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A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

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Study Statistician [redacted] 30JUL2019
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TABLE OF CONTENTS PAGE

TITLE PAGE 1
SIGNATURE OF STUDY STATISTICIAN 2
SIGNATURE OF GLOBAL PRODUCT STATISTICIAN 3
TABLE OF CONTENTS 4
LIST OF ABBREVIATIONS 8
AMENDMENT HISTORY 11
1. STUDY DETAILS 14
1.1 Study objectives 14
1.1.1 Primary objective 14
1.1.2 Secondary objectives 14
1.1.3 Safety objective 16
1.2 Study design 16
1.2.1 Restricted medications leading to non-response for key endpoints 17
1.2.2 Steroid burst 18
1.2.3 Protocol-specified steroid tapering 18
1.3 Number of subjects 19
1.3.1 Original sample size and power estimation 19
1.3.2 Updated power estimation 20
2. ANALYSIS SETS 20
2.1 Definition of analysis sets 20
2.1.1 All subjects 20
2.1.2 Full analysis set 20
[redacted]
2.2 Protocol deviations 21
3. PRIMARY AND SECONDARY VARIABLES 21
3.1 Primary outcome variable 22
3.2 Key secondary outcome variables 23
3.2.1 BICLA response at Week 52 in IFN test-high subjects 23
3.2.2 Oral corticosteroid management 23
3.2.3 Skin lesions 56
3.2.4 Joints 56
3.2.5 Flares 57
[redacted]

3.3.2 Supportive outcome variables of the individual components of BICLA [redacted] 58
[redacted]
3.3.4 Supportive outcome variables for the assessment of OCS use 61
3.3.5 Supportive outcome variables for the assessment of skin lesions 61
3.3.6 Supportive outcome variables for the assessment of joints 61
3.3.7 Supportive outcome variables for the assessment of flares 62
[redacted]
3.4 Assessment of study population 68
3.4.1 Demographic and baseline characteristic variables 68
3.4.2 Medical history 68
3.4.3 Prior and concomitant medications 68
3.4.4 Exposure to investigational product 78
3.5 Safety variables 78
3.5.1 Adverse events 79
3.5.1.1 Other significant adverse events 82
3.5.2 Laboratory variables 82
3.5.3 ECGs 83
3.5.4 Modified SELENA Flare Index based flares 83
3.5.5 Physical examination 84
3.5.6 Vital signs 84
3.5.7 Cushingoid features 85
3.5.8 C-SSRS 85
3.5.9 Personal Health Questionnaire Depression Scale-8 86
[redacted]
4. ANALYSIS METHODS 89
4.1 General principles 89
4.1.1 Data excluded from analysis 89
4.1.2 Database lock and unblinding 90
4.1.3 Visit windows 90
4.1.4 Presentation of results 91

4.1.5 Testing strategy to account for multiplicity considerations 92
4.1.6 Missing Data 94
4.1.7 Examination of model assumptions 104
4.2 Analysis methods 104
4.2.1 Analysis of the primary variable 104
4.2.2 Key secondary outcome variables 109
4.2.2.1 BICLA at Week 52 in IFN test-high subjects 109
4.2.2.2 Oral corticosteroid management 110
4.2.2.3 Skin lesions 110
4.2.2.4 Joints 111
4.2.2.5 Flares 111
4.2.3 Analysis methods for other secondary efficacy variables 113
4.2.3.1 Assessment of disease activity 113
4.2.3.2 Subject reported outcome variables 116
4.2.4 Presentation of study population 118
4.2.4.1 Subject disposition 118
4.2.4.2 Demographic and baseline characteristic 119
4.2.4.3 Restricted medications 119
4.2.4.4 Exposure 119
4.2.5 Analysis methods for safety variables 119
4.2.5.1 Adverse events 120
4.2.5.2 Laboratory variables 122
4.2.5.3 ECGs 123
4.2.5.4 Modified SELENA Flare Index based flares 123
4.2.5.5 Physical examination 123
4.2.5.6 Vital signs 123
4.2.5.7 Cushingoid features 124
4.2.5.8 C-SSRS 124
4.2.5.9 Personal Health Questionnaire Depression Scale-8 124
[redacted]
4.3 Subgroup analysis 126
5. INTERIM ANALYSES 127
6. CHANGES OF ANALYSIS FROM PROTOCOL 127
7. REFERENCES 128
8. APPENDIX 129
APPENDIX A - SUPPLEMENTAL PROCESS DESCRIPTION: RESTRICTED MEDICATIONS 130

APPENDIX B - SUPPLEMENTAL PROCESS DESCRIPTION: ORAL CORTICOSTEROIDS 162
APPENDIX C - DERIVATION RULES FOR IMPUTATION OF PARTIAL OR MISSING DATES 173
APPENDIX D - REFERENCE RANGES AND TELVC FOR LABORATORY VALUES 174
APPENDIX E - ECG: POTENTIALLY CLINICALLY SIGNIFICANT POST BASELINE VALUES 176
APPENDIX F - REFERENCE RANGES AND TELVC FOR VITAL SIGNS 177
APPENDIX G - DERIVATION OF IFN21 PARAMETERS 178

LIST OF TABLES

[redacted]
[redacted]
Table 4 Visit windows 90
Table 5 Overview of subgroup analyses 127

LIST OF FIGURES

Figure 1 Alpha recycling 93

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
AUC	Area under the curve
BDR	Blind data review
BICLA	British Isles Lupus Assessment Group-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BMI	Body mass index
C-SSRS	Columbia–Suicide Severity Rating Scale
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMH	Cochran-Mantel-Haenszel
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DBL	Database lock
[redacted]	[redacted]
ECG	Electrocardiogram
EDV	Early Discontinuation Visit
[redacted]	[redacted]
[redacted]	[redacted]
GGT	Gamma glutamyl transferase
IFN	Interferon
IPD	Important protocol deviation
IV	Intravenous
[redacted]	[redacted]

Abbreviation or special term	Explanation
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LTE	Long-term extension
MACE	Major adverse cardiovascular events
MAR	Missing at Random
MCS	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralising antibodies
[redacted]	[redacted]
OCS	Oral corticosteroids
PCS	Physical Component Score
[redacted]	[redacted]
PGA	Physician's Global Assessment
PHQ-8	Personal Health Questionnaire Depression Scale-8
[redacted]	[redacted]
[redacted]	[redacted]
Q	Question
Q-Q	Quartile-quartile
Q4W	Every 4 weeks
[redacted]	[redacted]
SAE	Serious adverse event
SD	Standard deviation
[redacted]	[redacted]
SE	Standard Error
[redacted]	[redacted]
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOC	Standard of care
[redacted]	[redacted]
TELVC	Treatment emergent laboratory/vital signs changes
TFL	Tables, Figures and Listings

Abbreviation or special term	Explanation
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO-DD	World Health Organization Drug Dictionary
[redacted]	[redacted]

AMENDMENT HISTORY

Date	Brief description of change
15 May 2017	Updates according to the changes in the table, figure and listing (TFL) shells after review Updates to provide additional details to support programming activities Updates to specify handling and examination of missing data (sensitivity and tipping point analyses) Updates to clarify database lock and unblinding after all subjects completed Week 52.

Date	Brief description of change
24 May 2019(v3.0)	Updates which are editorial in nature and do not impact the analyses are not listed. • Updates based on blind data review findings, including the removal of SMQ to define hypersensitivity reactions. Definition of hypersensitivity added. • Added the supplemental process documents for restricted medications (Version dated 21-Jan-2019) and oral corticosteroids (Version dated 18-Feb-2019) into the appendices of the SAP ([redacted] • Additional clarification added regarding the impact of restricted medications on the definition of non-responders for the primary and secondary efficacy endpoints; including BICLA, OCS reduction, CLASI, joints[redacted] • Updates to the assignment of primary and key secondary endpoints. Rationale for these updates are provided in the revised clinical study protocol. • Addition of supportive analysis for time to BICLA response sustained up to Week 52. • Addition of sensitivity analyses for BICLA and flares based on the modified BILAG. Added analysis of improvement over time by BILAG body system. • [redacted] • [redacted]

Date	Brief description of change
	• Added clarification that tipping point analyses will only be conducted if the primary analysis for the endpoint achieves nominal statistical significance. • Updates to remove details regarding two separate database locks. A single database lock is planned after last subject last visit. • Additional details added to document the process used to identify and report on important protocol deviations. • Added sensitivity analysis for flares using on-treatment data. • [redacted] • [redacted] • [redacted]
24 Jul 2019 (v4.0)	Updates which are editorial in nature and do not impact the analyses are not listed. • Clarified the date to be used in the determination of the key secondary endpoint, maintained OCS reduction. • Added clarification to the guidance for missing data when calculating scores. • Updated the supplemental process documents for restricted medications from version dated 21-Jan-2019, to version dated 17-Jul-2019. • Addition of sensitivity analysis for BICLA removing the criterion of no use of restricted medications beyond the protocol-allowed threshold.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measures:
To evaluate the effect of anifrolumab compared to placebo on disease activity as measured by the difference in the proportion of subjects achieving the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at Week 52	Composite variable (BICLA), defined by meeting all of the following criteria: - Reduction of all baseline British Isles Lupus Assessment Group (BILAG)-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B - No worsening from baseline in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), where worsening is defined as an increase from baseline of >0 points in SLEDAI-2K - No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS); - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment

[a] Any medication classified as restricted medications as described in [redacted]

1.1.2 Secondary objectives

Key Secondary Objectives:	Outcome Measures:
To evaluate the effect of anifrolumab compared to placebo on:	
The proportion of subjects with BICLA response at Week 52 in the interferon (IFN) test-high sub-group	BICLA (see outcome measure for primary objective)

The proportion of subjects who achieve an Oral corticosteroids (OCS) dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the sub-group of subjects with baseline OCS ≥10 mg/day	Maintained OCS reduction defined by meeting all of the following criteria: - Achieve an OCS dose of ≤7.5 mg/day prednisone or equivalent by Week 40 - Maintain an OCS dose ≤7.5 mg/day prednisone or equivalent from Week 40 to Week 52 - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The proportion of subjects with a ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score at Week 12 in the sub-group of subjects with baseline CLASI activity score ≥10	50% reduction in CLASI activity score compared to baseline defined by meeting all of the following criteria: - Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The proportion of subjects with ≥50% reduction in joint counts at Week 52 in the sub-group of subjects with ≥6 swollen and ≥6 tender joints at baseline	50% reduction in the number of swollen and tender joints compared to baseline defined by meeting all of the following criteria: - Achieve ≥50% reduction in the number of swollen joints and tender joints, separately - No discontinuation of investigational product - No use of restricted medications beyond the protocol-allowed threshold[a] before assessment
The annualised flare rate through 52 weeks	Annualised flare rate with flare defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit

[redacted]

1.1.3 Safety objective

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of anifrolumab	Adverse events (AEs) (including AEs of special interest [AESIs]), vital signs, physical examination, 12-lead electrocardiograms (ECG), flares as defined by a modification of the SELENA Flare Index using the SLEDAI-2K, clinical laboratory tests (haematology, clinical chemistry, urinalysis), Columbia Suicide Severity Rating Scale (C-SSRS), and Personal Health Questionnaire Depression Scale-8 (PHQ-8)

1.2 Study design

This is a Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an intravenous (IV) treatment regimen of 300 mg anifrolumab versus placebo in adult subjects with moderately to severely active SLE who are receiving standard of care (SOC) treatment. The study will be performed in adult subjects aged 18 to 70 years of age.

