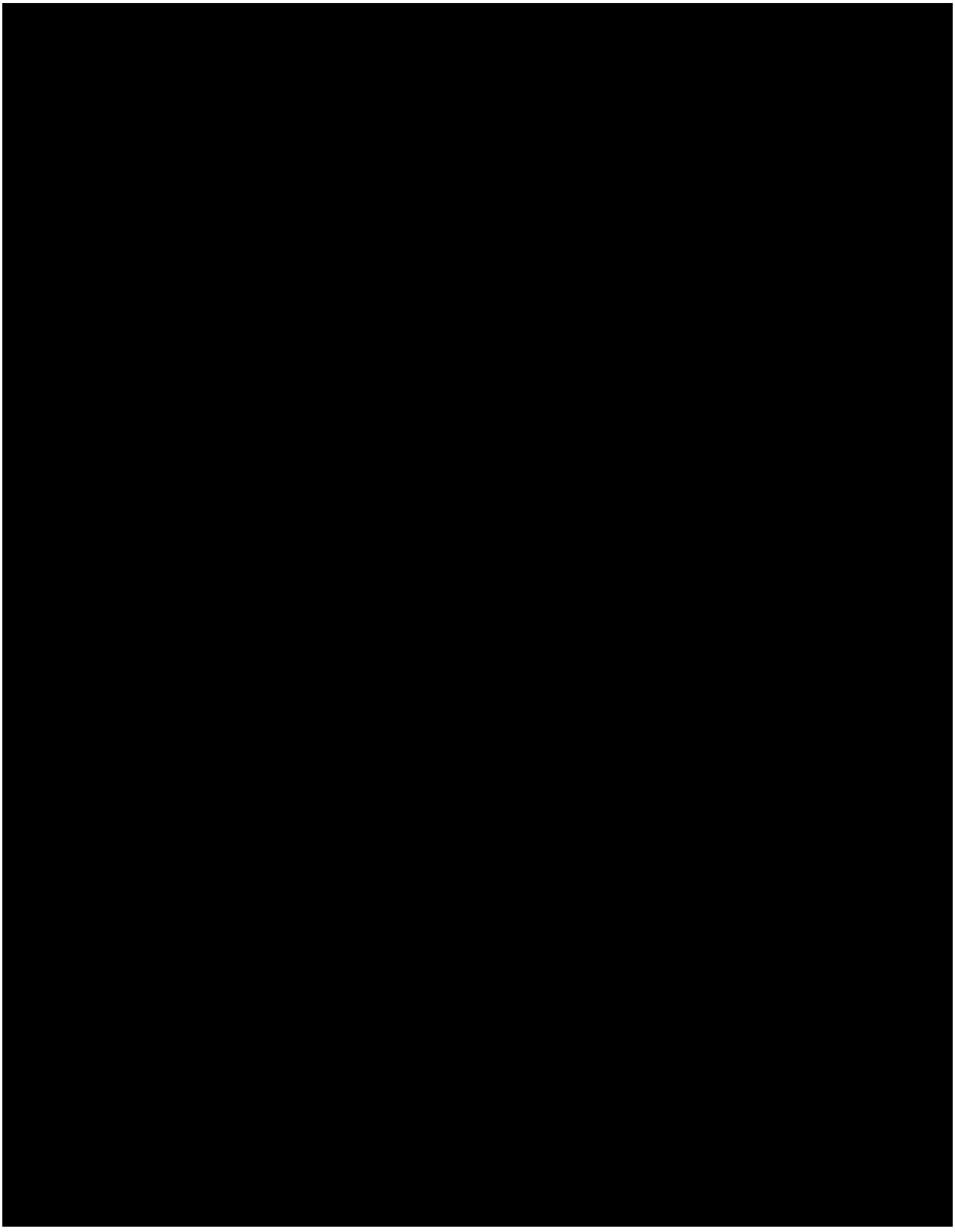
In order to identify potential Hy's Law cases, a shift table of maximum on-treatment total bilirubin against maximum on-treatment ALT, and maximum on-treatment AST expressed as multiples of ULN will be presented.