Approximately 360 subjects receiving SOC treatment will be randomised in a 1:1 ratio to receive a fixed IV dose of 300 mg anifrolumab or placebo every 4 weeks (Q4W) for a total of 13 doses (Week 0 to Week 48) with the primary endpoint evaluated at the Week 52 visit. Investigational product will be administered as an IV infusion via an infusion pump over a minimum of 30 minutes, Q4W.

Randomisation will be stratified using the following factors:

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
- Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent)
- Results of the IFN test (high versus low)

This study includes:

- **A Screening Period**: Up to 30 days
- **Treatment Period**: A 52-week double-blind treatment period with investigational product administration Q4W from Week 0 to Week 48 for a total of 13 doses
- **At Week 52**, subjects will have two options:
  - If eligible, enrol into the long-term extension (LTE) study in which anifrolumab 300 mg or placebo will be administered Q4W

    OR
  - Continue in the current 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 in Week 48)

The total study duration could be up to approximately 64 weeks for subjects who do not enrol into the LTE study (including screening period) and up to approximately 56 weeks (including screening period) for those subjects who do enrol into the LTE study.

Database lock (DBL) and unblinding will occur after the Last Subject Last Visit (LSLV). Blinding of subjects and investigators will be maintained to the greatest extent possible after DBL until LSLV in the LTE study.

1.2.1 Restricted medications leading to non-response for key endpoints

Subjects treated with concomitant medications beyond the protocol allowed threshold (restricted medications), as detailed in [redacted] while on investigational product may be considered non-responders for assessments of the primary and secondary efficacy endpoints including BICLA, OCS reduction, CLASI, joints [redacted]

A summary of the categories of restricted medications that may lead to a subject being considered as a non-responder is provided below, with a detailed description of the rules available in [redacted]

- Corticosteroids
  - Steroid burst and taper (see also Section 1.2.2)
  - Protocol-specified steroid tapering (see also Section 1.2.3)

- Antimalarials and Immunosuppressants
- Biologics
- NSAIDs
- Other restricted medications
  - Danazol, Dapsone, Sulfasalazine, Memantine: New or increased dose during the treatment period with certain exceptions
  - Investigational agents
  - Live or attenuated vaccines, BCG vaccine
  - Cyclophosphamide
  - IFN therapy
  - Plasmapheresis
  - Immunoglobulin therapy
  - Acthar gel
  - Retinoids

1.2.2 Steroid burst

From Week 0 (Day 1) to Week 12, subjects may receive **only** 1 burst of corticosteroids for an increase in SLE disease activity or to control non-SLE related disease (eg, asthma or chronic obstructive pulmonary disease exacerbation). Subjects receiving more than 1 burst during the first 12 weeks of treatment will be considered non-responders for subsequent assessments of disease activity, regardless of the reason for the burst (SLE or non-SLE activity). More details are given in [redacted] as well as Section 3.3.2 in the Clinical Study Protocol (CSP).

1.2.3 Protocol-specified steroid tapering

Steroid tapering to a target OCS dose of ≤7.5 mg/day **must** be attempted in all subjects with a baseline OCS dose ≥10.0 mg/day. This will commence at Week 8 and continue stepwise until the target is reached, unless at least 1 of the following criteria is met:

- SLEDAI-2K activity which is worsened compared to baseline in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever, thrombocytopenia, or haemolytic anaemia, or gastrointestinal activity)
- Newly-affected organ system(s) based on the SLEDAI-2K, excluding serological abnormalities (dsDNA antibodies, hypocomplementemia)
- Moderate to severe skin disease as reflected by a CLASI activity score of ≥10
- Moderate to severe arthritis disease as reflected by an active joint count of ≥8 tender and/or swollen joints

Investigators will not be required, but may continue, to taper OCS dose beyond the target of 7.5 mg/day up to Week 40 based on disease activity. If a subject has an increase in disease activity secondary to OCS tapering, they may increase the dose up to a maximum of the

baseline OCS therapy dose from Week 8 up to Week 40 without the subject being considered a non-responder for subsequent assessments of disease activity. Subjects who require OCS dose above their baseline level may continue in the study but will be considered non-responders for subsequent assessments of disease activity (refer to [redacted] for additional details).

Steroid tapering will not be permitted after Week 40.

1.3 Number of subjects

A total of 360 subjects receiving SOC treatment will be randomised 1:1 to treatment with anifrolumab or placebo.

The sample size and power estimations are based on the primary and key secondary endpoints. An update was made to the primary and 2 key secondary endpoints; therefore, a power analysis was conducted based on the updated primary endpoint

The primary endpoint was [redacted] later updated to the difference in the proportion of subjects achieving BICLA response at Week 52. The intercurrent events of discontinuation of the investigational product and receipt of restricted medications were incorporated into the primary and key secondary endpoints (except flares). The rationale for changes to primary and key secondary endpoints is provided in the CSP.

1.3.1 Original sample size and power estimation

The sample size is primarily driven by the need to acquire an adequate safety database size, as well as the ability to assess key secondary endpoints. [redacted]

It is not straightforward to precisely arrive at the power estimate for the assessments of key secondary endpoints due to the multiplicity procedure used to preserve the type I error, as well as uncertainties of the size of subgroups in most assessments. Approximate estimates of power for 2 example endpoints are listed below. These calculations assume that the primary endpoint is met, and the testing of the key secondary endpoints is therefore allowed. Each endpoint is tested using a weighted Holm procedure, and the alpha given by the assigned weight in the first step of the algorithm:

- [redacted]

[redacted]

- Difference in the proportion of subjects who achieve an OCS dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the sub-group of subjects with baseline OCS ≥10 mg/day: Given 60% of subjects have an OCS dose of at least 10 mg at baseline; proportions of subjects tapering the OCS dose of 32% and 59% in the placebo and anifrolumab treatment groups, respectively; a 2-sided alpha of 0.004 yields 87% power.

The assumptions of the effect sizes and sizes of subgroups used for the calculations above are based on the observed results in the interim analyses of study CD IA MEDI 546-1013.

1.3.2 Updated power estimation

An updated power analysis was performed based on the previously planned sample size and amended primary endpoint. There were no changes made to the study sample size. Power calculations were performed solely to justify the update to the primary and key secondary endpoints.

The primary endpoint is the difference in proportion of subjects achieving BICLA response at Week 52, comparing anifrolumab 300 mg to placebo. With assumed proportions of BICLA responders of 30% and 46% in the placebo and anifrolumab 300 mg groups, respectively, 180 subjects/arm yields approximately 88% power to reject the hypothesis of no difference using a 2-sided alpha of 0.05. The minimal detectable difference in BICLA response between anifrolumab 300 mg versus placebo is approximately 10% with this sample size. Calculations are based on a 2-group chi-squared test of equal proportions (nQuery version 8.1.2.0).

The assumptions for effect sizes used in the above calculations are based on the observed results from study D3461C00005.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 All subjects

This analysis set will comprise all subjects screened for the study and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set

The full analysis set will be used as the primary population for reporting efficacy and safety data. This comprises all subjects randomised into the study who receive at least 1 dose of investigational product and will be analysed according to randomised treatment (modified Intention-To-Treat). Any major deviations from randomised treatment will be listed and considered when interpreting the safety data.

[redacted]

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) are a subset of protocol deviations that may significantly 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 data reviews (BDR). The Sponsor then reviews the classification and provides the final determination. The list of important protocol deviations will be finalized and documented prior to database lock and unblinding.

Only important protocol deviations will be listed and tabulated in the Clinical Study Report (CSR).

3. PRIMARY AND SECONDARY VARIABLES

Baseline is defined as the last measurement prior to randomisation and 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.

At some sites, the device to collect subject reported outcomes was not synchronized with the real time. Therefore, baseline for the following subject reported outcomes will be derived based on the date only, and not time of the assessment.

[redacted]

- C-SSRS

- Personal Health Questionnaire Depression Scale – 8

If not stated otherwise, change from baseline will be calculated as value at the respective time point minus value at baseline. The percent change from baseline is defined as change from baseline divided by baseline value multiplied with 100.

Values of BILAG-2004, SLEDAI-2K, CLASI, PGA, [redacted] central reviewers, including adjudication of BILAG scoring. Modified BILAG values will be used as a sensitivity analysis to the primary endpoint and flares. Details regarding modified BILAG are provided in Section 3.3.2 as well as in the CSP.

3.1 Primary outcome variable

The primary endpoint used to evaluate the effect of anifrolumab compared to placebo on disease activity is the difference in the proportion of subjects achieving BICLA response at Week 52, where a subject is a BICLA responder if all the following criteria are met:

- Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
- No worsening from baseline in SLEDAI-2K, where worsening is as defined as an increase from baseline of >0 points in SLEDAI-2K

  Increase from baseline corresponds to the change from baseline. SLEDAI-2K will be derived as the sum of the scores for all items.
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No permanent premature discontinuation of investigational product (according to eCRF form "Discontinuation of Investigational Product")
- No use of restricted medications beyond the protocol-allowed threshold on or before the date of last Week 52 assessment used to derive BICLA response

  Restricted medications are defined in [redacted].

Subjects with no BILAG A or B at baseline and no worsening in any organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B, as well as subjects with a baseline PGA VAS score > 2.7 will be considered as having met the criteria for BILAG and PGA VAS, respectively.

If any of the criteria cannot be evaluated at Week 52 (eg, due to missing values) that criterion will be imputed using LOCF and BICLA response derived based on the complete data. This applies only if Week 48 data is not missing, otherwise the subject will be defined as a BICLA non-responder at Week 52.

In addition, time to BICLA response sustained up to Week 52 will be assessed. Time to BICLA response sustained up to Week 52 is defined as the visit of first BICLA response

which is sustained up to, and including, Week 52. A subject is considered to have achieved BICLA response sustained up to Week 52 if response is achieved at Week 52 with "time to" defined as the first timepoint where BICLA response is achieved when maintained through Week 52.