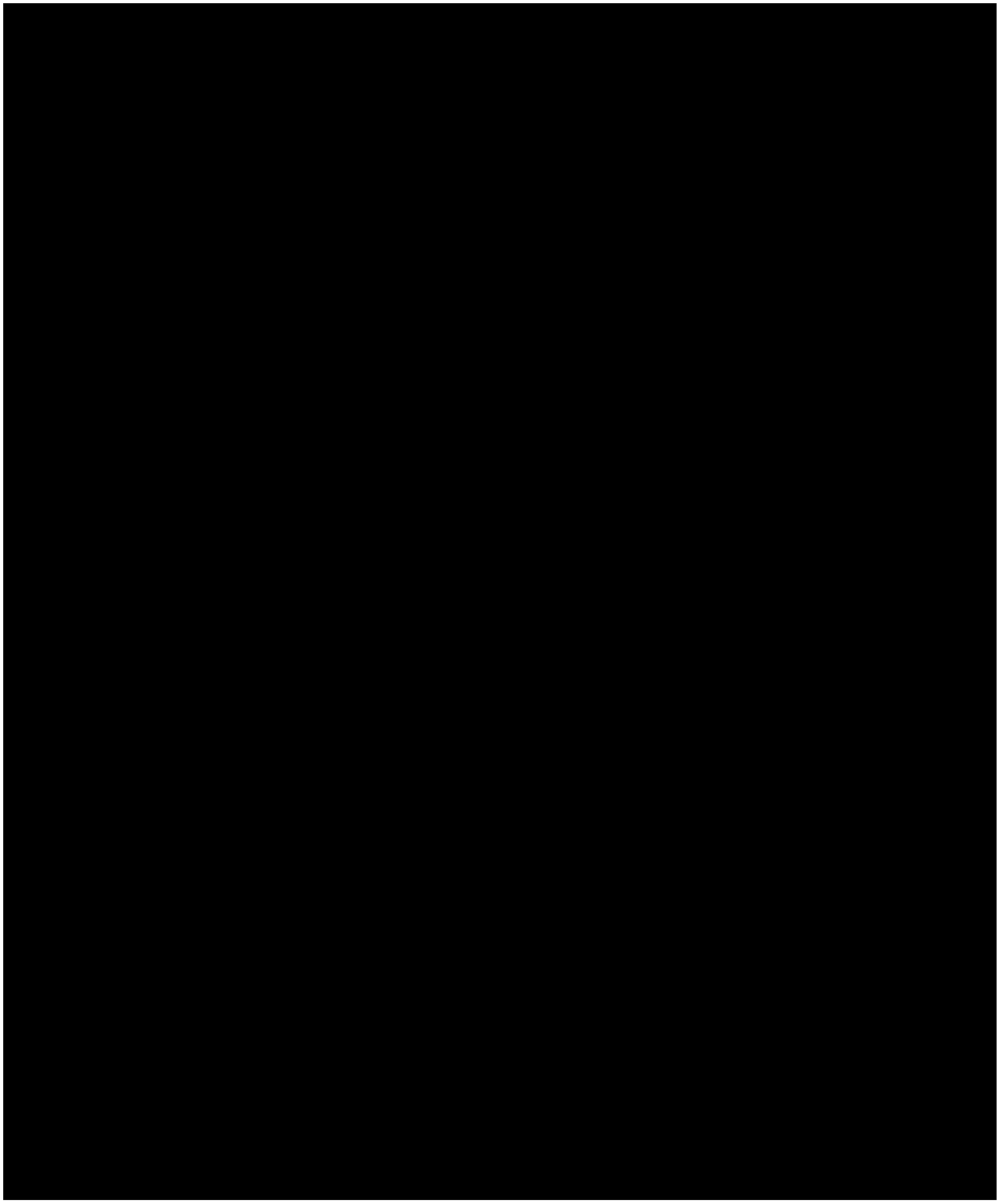
A Listing including all subjects who meet the biochemical criteria for Hy's Law (potential Hy's Law), will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these subjects.











4.2.3 Presentation of study population

4.2.3.1 Subject disposition

Beside the summary of protocol deviations, all summaries of subject disposition will be presented by combined treatment group as well as by LTE treatment group for the full analysis sets.

The number and percentage of subjects with the following study outcomes will be summarised. In the presentation by LTE treatment group, the first 5 categories will not be presented.

- Completed the Phase 3 feeder studies up to and including Week 52 (Visit 14/EDV) and either enrolled to LTE, or completed 12 weeks of follow-up after their last dose of IP (Follow-up Visit 2, or Week 52 for subjects who prematurely discontinued IP > 12 weeks prior)
- Withdrew from the Phase 3 feeder studies including reason for withdrawal
- Completed treatment with investigational product in the Phase 3 feeder studies up to and including Week 48 (i.e., with last administration of investigational product at Visit 13)
- Permanently discontinued the treatment with investigational product in the Phase 3 feeder studies including reason for withdrawal
- Randomised to the LTE study
- Completed the LTE study up to and including Week 208 (LTE Visit 40/EDV)
- Withdrew from the LTE study including reason for withdrawal
- Completed treatment with investigational product in the LTE study up to and including Week 204 (LTE Week 152, ie, with last administration of investigational product at LTE Visit 39)
- Permanently discontinued the treatment with investigational product in the LTE study including reason for withdrawal

This summary will be repeated for the first 5 categories by feeder study (D3461C00004 and D3461C00005) and corresponding feeder study treatment group. The number and percentage of subjects randomised to the respective study as well as the randomised treatment in the LTE study will also be included in the summary by feeder study.

Furthermore, the number and percentage of subjects remaining on investigational product, discontinued investigational product but remain on study, and withdrawn from study will be summarised by 6-month intervals (i.e., at weeks 24, 52 [both for combined data from feeder and LTE study only], 76, 104, 128, 156, 180, and 204). This summary will be presented for all given time points even with less than 25 subjects.