Subjects without a BICLA response sustained up to Week 52 will be censored at the date of premature discontinuation of IP, or Week 52, whichever occurs earlier. If subject did not prematurely discontinue treatment, but did not have a week 52 assessment either, then the date of last available BICLA assessment (latest of BILAG, SLEDAI and PGA date) prior to Week 52 will be used as the censoring date.

The individual conditions of BICLA (reduction of all BILAG-2004 A and B, no worsening from baseline in SLEDAI-2K, no worsening in subjects' lupus disease activity, no permanent discontinuation of investigational product, and no use of restricted medication) will be assessed at Week 24 and Week 52 by treatment.

The difference between anifrolumab and placebo in the proportion of subjects achieving BICLA response will also be assessed longitudinally over time up to Week 52.

The primary endpoint will also be calculated using the modified BILAG assessments, as described in Section 3.3.2. The primary endpoint will also be calculated removing the criterion of no use of restricted medications beyond the protocol-allowed threshold.

3.2 Key secondary outcome variables

3.2.1 BICLA response at Week 52 in IFN test-high subjects

The key secondary endpoint used to evaluate the effect of anifrolumab compared to placebo on disease activity in the IFN test-high subgroup is the difference in the proportion of subjects achieving BICLA response at Week 52 in subjects classified as IFN test-high at baseline. BICLA response is defined in Section 3.1.

3.2.2 Oral corticosteroid management

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on the ability to reduce the OCS dose in subjects with baseline OCS ≥10 mg/day prednisone or equivalent is the difference in the proportion of subjects with maintained OCS reduction. A maintained OCS reduction is defined as meeting all the following criteria:

- Achieve an OCS dose of ≤7.5 mg/day prednisone or equivalent by Week 40

  The date of last assessment used for efficacy analysis (SLEDAI-2K, PGA and BILAG) in the time window of Week 40 (as described in Section 4.1.3) will be used as date of Week 40. If no such assessment falls into the respective time window, then the target date for the timepoint will be used instead. The dose of OCS at Week 40 used in the evaluation of this endpoint will be the dose on the date of Week 40 + 1 day.
- Maintain an OCS dose ≤7.5 mg/day prednisone or equivalent from Week 40 to Week 52

  A maintained OCS dose is defined as no dose increase (ie, no dose greater than the dose at Week 40 + 1 day) between Week 40 + 2 days and Week 52, inclusive.

  The date of last assessment used for efficacy analysis (SLEDAI-2K, PGA and BILAG) in the time window of Week 52 (as described in Section 4.1.3) will be used as date of Week 52. If no such assessment falls into the respective time window, then the target date for the timepoint will be used instead.
- No permanent premature discontinuation of investigational product (according to eCRF form "Discontinuation of Investigational Product")
- No use of restricted medications beyond the protocol-allowed threshold on or before the date of Week 52 (as given above)

  Restricted medications are defined in [redacted]

If any of the conditions cannot be evaluated at Week 52 (eg, due to missing values) the subject is defined as not reaching a maintained OCS reduction.

[redacted]

3.2.3 Skin lesions

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on inflammatory cutaneous lupus lesions in subjects with baseline CLASI activity score ≥10 is the difference in the proportion of subjects with an at least 50% reduction in CLASI activity score at Week 12. An at least 50% reduction in CLASI activity score is defined as meeting all of the following criteria:

- Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline
  The CLASI activity score will be derived as the sum of all single activity scores (13 locations of erythema, 13 locations of scale/hypertrophy, mucous membrane lesions, recent hair loss, and non-scarring alopecia). A ≥50% reduction is reached if the percentage change is ≤-50%.
- No permanent premature discontinuation of investigational product before assessment (ie, duration of exposure ≥ study day of date of CLASI assessment at Week 12)
- No use of restricted medications beyond the protocol allowed threshold on or before the date of CLASI assessment at Week 12
  Restricted medications are defined in [redacted]

If any of the criteria cannot be evaluated at Week 12 (eg, due to missing values) that criterion will be imputed using LOCF and an at least 50% reduction in CLASI activity score derived based on the complete data. This applies only if Week 8 data is not missing, otherwise the subject will be defined as not reaching a ≥50% reduction in CLASI activity score at Week 12.

3.2.4 Joints

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on swollen and tender joints is the difference in proportion of subjects with at least 6 swollen and at least 6 tender joints at baseline who achieve at least a 50% reduction from baseline in both the number of swollen and tender joints at Week 52.

An at least 50% reduction is reached if all the following criteria are met:

- The percentage reduction from baseline in both the number of swollen joints and the number of tender joints, separately, is ≥50%
- No permanent premature discontinuation of investigational product (according to eCRF form “Discontinuation of Investigational Product”)
- No use of restricted medications beyond the protocol allowed threshold on or before the assessment
  Restricted medications are defined in [redacted]

If the change from baseline in the number of swollen and tender joints cannot be evaluated at Week 52 (eg, due to missing values) the change from baseline will be imputed using LOCF. This applies only if Week 48 data is not missing, otherwise the subject will be defined as not achieving a 50% reduction.

3.2.5 Flares

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on flares is the difference in annualized flare rate through Week 52.

A flare is defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit (ie, a worsening from an E, D, or C score to a B score in at least 2 organ systems or a worsening from an E, D, C, or B score to an A score in any one organ system compared to the previous visit).

The occurrence of a new flare will be checked for each available visit versus the previous available visit up to Week 52. If no flare occurred, the number of flares will be set to 0. Otherwise all flares will be counted leading to a maximum number of flares of 13.

The annualized flare rate will be calculated as the number of flares divided by the flare exposure time in days multiplied with 365.25. The flare exposure time is the time up to Week 52 (date of BILAG-2004 assessment at Week 52) or up to the date of last available BILAG-2004 assessment up to and including week 52 in case of premature study discontinuation and will be derived as date of Week 52/ date of last BILAG-2004 assessment minus date of first administration of investigational product + 1.

For the sensitivity analyses of flares while on treatment, the flare exposure time is the time between day of first dose of investigational product and day of last dose of investigational product plus 28 days, both inclusive. All flares occurring within the flare exposure time will be considered for this analysis (even if occurring after the week 52 visit timepoint).

An additional sensitivity analysis for flare rate through Week 52 will use the modified BILAG as described in Section 3.3.2.

[redacted]

[redacted]

3.3.2 Supportive outcome variables of the individual components of BICLA[redacted]

SLEDAI-2K

SLEDAI-2K (derived as the sum of the scores for all items) will be evaluated using the difference in mean change from baseline longitudinally over time to Week 52.

Scores for the SLEDAI organ systems will be derived in the same way as SLEDAI-2K but using the scores for the respective items only. The SLEDAI organ systems are defined as follows:

- Central nervous system: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, and lupus headache
- Vascular: CVA (cerebrovascular accident) and vasculitis
- Musculoskeletal: arthritis and myositis
- Renal: urinary casts, haematuria, proteinuria, and pyuria
- Mucocutaneous: rash, alopecia, and mucosal ulcers
- Cardiovascular system and respiratory: pleurisy and pericarditis

- Immunology: low complement and increased DNA binding
- Haematological and fever: fever, thrombocytopenia, and leukopenia

For each SLEDAI organ system, the proportion of subjects with an improvement (ie, a SLEDAI organ system score less than the corresponding score at baseline) at Week 24 and Week 52, respectively, will be assessed for subjects with an organ system involvement at baseline (ie, a SLEDAI organ system score greater than 0).

Physician's Global Assessment

The difference between anifrolumab and placebo in the mean change from baseline in PGA (measured on a VAS ranging from 0 to 3) will be assessed by visit up to Week 52.

BILAG-2004

BILAG-2004 contains 97 clinical and laboratory parameters divided into the 9 body systems. The first 7 body systems (Constitutional, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardiorespiratory, Gastrointestinal, Ophthalmic) contain clinical parameters which are assessed by the treating physician as new (4), worse (3), same (2), improving (1) and not present (0). The Renal and Haematologic scoring is based on laboratory values. The original central review process used the 1 September 2009 BILAG 2004 version of the BILAG Index Scoring. BILAG body system scores were assigned A, B, C, D or E scores to all study visits by strictly following this Index Scoring. Results from the original scores are used for calculation of the primary efficacy endpoint, BICLA response at Week 52, defined in Section 3.1.

The majority of As and Bs assigned via the scoring algorithms of the BILAG-2004 are considered a legitimate representation of clinically significant worsening disease activity; however, there is a feature within the BILAG-2004 Index Scoring algorithms that can result in an A or B assigned to a body system which had improved, and then remained at the 'same' level of improvement compared to previous visits. Items marked 'same' frequently warrant assignment of an A or B category following the BILAG-2004 Index Scoring based on the BILAG principle of intention to treat. These are "false" A or B categories because they are not true worsening of disease activity but are due to unchanged or the same disease activity that has previously improved. These "false" A and B can only be determined and subsequently re-scored after a subject had completed a series of visits that define true state of SLE disease activity.

The Disease Activity Adjudication Group will differentiate "false" A and B scores from true clinically significant worsening by reviewing all BILAG-2004 Index scores for each subject's visits. A modified BILAG-2004 Index Scoring Rules will be used. The Modified BILAG rules and the review process and scoring as well as references used that justify the modification are detailed in a charter developed for this exercise. Modified BILAG rules will be used in sensitivity analyses for the primary endpoint and for flares.

BILAG-2004 grades will be presented by organ system. Furthermore, a BILAG-2004 global score will be derived by summing-up the numerical score equivalents for each organ system with the numerical score equivalents given as: A = 12, B = 8, C = 1, D = 0, and E = 0.

For each BILAG body system and regardless of involvement at baseline, improvement over time will be summarized as the number and percentage of subjects with involvement at baseline (A,B, or C), no involvement at baseline (E), or no involvement at baseline but had previous experience (D); unchanged at Week X (same score as baseline); improvement at Week X (changing score to a lower activity, eg, from A to B/C/D); worsening at Week X (eg, from B/C to A); new at Week X (eg, from D or E to A/B/C); missing at Week X. No imputation will be performed for missing values.

[redacted]

[redacted]

3.3.4 Supportive outcome variables for the assessment of OCS use

The total daily OCS dose will be assessed longitudinally over time up to Week 52. For the derivation of OCS dose at a specific visit, the target date for the respective visit (as described in Section 4.1.3) will be used.

The standardised area under the curve (AUC) of OCS dose up to Week 52 will be calculated as follows:

For each single daily dose, the duration of the single dose will be calculated as end date – start date + 1. If the start date is before Day 1, Day 1 will be used instead. If the end date is after the date of Week 52 (date of Visit 14), the date of Visit 14 will be used instead. The AUC for each single dose will be derived by the daily dose (mg/day) multiplied with the duration (days). The AUC up to Week 52 is the sum of the AUCs of the single doses. The AUC of OCS dose will only be calculated if all necessary data are available up to Visit 14 (ie, daily prednisone equivalent OCS dose can be calculated). For subjects who discontinued the study before Visit 14, the AUC will be calculated up to the date of study discontinuation. If a subject does not receive any OCS dose (ie, no corresponding medication documented) the AUC for this subject will be set to 0. The standardised AUC will be derived as AUC divided by the available days (date of Visit 14 / date of early discontinuation – date of Day 1 + 1) multiplied by 364 (52 weeks).

3.3.5 Supportive outcome variables for the assessment of skin lesions

For all subjects with a CLASI activity score ≥10 at baseline the reduction of CLASI will be compared between Week 12 and Week 52. An at least 50% reduction in CLASI activity score at Week 12 is defined in Section 3.2.3. The reduction at Week 52 is defined in the same way with using assessments at Week 52 (with allowed LOCF of Week 48 data) instead of Week 12 and no permanent premature discontinuation of investigational product (according to eCRF form “Discontinuation of Investigational Product”). Maintenance of effect in CLASI activity score is defined as an at least 50% reduction in CLASI activity score at Week 12 and Week 52.

The difference between anifrolumab and placebo in the mean change from baseline in CLASI activity as well as CLASI damage score will be evaluated longitudinally over time up to Week 52. The CLASI damage score will be calculated as the sum of the scores for dyspigmentation for 13 locations, scarring/atrophy/panniculitis for 12 locations, and scarring of the scalp. If dyspigmentation lasts more than one year, the sum of the dyspigmentation scores from the 13 locations will be multiplied with 2 in the above formula.

3.3.6 Supportive outcome variables for the assessment of joints

In addition to the variable in Section 3.2.4, secondary endpoints to evaluate the effect of anifrolumab versus placebo on joints are:

- Difference in change from baseline to Week 52 in the number of active, swollen, and tender joints, respectively;
- Difference in proportion of subjects with at least 6 swollen and at least 6 tender joints at baseline who achieve at least a 20% reduction from baseline in both the number of swollen and tender joints at Week 52, using similar definition as in Section 3.2.4;
- Difference in proportion of subjects with at least 8 swollen and at least 8 tender joints at baseline who achieve at least a 20% and at least a 50% reduction, respectively, from baseline in both the number of swollen and tender joints at Week 52, using similar definition as in Section 3.2.4.

An active joint is defined as a joint with both swelling and tenderness.

Furthermore, the change from baseline in the number of active, swollen and tender joints, respectively, will be explored longitudinally up to Week 52 for all subjects.

3.3.7 Supportive outcome variables for the assessment of flares

In addition to the variable in Section 3.2.5, the annualised flare rate will also be evaluated for the following definition of flares using baseline as the reference point, and will be derived similarly as described in Section 3.2.5.

- A flare is defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B compared to baseline and a change versus the previous visit. This implies that a new BILAG-2004 A score maintained in subsequent visits will not be counted as a new flare. However, a change of the situation in a subsequent visit (eg, one of the 2 new BILAG-2004 B scores of the previous visit improves to C but another worsens to B or an occurrence of a new BILAG-2004 B score in addition to the BILAG-2004 A score defining the previous flare) will lead to a new flare.

In addition, time to first flare will be assessed for flares as defined in Section 3.2.5 as well as for flares versus baseline as defined above. The time to first flare will be derived as date of first flare minus date of first administration of investigational product. If the subject did not have a flare, the time to flare will be censored at the end of the flare exposure time (as defined in Section 3.2.5).

3.4 Assessment of study population

3.4.1 Demographic and baseline characteristic variables

Demographic characteristics (including geographic region, age, sex, ethnicity and race) and baseline characteristics (including height, weight, body mass index [BMI] and disease characteristics) will be assessed.

The clinical SLEDAI-2K score will be derived as the sum of the scores for the SLEDAI-2K items vasculitis, arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, and pericarditis.

3.4.2 Medical history

Medical histories will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be evaluated separately for past and current conditions as given in the eCRF.

3.4.3 Prior and concomitant medications

Prior medications are reported according to the eCRF completion guidelines (ie, dependent of the relevance of the medication, the intake during the last few weeks before the first administration of IP, all medication taken during lifetime, or anything in-between will be reported). 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 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 Week 52 (Visit 14/EDV), inclusive, will be considered concomitant medication. Any medication started prior to the first dose of investigational product and did not end before first dose or was ongoing will be considered as both prior and concomitant medication.

Disease related treatments at baseline are defined as all medications with therapy reason containing “disease under study” with an intake at the date of first dose of investigational product (ie, start date on or before the date of first dose and end date on or after date of first dose or was ongoing). 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
  as defined in [redacted] rule # 76.
- Other SLE medication
  defined as SLE medications not covered within the above categories

[redacted] will be applied to classify medication as prior and/or concomitant, as appropriate.

Concomitant medications beyond the protocol allowed threshold (restricted medications) that are considered in the evaluation of the efficacy endpoints are described in Section 1.2.1 and [redacted]

3.4.4 Exposure to investigational product

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:

Duration of exposure (days) = (Last dosing date + 28 days) – first dosing date + 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 will be counted per subject. Furthermore, the number of subjects with an infusion will be assessed in 4-weekly categories (ie, 4 weeks, 8 weeks, 12 weeks, …, 48 weeks). An infusion will be counted if it was given in the corresponding time window. Missed infusions will not be counted. Additionally, the number of subjects with duration of exposure longer than each of the 4-weekly categories (ie, ≥4 weeks, ≥8 weeks, ≥12 weeks, …, ≥48 weeks) will be presented. As the duration of exposure takes into account the total exposure time from the last dose + 28 days (as defined above), any missed or delayed infusions will contribute to exposure time, but not to the number of infusions. For example, if a subject interrupted treatment and received no infusion at week 4 he/she will be counted as "No infusion" at week 4, but will be counted as having "Exposure >= 8 weeks" if he/she received an infusion at any time after week 4.

The time to discontinuation of investigational product is the same as the duration of exposure. However, for subjects continuing in the LTE study, the time to discontinuation will be censored at the last dosing date + 28 days.

3.5 Safety variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, haematology, clinical chemistry, urinalysis, cushingoid features, C-SSRS, PHQ-8, modified SELENA Flare Index based flares, and AEs (including AESIs).

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.

3.5.1 Adverse events

Adverse events experienced by the subjects will be collected throughout the entire study and will be coded using the latest version of MedDRA.

Adverse event data will be categorized according to their onset date into the following study periods:

- AEs occurring during screening:
  An AE during screening is defined as an AE with a date of onset ≥ date of first screening visit (S1) and < date of the first dose of investigational product.
  AEs occurring during screening will only be listed.
- 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:
  The period "during treatment and follow-up" combines the periods "during treatment" and "during 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.
- AEs occurring after follow-up:
  An AE after follow-up is defined as an AE with a date of onset > date of last dose of investigational product + 84 days.
  AEs occurring after follow-up will only be listed.

If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered as an AE during treatment. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an AE during treatment.

Adverse events of special interest are marked as such in the eCRF. Major adverse cardiovascular events (MACEs) will be determined according to the assessments of the Cardiovascular Event Adjudication Committee.

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.

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 SOC infections and infestations.

Opportunistic infections are defined by the investigator 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]

Adverse events during treatment 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 (ie, 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). For partial or missing dates, the rules as described above will be used, i.e. the AE will be considered as an AE during treatment unless the available information indicates otherwise and as occurring in the earliest possible time interval given the available (start and stop) date information. The following time intervals are defined:

- Day 1 to < Week 12:
  AEs with date of onset ≥ date of first administration of investigational product and < date of first administration of investigational product plus 84 days
- Week 12 to < Week 24:
  AEs with date of onset ≥ date of first administration of investigational product plus 84 days and < date of first administration of investigational product plus 168 days
- Week 24 to < Week 36:
  AEs with date of onset ≥ date of first administration of investigational product plus 168 days and < date of first administration of investigational product plus 252 days
- Week 36 to < Week 48:
  AEs with date of onset ≥ date of first administration of investigational product plus 252 days and < date of first administration of investigational product plus 336 days

- ≥ Week 48:
  AEs with date of onset ≥ date of first administration of investigational product plus 336 days

The event rate per 100 subject years is defined as

Number of subjects with an event / [sum of total exposure time in days/ (365.25*100)].

The exposure in a time period for each subject will be calculated as end of period – start of period + 1 (eg, date of last dose of investigational product + 28 days - day of first dose of investigational product + 1 day for summary of AEs during treatment). If a subject discontinued from the study during a period, switched to the LTE study 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 herpes zoster AESI, an alternative event rate per 100 subject years will be derived as

Number of subjects with an event / [sum of time at risk in days / (365.25*100)].

The time at risk is defined as time (including start and end date) from start of period (eg, date of first administration of investigational product for events during treatment) to the date of first event, death, withdrawal of consent, or end of period, whatever comes first. If an AE has a (partially) missing onset date, the missing parts will be considered on treatment, unless available information indicates otherwise and will be imputed with the earliest possible date given the available information before calculating the alternative event rate. This alternative event rate may also be calculated for other AESIs if suggested by data. This will be discussed during the BDR meeting and the decision will be made before unblinding the data.

The time to first onset of herpes zoster during treatment will be derived as date of first onset of herpes zoster – date of first administration of investigational product + 1. AEs with an onset date before the date of first administration of investigational product and AEs with an onset after 28 days after the date of last administration of investigational product will not be considered for the time to first onset of herpes zoster during treatment. If an AE has a (partially) missing onset date, the missing parts will be considered on treatment, and the missing parts will be imputed with the earliest possible date given the available information before calculating time to event. If a subject has no herpes zoster during treatment, the time to first onset will be censored at the date of last administration of investigational product + 28 days.

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 + 28 days for the last visit with investigational product).

3.5.1.1 Other significant adverse events

During the evaluation of the AE data, a medically qualified expert will review the list of AEs that were not reported as serious AE (SAEs) or AEs leading to discontinuation.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the AstraZeneca 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 led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

3.5.2 Laboratory variables

The parameters haematology, serum chemistry, urinalysis (outlined in Table 5 in Section 5.3.10 of the clinical study protocol) and of fasting lipid profile (high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides) will be explored.

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 as given in [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 (TELVC) will be defined for post-baseline values according to the reference ranges given in [redacted]

Urinalysis data will be categorised as negative (0), 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/+ at baseline to ++, +++, ++++ at any post-baseline value OR
- Increase of 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 (see [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

3.5.3 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.