A summary of number and percentage of subjects in each population will be provided.

Important protocol deviations, COVID-19 related important protocol deviations, and important protocol deviations not related to COVID-19 occurring during the LTE study will be summarised by LTE treatment group.

The number and percentage of subjects with the following study outcomes will be summarised for the LTE study by LTE treatment group.

- Subjects randomised prior to the start of the COVID-19 pandemic
  - Subjects no longer in the study at the start of the COVID-19 pandemic
  - Subjects ongoing in the study at the start of the COVID-19 pandemic
- Subjects with at least one disruption due to the COVID-19 pandemic
  - Subjects with visit impaired
  - Subjects with study drug impacted
  - Subject who discontinued treatment due to COVID-19
  - Subjects who withdrew from study due to COVID-19.

Start date of the COVID-19 pandemic is 11-Mar-2020 as declared by the World Health Organization.

4.2.3.2 Demographic and baseline characteristics

All summaries of demographic and baseline characteristics will be presented for the full analysis set.

Summaries of demographic data, past and current medical history (including cardiovascular risk factor summary) and prior medication use will be based on information as recorded in the phase 3 feeder study for all subjects, regardless of whether the data from the phase 3 feeder studies will be included in post-baseline summaries for this treatment group. E.g. for the All Anifrolumab treatment group, demographics, medical history and prior medications from the phase 3 feeder study will be presented for the subjects randomised to placebo in the phase 3 feeder studies.

Demography and baseline characteristics will be presented by descriptive statistics and by combined treatment group, by LTE treatment group, and overall (i.e., including a total column).

Past and current medical history will be summarised separately by combined treatment group, MedDRA system organ class, and preferred term. Furthermore, the number and percentage of subjects with the cardiovascular risk factors will be presented by risk factor.

Prior and concomitant medications will be summarised separately by combined treatment group, WHO-DD Anatomical Main Group (ATC level 1), and preferred term.

Disease related treatments will be summarized by combined treatment group and by LTE treatment group. The number and percentage of subjects with at least 1 treatment in the categories given in Section 3.3.3 will be presented at baseline and every 3 months starting with Week 52 (high-level categories as given in Section 3.3.3) together with the

corresponding change from baseline (added, no change, discontinued). Percentages will be based on the number of subjects with at least one assessment at the corresponding visit.

4.2.3.3 Exposure

All summaries of exposure will be presented by combined treatment group as well as by LTE treatment group for the full analysis set.

Summary statistics will be provided for the duration of exposure. Descriptive statistics including quartiles will be provided in addition to the number and percentage of subjects treated ≥24 weeks, ≥52 weeks (both for combined data from feeder and LTE study only), ≥76 weeks, ≥104 weeks, ≥128 weeks, ≥156 weeks, ≥180 weeks, and ≥208 weeks. Furthermore, the total treatment days and total subject-years of exposure will be presented.

The number and percentage of subjects with infusions (for combined data from feeder and LTE study) and infusions during LTE (for LTE study), respectively, will be presented by total number of infusion (i.e., 1, 2, 3, etc). For weeks 24 (for combined data from feeder and LTE study only) and all scheduled visits in the LTE study (including week 52/LTE Day 1), the number and percentage of subjects with infusion/ no infusion will also be presented.

Furthermore, the time to discontinuation of investigational product will be presented as Kaplan-Meier plot including the number of subjects at risk (ie, still on investigational product) at weeks 24, 52, 76, 104, 128, 156, 180, and 208. Subjects in the “Randomised Placebo” treatment group who switched to anifrolumab will be censored using the last infusion of placebo as the censoring date and in the All Anifrolumab treatment group (using the first infusion in the LTE as day of first infusion). In interim analyses subjects who did not discontinue IP or completed/withdrew from study will be censored using the last infusion as the censoring date.

4.3 Subgroup analysis

No subgroup analyses are planned for this study.

5. INTERIM ANALYSES

Interim analyses may be performed based on regulatory or other requirements. Treatment allocation in the LTE study will become known to the Sponsor and staff and/or designated CRO. The blind will be maintained for the investigator, investigational site staff, and for the subject. Further details are described in a separate unblinding plan.

An interim analysis was performed at the time of the conclusion of the Phase 3 feeder studies (D3461C00004 or D3461C00005) and to support the 4-month safety update for the SLE IV submission..

6. CHANGES OF ANALYSIS FROM PROTOCOL

The definitions of the treatment groups for analyses were updated to clarify which data will be included in each group. The additional supportive treatment group Placebo Feeder + Placebo LTE during the LTE study only was removed. An additional analysis set was defined to cover the outputs for the LTE study only- Full Analysis Set- LTE Study. [redacted]

7. REFERENCES

Rothman and Greenland, 1998
Rothman KJ, Greenland S. Modern Epidemiology, 2nd Edition. Lippincott-Raven Publishers, Philadelphia, 1998.