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 Clinical Significant post-baseline values or changes from baseline are defined in [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 available values at the respective visit will be used for the analyses of the continuous ECG variables and the determination of Potentially Clinical Significant values.

3.5.4 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 further 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 one 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 or more
- At least one 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 one 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

3.5.5 Physical examination

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

3.5.6 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.

Where applicable, absolute values will be compared to the reference ranges given in [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 TELVC according to reference ranges given in [redacted]

For infusion visits, only measurements before start of investigational product will be considered for by visit presentations. In 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.

3.5.7 Cushingoid features

The presence of cushingoid features (moon face, buffalo hump, purple or violaceous striae, central obesity, hirsutism, acne, easy bruising, and fragile skin) will be explored by visit.

3.5.8 C-SSRS

The C-SSRS is an assessment tool that evaluates suicidal ideation and behaviour.

Two different versions of the questionnaire were used:

- Baseline/Screening version, assessing the last 12 months prior to the assessment
- Since Last Visit Version, assessing the time since last visit.

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale in an increasing order of severity from 1 to 10 to facilitate the definitions of the comparative variables.

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behaviour
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

The Suicidal Ideation or Behaviour Score will be derived from the C-SSRS categories as the maximum suicidal ideation or behaviour category (1-10 on the C-SSRS) present at the

assessment. The score will be derived at each assessment for each subject. Non-suicidal self-injurious behaviour will be assigned if no ideation or behaviour is present.

Composite variables based on the above re-ordered categories are defined for assessments during screening, during treatment, and during follow-up, respectively as follows:

- Suicidal ideation: A "yes" answer at any time in the respective study period to any one of the 5 (re-ordered) suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behaviour: A "yes" answer at any time in the respective study period, to any one of the 5 (re-ordered) suicidal behaviour questions (Categories 6-10) on the C-SSRS.
- No suicidal ideation or behaviour: No "yes" answer at any time in the respective study period to any one of the 10 (re-ordered) suicidal ideation and behaviour questions (Categories 1-10) on the C-SSRS.

The total number of attempts, total number of interrupted attempts, and total number of aborted attempts will be derived for the different study periods by summing up all respective attempts during screening, during treatment and during follow-up, respectively.

For summary of C-SSRS data, the following period definitions will be used:

- Screening Period:
  Assessments with a date ≥ date of first screening visit (S1) and ≤ date of the first dose of investigational product.
- During treatment Period:
  Assessments with a date > date of first dose of investigational product and ≤ date of last dose of investigational product + 28 days.
- Follow-up Period:
  Assessments with a date > date of last dose of investigational product + 28 days and ≤ date of last dose of investigational product + 84 days.

If the wrong questionnaire version (Baseline/Screening rather than Since last visit or vice versa) was used for an assessment, the assessment will be assigned to a period based on assessment date, regardless of the version that was completed.

3.5.9 Personal Health Questionnaire Depression Scale-8

The PHQ-8 assesses symptoms of depression over the last 2 weeks. The difference between anifrolumab and placebo in the mean change from baseline in PHQ-8 total score will be assessed by visit up to Week 52. The PHQ-8 total score will be derived as the sum of the 8 single item scores ranging from 0 (not at all) to 3 (nearly every day).

[redacted]

4. ANALYSIS METHODS

4.1 General principles

Due to vendor database limitations in Korea, the site number mapping listed in Table 3 will be performed programmatically to link the ePRO vendor data to the correct subjects.

Table 3 Site ID mapping

Site ID in raw ePRO vendor data	Mapped Site ID for analysis
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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 (eg, 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] 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.

Therefore, the 8 randomised subjects [redacted] as well as the 5 screen failures [redacted] at site [redacted] will not be considered in analyses and summaries. Separate listings for exposure, AEs, [redacted] medical history, concomitant medication, and SLEDAI-2K will be provided for the treated subjects.

4.1.2 Database lock and unblinding

Live unblinded randomisation data will be periodically released to an independent [redacted] analyst and an independent [redacted] analyst from PPD, to allow them to perform [redacted] analysis. The unblinded randomisation data will only be released to specific named personnel for this purpose and will not be made available to any staff from AstraZeneca or Sponsor's delegate.

After completion of LSLV, all data available in the database will undergo a thorough data cleaning process. When all relevant data have been coded, validated, signed, and locked, database lock will be declared.

Once database lock is declared, the study will be unblinded. Blinding of subjects and investigators will be maintained to the greatest extent possible until LSLV in the LTE study. No changes to locked data will be accepted after completion of database lock.

4.1.3 Visit windows

For visit based analyses, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows are summarized below:

Table 4 Visit windows

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Baseline / Day 1	1	Study Day ≤1
Week 4	29	2≤ Study Day ≤42
Week 8	57	43≤ Study Day ≤70
Week 12	85	71≤ Study Days ≤98
Week 16	113	99≤ Study Day ≤126
Week 20	141	127≤ Study Day ≤154
Week 24	169	155≤ Study Day ≤182
Week 28	197	183≤ Study Day ≤ 210
Week 32	225	211≤ Study Day ≤238
Week 36	253	239≤ Study Day ≤266
Week 40	281	267≤ Study Day ≤294
Week 44	309	295≤ Study Day ≤322
Week 48	337	323≤ Study Day ≤350
Week 52	365	351≤ Study Day ≤378
Week 56	393	379≤ Study Day ≤406
Week 60	420	407≤ Study Day

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 4 will be study day 29 (=28+1) for example.

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

- If there are two 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 two observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If two observations are collected on the same day, then the non-missing one with the earlier collection time will be included in the analysis.

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

For the Baseline / Day 1 visit window, the visit label "Baseline" will be used for all measurements before the first administration of IP. If the time of measurement at Study Day 1 is not available, it is assumed to be prior to first administration of IP. For measurements at Study Day 1 with a time of measurement after the start of IP administration, the visit label "Day 1" will be used (indicating a post-Baseline measurement).

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

4.1.4 Presentation of results

All analyses will use SAS® version 9.3 or higher. Summary tables will be presented by treatment group (anifrolumab 300 mg and placebo). All available data (with the exception as described in Section 4.1.1) for each analysis set will be used in the analyses. However, for visit based analyses, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows as given in Section 4.1.3. If not stated otherwise, these summaries will be restricted to data up to Week 52. Data (including derived variables) will be presented in listings sorted by 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 one 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 summarized 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 and median to a further decimal place and the SD to two additional decimal places. [redacted]

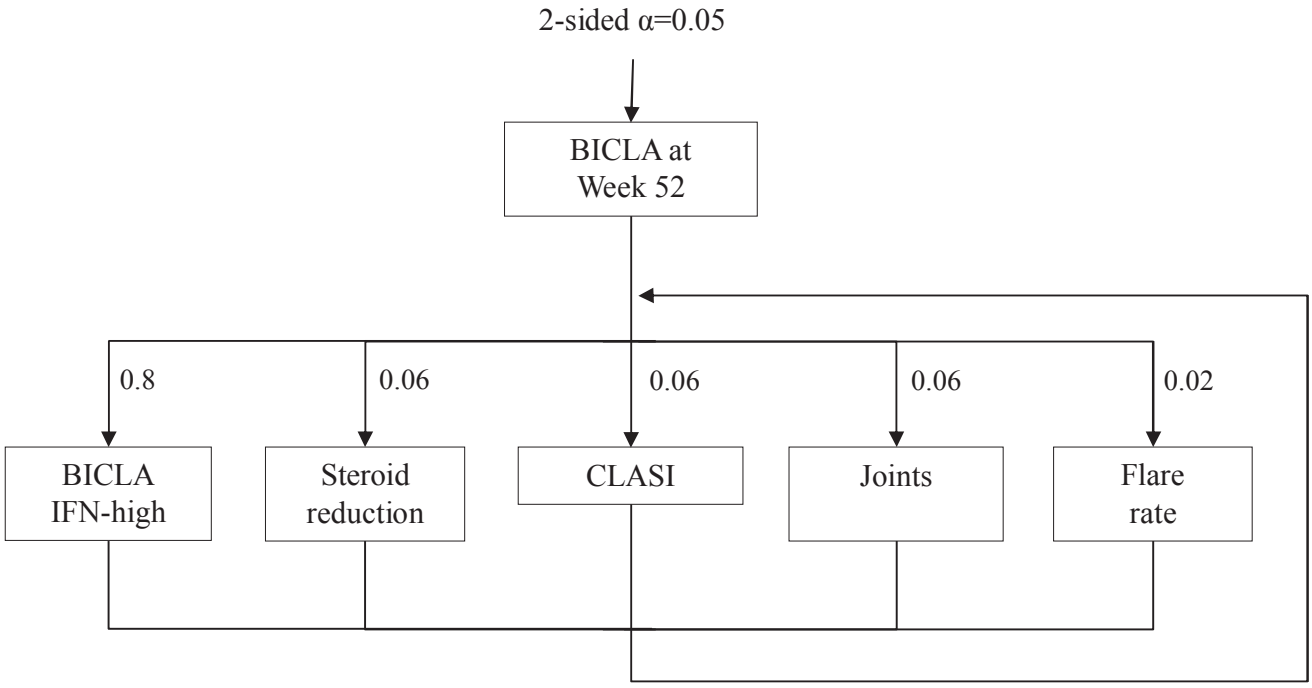
95% confidence intervals (CIs) will be presented for treatment comparisons. If a model is used to estimate the treatment difference, the corresponding CI according to the model will be presented. Otherwise, the unadjusted CI will be used. For the confirmatory treatment comparisons, p-values will be presented as described in section 4.1.5 and will be reported to 4 decimal places. For all other comparisons, no p-values will be presented.

4.1.5 Testing strategy to account for multiplicity considerations

To account for multiplicity to test the primary and five key secondary endpoints, a testing strategy will be followed to control the overall type I error rate in the strong sense. The primary endpoint, ie, the difference in the proportion of subjects achieving BICLA response at Week 52 comparing anifrolumab 300 mg to placebo, will be tested at an alpha level of 0.05. If the observed p-value is ≤0.05, a statistically significant difference in BICLA response between the treatment groups at Week 52 will be concluded, and the alpha of 0.05 will be preserved for testing of the key secondary endpoints. If the observed p-value is >0.05, no statistically significant difference between treatment groups will be declared, and no formal testing of the key secondary endpoints will be carried out.

If the primary endpoint is statistically significant, then the five key secondary endpoints will be tested and the weighted Holm procedure (Zhang, 1997 and Burman, 2009) will be used in order to strongly control the family-wise error rate at the 2-sided 5% level. The procedure applies alpha recycling according to the weights given in Figure 1. The weights were chosen based on a combination of estimated power for the individual key secondary endpoints and their relative clinical importance.

Figure 1 Alpha recycling



In a first step of the weighted Holm procedure, the five key secondary endpoints (BICLA in the IFN test-high subgroup, steroid reduction, CLASI, joints, and flare rate) will be tested at alpha levels of 0.04, 0.003, 0.003, 0.003, and 0.001, respectively. If 1 or more of the hypotheses will be rejected at these levels, the corresponding alpha will be distributed to the endpoints not rejected according to the assigned weights. As an example, the null hypothesis for BICLA in the IFN test-high sub-group will be rejected with a p-value ≤0.04 and all other hypotheses will not be rejected due to p-values >0.003 and 0.001, respectively. The alpha level of 0.04 will be distributed to the remaining four key secondary endpoints (steroid reduction, CLASI, joints, and flare rate) resulting in new alpha levels of 0.015, 0.015, 0.015, and 0.005, respectively. If any of the tests of these four endpoints results in a p-value smaller or equal to the corresponding new alpha level, the corresponding alpha level will again be distributed across the remaining endpoints.

This corresponds to the following mathematical notation:

We have 5 tests, and each hypothesis has a weight w_i for i = 1, …, 5 with sum(w_i) = 1

Let $p_{wi} = p_i/w_i$. Order the weighted p-values as $p_{(w1)} \leq p_{(w2)} \leq ... \leq p_{(w5)}$, being $H_{(wi)}$ the hypothesis associated with p-value $p_{(wi)}$ and $w_{(i)}$ the corresponding weights.

The weighted Holm's method can be described as

1. If $p_{(w1)} > \alpha$, fail to reject all 5 hypotheses
2. If $p_{(w1)} \leq \alpha$, reject $H_{(w1)}$, and move to $H_{(w2)}$
3. If $p_{(w2)} > \alpha/(1-w_{(1)})$, fail to reject $H_{(wi)}$ for $i \geq 2$
4. If $p_{(w2)} \leq \alpha/(1-w_{(1)})$, reject $H_{(w2)}$, and move to $H_{(w3)}$
5. Proceed with all remaining hypothesis until the first j such that $p_{(wj)} > \alpha/[1\text{-sum}(w_{(k)})]$ for k = 1,…, j-1

The adjusted p-values $p_{(i)}$ corresponding to hypothesis $H_{(wi)}$ will be calculated as $p_{(i)} = \max_{k \leq i}(r_{(i)})$, where $r_{(i)} = p_{(wi)}\left[1 - \sum_{k=1}^{i-1} w_{(k)}\right]$. (**Wright, 1992**) If $p_{(i)} \geq 1$ its value will be presented as >0.999.

4.1.6 Missing Data

Subjects who discontinue investigational product will be asked to come to each visit for the scheduled assessments through Week 52 (Visit 14/EDV). The definition of the primary variable includes 2 criteria that correspond to a non-responder imputation for subjects who prematurely discontinue from investigational product, or who receive restricted medications beyond the protocol-allowed threshold. This is the same for the definitions of key secondary binary variables.

Based on the results from the Phase 2 study (CD IA MEDI 546-1013), the majority of missing data is expected to be due to permanent discontinuation of IP, which for the binary responder endpoints will be imputed as non-responders per the endpoint definitions. It is expected that at each visit between 4% and 7% of subjects will have missing data due to a reason other than early discontinuation of IP (eg, missing visit [intermediate missing]), based on the results from the Phase 2. Given the expected small amount if intermediate missing data, it is expected to have a limited impact in the overall conclusions.

For binary responder efficacy endpoints, any component with missing value will be imputed using last observation carried forward (LOCF) if only a single (non-consecutive) visit has missing data for that component. In the event of two or more consecutive visits with missing data for the same component, LOCF will be used for the first missing value of each sequence, after which the data will be imputed as non-responders for the specific responder endpoint. The responder endpoint is derived based on the imputed values. If a component (eg, SLEDAI-2K) is based on several data points, LOCF will be done for the single data points.

To examine the impact of missing data, including the impact of non-responder imputation due to permanent discontinuation of IP, on the primary and key secondary endpoints tipping point analyses will be performed. These analyses will vary the assumptions about outcomes among the subsets of subjects on the treatment arms who discontinue IP early. For the primary

endpoint an extra sensitivity analysis will be performed to examine the impact of intermediate missing data. Tipping point analyses are intended to identify the point at which the results would tip from statistically significant to not statistically significant. Thus, the tipping point analyses will only be performed for the primary and key secondary endpoints that achieve a nominally statistically significant result (ie., nominal p-value<0.05).

For the derivation of the SLEDAI-2K total score, any laboratory items with missing value will be imputed using LOCF if only a single (non-consecutive) visit has missing data for that item. In the event of two or more consecutive visits with missing data for the same item, LOCF will be used for the first missing value of each sequence, after which the data will remain missing. Laboratory items of SLEDAI-2K are urinary casts, haematuria, proteinuria, pyuria, low complement, increased DNA Binding, thrombocytopenia, and leukopenia.

Unless otherwise defined, scores that are derived from summing up items will be considered missing if any of the items are still missing after applying the LOCF rules.

Missing safety data will generally not be imputed. However, safety assessment values of the form of <x (ie, below the lower limit of quantification (LLOQ)) or >x (ie, 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]

[redacted]

4.1.7 Examination of model assumptions

Model assumptions for repeated measures models will be checked with graphical displays (plot of residuals versus predicted values, a histogram with normal density overlaid, and a quantile-quantile (Q-Q) plot showing the residual quantiles versus quantiles of a normal distribution). If the model assumptions are not met, appropriate data transformations or the use of non-parametric approaches will be discussed during the BDR meeting. The decision about an appropriate approach will be made before unblinding the data.

The assumption of proportionality for Cox proportional hazard models will be assessed by producing complementary log-log plots presenting log (-log (estimated survivor function)) versus log (time). (In the presence of non-proportionality, the hazard ratio will be interpreted as an average hazard ratio over the flare exposure time.) If these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation. This will be discussed during the BDR meeting and the decision about an appropriate approach will be made before unblinding the data.

4.2 Analysis methods

4.2.1 Analysis of the primary variable

The primary endpoint used to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity is the difference in proportion of subjects achieving BICLA response at Week 52, as defined in Section 3.1.

The estimand of primary interest is the difference in the proportions of response between anifrolumab and placebo at Week 52 in the full analysis set, where the response is captured with a composite binary endpoint and is defined by improvement from baseline in disease activity as measured by BILAG-2004, no worsening in SLEDAI-2K and PGA and ability to adhere to the planned course of the treatment. The intercurrent events: discontinuation of IP and receipt of restricted medications are unfavourable outcomes. Therefore, subjects treated with restricted medications beyond protocol-allowed threshold, and those who discontinued IP for any reasons, will be non-responders. This estimand answers a clinically relevant question comparing the number of subjects able to both complete the study treatment and to achieve adequate response without further medication being required. The response is measured by the primary efficacy endpoint, defined as the difference in the proportion of subjects achieving BICLA response at Week 52, comparing the anifrolumab to the placebo groups.

The null hypothesis is that the proportion of subjects achieving BICLA response on anifrolumab is equal to that on placebo. The alternative hypothesis is that the proportion of subjects achieving BICLA response on anifrolumab is not equal to that on placebo, ie,

H_0: difference in proportion achieving BICLA response (anifrolumab vs Placebo) = 0
H_a: difference in proportion achieving BICLA response (anifrolumab vs Placebo) ≠ 0.

The proportion of subjects achieving BICLA response in the anifrolumab treatment group will be compared to that in the placebo group using a Cochran-Mantel-Haenszel (CMH) approach (Stokes, 2012) stratified by:

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
  If different measurements are available for re-screened subjects, the value at re-screening will be used.
- Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent)
  For the classification, the derived OCS dose rounded to 1 decimal place will be used.
- Results of a type 1 IFN test (high versus low)

SLEDAI-2K score at Screening and Week 0 (Day 1) OCS strata will be derived programmatically from the data recorded in the database. Type 1 IFN test stratum will be taken as recorded at randomisation by the Interactive voice/web response system (IXRS). Strata with low counts will be pooled with adjacent strata prior to the analysis. If a sub-stratum within the IFN-low stratum has less than 20 subjects (in the pooled treatment group), then all IFN-low strata will be pooled together. If a sub-stratum within the IFN-high stratum has less than 20 subjects (in the pooled treatment group), then within the IFN-high stratum the SLEDAI-2K score <10 points sub-strata will be pooled together and the SLEDAI-2K score ≥10 points sub-strata will be pooled together. If any of these two sub-strata within the IFN-high stratum still has less than 20 subjects (in the pooled treatment group), then all IFN-high sub-strata will be pooled together. If all IFN-low sub-strata are pooled together and all IFN-high sub-strata are pooled together and any of these strata has less than 20 subjects (in the pooled treatment group) then all strata are pooled together.

The analysis can be described as follows:

A. There are *nij* subjects in each stratum, where *i* is the stratum, and *j* is the treatment group. The number of subjects achieving BICLA response is *xij*. The proportion of subjects achieving BICLA response is denoted as *pij* = *xij* / *nij*..

B. For each stratum, the difference in proportion of subjects achieving BICLA response is calculated as *di* = *piA* – *piP*, where *A* and *P* denote the different treatment groups (anifrolumab and placebo, respectively).

C. Weights for each stratum, *wi*, are calculated as *niP* * *niA* / (*niA* + *niP*). The weighted difference is calculated as

$$WD = \frac{\sum w_i d_i}{\sum w_i}$$

D. The standard error (SE) of the weighted difference under the null hypothesis is given by

$$SE = \sqrt{\frac{\Sigma[w_i^2 Var(d_i)]}{(\Sigma w_i)^2}}$$ where

$$Var(d_i) = \frac{p_{i.}(1-p_{i.})n_i}{w_i(n_i-1)}$$ and

$$p_{i.} = \frac{x_{i.}}{n_{i.}} = \frac{x_{iA}+x_{iP}}{n_{iA}+n_{iP}}$$

E. For deriving the CI for the weighted difference in proportions, a correction will be applied to the variance, providing a CI with more accurate coverage. This will be applied to all strata, and is derived as follows.

$$Var(d_i) = \frac{p^*_{iA}(1-p^*_{iA})}{n_{iA}} + \frac{p^*_{iP}(1-p^*_{iP})}{n_{iP}}$$ with

$$p^*_{ij} = \frac{x_{ij}+2}{n_{ij}+4}$$

The 95% CI can be generated using the weighted difference ± $z_{0.975}$ * SE.
The value of the test statistic is calculated as $\frac{WD}{SE}$. The p-value from the two-sided test of no difference in treatment groups is calculated as $2\left(1-Prob\left(\left|\frac{WD}{SE}\right|\right)\right)$, where Prob() is the distribution function of the standard normal distribution.

F. The 95% CI for the weighted proportion ($\Sigma_i w_i p_{ij}/w$) in a treatment group j can be generated using a normal approximation and assuming independence between strata, where pij* are used as above.

$$s_{ij}^2 = Var(p_{ij}) = p^*_{ij}(1-p^*_{ij})/n_{ij}$$
$$s_j^2 = \Sigma_i w_i^2 s_{ij}^2/w^2,\ w = \Sigma_i w_i$$

If the resulting lower or upper limit is <0% or >100%, it will be set to 0% or 100%, respectively.

The estimated treatment effect (ie, the difference in response rate for anifrolumab versus placebo), corresponding 95% CI, and 2-sided p-value for the difference at Week 52 will be presented. In addition, the estimated response rate (weighted proportion) and the corresponding 95% CI within each treatment group will be presented.

The supportive outcome of time to BICLA response sustained up to Week 52 will be analyzed using a Cox proportional hazard models (using a profile likelihood approach with ties=Efron) including the covariates of treatment and the stratification factors. The estimated hazard ratios and corresponding CIs will be presented for the effect of the treatment group. Furthermore, the time to BICLA response sustained up to, and including, Week 52 will be presented as Kaplan-Meier plot including the number of subjects at risk at each visit.

Longitudinal presentations of results over time (ie, for each post-baseline visit up to Week 52) based on the same analysis, with the corresponding 95% CI, will be created.

A bar plot showing the estimated response rates for subjects achieving BICLA response at Week 52 by treatment group (including CIs, number of subjects included in the analysis, and the p-value for the test of differences) will be provided.

In addition, the individual conditions of BICLA response (reduction of all BILAG-2004 A and B, no worsening from baseline in SLEDAI-2K, no worsening in subjects' lupus disease activity, no permanent discontinuation of investigational product, and no use of restricted medication) at Week 24 and Week 52 will be summarised with counts and percentages by treatment group.

All analyses on the primary variable will be conducted with the full analysis set.

Sensitivity analysis - impact of premature discontinuation of IP

Permanent premature discontinuation of IP is part of the BICLA response definition. In order to examine the impact of different discontinuation rates between treatment groups, a tipping point analysis will be performed if a statistically significant result is achieved for the primary analysis. This analysis will vary the assumptions about outcomes among the subsets of subjects on the treatment arms who prematurely discontinue IP and can be described as:

- The proportions of subjects achieving BICLA response will be analysed using a Pearson's chi-squared test, thus the stratification factors that are used in the main analysis (CMH) will be disregarded. Since the strata will be balanced in respect of treatment assignment by virtue of the stratified randomisation scheme used, the only impact of this simplification should be that the inferences from the unstratified analysis will be somewhat conservative.
- For the primary analysis, subjects who prematurely discontinue IP having not received restricted medications prior to discontinuation of IP are by definition imputed as non-responders. For this sensitivity analysis, these subjects will be altered from non-responder to responder in an iterative manner.
- At each step of the analysis one of these subjects switches from not achieving BICLA response to achieving BICLA response, and the Pearson's chi-squared test is re-run. The results (statistical significance) are presented in a grid where the x-axis and the y-axis represent the number of subjects assumed to be achieving BICLA response for placebo and anifrolumab 300 mg, respectively. The region where the conclusion changes, will be considered as the tipping point.
- The grid will be divided in 3 regions, limited in the top by the expected number of subjects with missing values in the anifrolumab 300 mg arm which would have achieved BICLA response if not prematurely discontinuing IP (based on the proportion of subjects achieving BICLA response in subjects who completed IP in the anifrolumab 300 mg arm):
    - Likely – Its right limit is the expected number of subjects with missing values in the placebo arm which would have achieved BICLA response if not prematurely discontinuing IP (based on the proportion of subjects achieving BICLA response in subjects who completed IP in the placebo arm);

- Uncertain – its right limit is the expected number of subjects with missing values in the placebo arm which would have been responders if not prematurely discontinuing IP (based on the proportion of subjects achieving BICLA response in subjects who completed IP in the anifrolumab 300 mg arm);
- Unlikely – It is the region to the right of the uncertain region.

Sensitivity analysis – impact of intermediate missing data

To examine the impact of intermediate missing data, the following sensitivity analysis with multiple imputations will be performed. Intermediate missing values for SLEDAI-2K, BILAG-2004, and PGA (ie, missing for other reason than early discontinuation of IP) will be imputed separately for each BICLA component.

Intermediate missing values of BICLA will be imputed based on the imputed values of the BILAG-2004, PGA and SLEDAI-2K components. For each outcome and visit, 100 imputations will be generated by randomised treatment group. The procedure will be initiated with a random seed of 12345. For analysis, each imputed dataset will be analysed separately, and the single estimates will be combined using PROC MIANALYZE. Each component will be imputed as follows:

- BILAG-2004 will be imputed as a binary variable reflecting the BICLA criterion, ie, "Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B". This binary BILAG variable for subject i at visit t will be modelled as $BILAG_{i(t)} \sim Binomial(1, \pi_{i(t)})$ where $\pi_{i(t)} = \theta_1 BILAG_{i(t-1)} + \theta_0(1 - BILAG_{i(t-1)})$ for t>1 and $\pi_{i(t)} = \theta_2$ for t = 1 (Week 4). Independent $Beta(1,1)$ priors will be specified for θ_0, θ_1 and θ_2. 10,000 burn-in iterations will be used, followed by 10,000 main iterations. Imputations will then be taken from every 100th iteration of the main chain (ie, after burn-in). From the resulting dataset, the imputations of intermediate missing values only will be extracted (ie, imputations of missing values due to early discontinuation of IP will not be considered).
- SLEDAI-2K total score will be imputed with PROC MI using the MCMC IMPUTE=FULL specification, and a VAR statement specifying the variables in order of visit. Specify MINIMUM=0 to ensure imputed values are non-negative. Specify MAXIMUM=105 to avoid imputation of values above the maximum possible score. 10,000 burning iterations to be used, with 100 iterations between each imputation. From the resulting dataset, the imputations of intermediate missing values only will be extracted (ie, imputations of missing values due to early discontinuation of IP will not be considered).
- PGA will be imputed in the same way as SLEDAI-2K total score , but using MAXIMUM=3 (instead of MAXIMUM=105).

Sensitivity analysis – modified BILAG

A sensitivity analysis for BICLA response, as described for the primary endpoint, will be repeated using the modified BILAG. The modified BILAG is described in Section 3.3.2.

Sensitivity analysis – excluding subjects with no baseline BILAG A or B or baseline PGA VAS > 2.7

A sensitivity analysis will be performed where subjects with no BILAG A or B at baseline, as well as subjects with a baseline PGA VAS score > 2.7 will be excluded from the analysis.

Sensitivity analysis – removing the criterion of no restricted medications

A sensitivity analysis for BICLA response, as described for the primary endpoint, will be repeated removing the criterion of no restricted medications beyond the protocol-allowed threshold. Therefore, this analysis will not count subjects as non-responders if they have used restricted medications beyond the protocol-allowed threshold.

4.2.2 Key secondary outcome variables

All analyses of the key secondary outcome variables will be conducted with the full analysis set. The intercurrent events of discontinuation of the investigational product and recipient of restricted medications are unfavourable outcomes. Therefore, subjects treated with restricted medications beyond protocol allowed threshold before the assessment, and those who discontinued IP for any reasons, before the assessment, will be non-responders for all key secondary endpoints.

4.2.2.1 BICLA at Week 52 in IFN test-high subjects

The key secondary endpoint used to evaluate the effect of anifrolumab compared to placebo on disease activity in the IFN test-high subgroup is the difference in proportion of subjects achieving BICLA response at Week 52 in subjects classified as IFN test-high.

All analyses as described in Section 4.2.1 for the primary endpoint, except select sensitivity analyses (multiple imputation, subjects with no BILAG A or B at baseline or with baseline PGA > 2.7, and modified BILAG), will be performed for the IFN test-high subgroup. For the stratified CMH analyses, the stratification factors will be reduced to SLEDAI-2K score at screening (<10 points versus ≥10 points) and Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent).

The tipping point analysis to assess the impact of premature discontinuation of IP as described in Section 4.2.1 will also be performed for the IFN test-high subgroup if the nominal unadjusted p-value is < 0.05 for the primary IFN test-high analysis.

A supplemental analysis of BICLA in subjects classified as IFN test-low will be conducted. The same CMH approach as described in Section 4.2.1 for the primary endpoint will be used to estimate the treatment difference between anifrolumab and placebo. The stratification factors will be reduced to SLEDAI-2K score at screening (<10 points versus ≥10 points) and Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent).

4.2.2.2 Oral corticosteroid management

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on the ability to reduce the OCS dose in subjects with baseline OCS ≥10 mg/day prednisone or equivalent is the difference in proportion of subjects with maintained OCS reduction.

The same CMH approach as described in Section 4.2.1 for the primary endpoint will be used to estimate the treatment difference between anifrolumab and placebo in subjects with baseline OCS ≥10 mg/day prednisone or equivalent. For the stratified CMH analyses, the stratification factors will be reduced to SLEDAI-2K score at screening (<10 points versus ≥10 points) and results of a type 1 IFN test (high versus low).

A bar plot showing the estimated response rates for subjects with maintained OCS reduction by treatment group (including CIs, number of subjects included in the analysis, and the p-value for the test of differences) will be provided.

The tipping point analysis to assess the impact of premature discontinuation of IP as described in Section 4.2.1 will also be performed for maintained OCS reduction if the nominal unadjusted p-value is < 0.05 for the primary OCS reduction analysis.

4.2.2.3 Skin lesions

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on inflammatory cutaneous lupus lesions in subjects with baseline CLASI activity score ≥10 is the difference in proportion of subjects with an at least 50% reduction in CLASI activity score at Week 12.

The same CMH approach as described in Section 4.2.1 for the primary endpoint will be used to estimate the treatment difference between anifrolumab and placebo in subjects with baseline CLASI activity score ≥10. Longitudinal presentations of the results over time (ie, for each post-baseline visit up to Week 52) based on this analysis will be created.

A bar plot showing the estimated response rates for subjects with a ≥50% reduction in CLASI activity score at Week 12 by treatment group (including CIs, number of subjects included in the analysis, and the p-value for the test of differences) will be provided.

The tipping point analysis to assess the impact of premature discontinuation of IP described in Section 4.2.1, will also be performed for an at least 50% reduction in CLASI activity score if the nominal unadjusted p-value is < 0.05 for the primary CLASI analysis.

A further sensitivity analysis will be provided if at least 10 subjects in a treatment arm have a burst and taper of OCS or IM steroids during the first 12 weeks of treatment. The CMH analysis will be repeated for the at least 50% reduction in CLASI activity score (including all criteria) at Week 12 excluding subjects administered a burst and taper of OCS or IM steroids during the first 12 weeks of treatment. A burst and taper of OCS or IM steroids is defined as an OCS increase above the daily dose at Day 1 or any IM steroid dose.

4.2.2.4 Joints

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on joints is the difference in proportion of subjects with at least 6 swollen and at least 6 tender joints at baseline who achieve an at least 50% reduction in swollen and tender joints, respectively, at Week 52 (as defined in Section 3.2.4).

For subjects with at least 6 swollen and at least 6 tender joints at baseline, the same CMH approach as described in Section 4.2.1 for the primary endpoint will be used to estimate the treatment difference between anifrolumab and placebo in the proportions of subjects achieving an at least 50% reduction in swollen and tender joints, respectively. Longitudinal presentations of the results over time (ie, for each post-baseline visit up to Week 52) based on this analysis will be created. This analysis will be repeated for subjects achieving an at least 20% reduction in swollen and tender joints.

A bar plot showing the estimated response rates for subjects with a ≥50% reduction in swollen and tender joints by treatment group (including CIs, number of subjects included in the analysis, and the p-value for the test of differences) will be provided for subjects with at least 6 swollen and at least 6 tender joints at baseline.

The tipping point analysis to assess the impact of premature discontinuation of IP described in Section 4.2.1, will also be performed for an at least 50% reduction in swollen and tender joints in subjects with at least 6 swollen and at least 6 tender joints at baseline, if the nominal unadjusted p-value is < 0.05 for the primary joints analysis.

4.2.2.5 Flares

The key secondary endpoint used to evaluate the effect of anifrolumab versus placebo on flares is the difference in annualized flare rates through Week 52 (as defined in Section 5).

The flare rate in the anifrolumab treatment group will be compared to the flare rate in the placebo group using a negative binomial regression model. The response variable in the model will be the number of flares over the 52-week treatment period (ie, up to Visit 14/EDV). The model will include covariates of treatment group, and the stratification factors. The logarithm (to base e) of the follow-up time (flare exposure time as defined in Section 5) will be used as an offset variable in the model to adjust for subjects having different exposure times. The estimated treatment effect and the corresponding 95% CI, as well as the 2-sided p-value will be presented.

A summary of the annualized flare rate by descriptive statistics as well as a summary of the number and percentage of subjects with no flares, at least one flare, 1 flare, 2 flares, and 3 or more flares, respectively, will be presented by treatment group.

Sensitivity analysis – multiple imputation

To examine the sensitivity of the results of the main analysis to deviations from the underlying assumptions, an additional analysis will be performed using the controlled multiple imputation method (Keene, 2014). As with the main analysis, the sensitivity analysis includes all data

until subjects complete the study/ withdraw from the study regardless of if they discontinue from randomised treatment.

For this method, the number of flares after withdrawal from study will be imputed conditional upon the observed number of flares prior to the withdrawal, a post-withdrawal model assumption, the baseline covariates included in the main analysis model and the time the subject would have remained in the study if not withdrawn (ie, date of first administration of IP + 364 days – date of last available BILAG-2004 assessment).

The method involves first fitting the main analysis (ie, negative binomial regression model as described above) to the observed data. For each imputed dataset, first an independent sample is drawn from the approximate posterior distribution of the model parameters. This consists of sampling new regression coefficients from a multivariate normal distribution, with mean equal to the observed data maximum likelihood estimate, and covariance matrix corresponding to the maximum likelihood covariance estimate. A new (log) shape parameter is drawn from a normal distribution in the same way, which is exponentiated to give a draw of the shape parameter k.

For each generated set of model parameters, the number of flares after withdrawal from study are imputed for each subject by drawing randomly from its conditional distribution given the subject's number of flares before withdrawal. For a given subject let T_1 and T_2 denote the time before and after withdrawal. Let $Y_1$and Y_2 denote the observed number of flares before withdrawal and unobserved number after withdrawal, respectively, which is to be imputed. Let λ_1 and $\lambda_2$denote the assumed rates before and after withdrawal. Let $\psi_1 = T_1\lambda_1$ and $\psi_2 = T_2\lambda_2$. Then, using SAS's RAND negative binomial parametrisation, the conditional distribution of Y_2 given Y_1 is negative binomial with 'number of successes' parameter $k + Y_1$ and 'probability of success' parameter equal to

$$\frac{k + \psi_1}{k + \psi_1 + \psi_2}.$$

The imputed number of flares is then combined with the observed flares and data is analysed using the main analysis methodology. This analysis is repeated multiple times and the results combined using Rubin's formulae (Fleming, 2011, Ratitch, 2013).

Sensitivity analysis – tipping point analysis

First a MAR analysis will be performed where for each subject the rate after withdrawal λ_1 is assumed to be the same as their rate before withdrawal λ_2, which itself is calculated based on their randomised treatment group and baseline covariates.

A tipping point analysis will then be performed if a nominally statistically significant (using the unadjusted p-value) result is achieved for the primary analysis, where the rate after withdrawal will be modified to $\delta\lambda_2$. A series of analyses will be performed with a range of increasing deltas for the two arms (δ_P and δ_A for placebo and anifrolumab 300 mg groups,

respectively) so that one could assess at which point the study conclusions would change from favourable to unfavourable; ie, to identify a tipping point.

In this assessment, the placebo group is assumed to improve after withdrawal and the anifrolumab group is assumed to worsen after withdrawal. Therefore, $\log(\delta_P)$ will be varied from -1.5 to 0 in increments of 0.5 and $\log(\delta_A)$ will be varied from 0 to 1.5 in increments of 0.5. This corresponds to deltas between 0.22 and 1 for the placebo group and deltas between 1 and 4.5 for the anifrolumab 300 mg group. If statistical significance is maintained among the matrix of possible δ combinations, the comparison is deemed robust to missing data. For a given comparison, if a tipping point is observed with analysis at 0.5 increments, the δ values will be further refined down to 0.25 increments for the relevant interval. For example, if a tipping point is identified when increasing $\log(\delta_A)$ from 1 to 1.5, the matrix will be expanded to include also the value $\log(\delta_A) = 1.25$. The values for δ (and the corresponding increments) will be checked during the BDRM and adapted as necessary.

Sensitivity analysis – flares while on treatment

The flare rate in the anifrolumab treatment group will be compared to the flare rate in the placebo group using a negative binomial regression model. The response variable in the model will be the number of flares while on treatment (ie, up to last administration of investigational product + 28 days). The model will include covariates of treatment group, and the stratification factors. The logarithm (to base e) of the follow-up time (flare exposure time as defined in Section 3.2.4) will be used as an offset variable in the model to adjust for subjects having different exposure times. The estimated treatment effect and the corresponding 95% CI will be presented.

Sensitivity analysis – flares based on modified BILAG

A sensitivity analysis of annualized flare rate, as described for the key secondary flare endpoint, will be repeated using the modified BILAG. The modified BILAG is described in Section 3.3.2.

4.2.3 Analysis methods for other secondary efficacy variables

All analyses of other secondary outcome variables will be conducted with the full analysis set.

4.2.3.1 Assessment of disease activity

[redacted]

Supportive outcome variables of the individual components of BICLA [redacted]

Change from baseline in SLEDAI-2K and PGA will be analysed using repeated measures models with fixed effects for baseline value, treatment group, visit, treatment*visit interaction and stratification factors. Covariance parameters will be estimated using restricted Maximum Likelihood method and Kenward Rogers denominator degrees of freedom will be used for the tests of fixed effects. An unstructured covariance matrix will be used. In case of convergence issues, the following alternative structures will be used for fitting (in that order): Heterogeneous Toeplitz, heterogeneous AR(1), Heterogeneous CS, Homogeneous CS. Results will be presented for each visit in terms of the adjusted means for each treatment group, estimates of treatment differences, and associated 2-sided CIs.

For each SLEDAI organ system (central nervous system, vascular, musculoskeletal, renal, mucocutaneous, cardiovascular system and respiratory, immunology, and haematological and fever) the number and percentage of subjects with an improvement at Week 24 and Week 52, respectively, will be given for subjects with corresponding organ system involvement at baseline.

For BILAG-2004, the number and percentage of subjects with a score of A, B, and C, D, or E, respectively, will be given by visit for the following organ systems:

- Constitutional
- Mucocutaneous
- Neuropsychiatric
- Musculoskeletal
- Cardiorespiratory
- Gastrointestinal
- Ophthalmic
- Renal
- Haematology

For each of the organ systems, a bar plot will be provided showing the distribution of the scores at baseline, Week 24, and Week 52 by treatment group. The figures will include the percentages and number of subjects.

Observed values and changes from baseline in BILAG-2004 global score will be presented by visit with descriptive statistics. Additionally, a shift table presenting BILAG-2004 improvement over time will be presented according to the categories given in Section 3.3.2.

[redacted]

[redacted]

Supportive outcome variables for the assessment of OCS use

Additionally, the daily OCS dose will be displayed graphically by a longitudinal plot presenting the means and corresponding SDs by visit. The number of subjects will also be included in the graph. Subjects without an OCS dose will be included with a value of 0. The graphical display will be repeated for subjects with baseline OCS ≥10 mg/day only.

A shift table will be provided for all subjects showing the daily OCS dose at baseline versus the daily OCS dose at Week 52. For this presentation, the daily OCS dose will be categorised as 0, >0 to ≤5mg, >5 to ≤7.5mg, >7.5 to ≤10mg, >10 to ≤15mg, >15 to ≤20mg, >20 to ≤30mg, >30 to ≤40mg, >40 mg, and missing.

Furthermore, the standardised AUC up to Week 52 will be summarized by treatment group for all subjects as well as for subjects with baseline OCS ≥10 mg/day.

For subjects with baseline OCS ≥10 mg/day prednisone or equivalent, a shift table of reaching a maintained OCS reduction at Week 52 (as defined in Section 3.2.2) versus achieving BICLA response at Week 52 (as defined in Section 3.1) will be provided.

Supportive outcome variables for the assessment of skin lesions

For subjects with baseline CLASI activity score ≥10, a shift table for an at least 50% reduction in CLASI activity score at Week 12 versus an at least 50% reduction at Week 52 will be presented to investigate the maintenance of effect in CLASI activity score.

Change from baseline in CLASI activity score and CLASI damage score, respectively, will be analysed using the same repeated measures models as described for the analysis of SLEDAI-2K and PGA in section 4.2.3.1. Thereby, an unstructured covariance matrix will be used. In case of convergence issues, the following alternative structures will be used for fitting (in that order): Heterogeneous Toeplitz, heterogeneous AR(1), Heterogeneous CS, Homogeneous CS.

Supportive outcome variables for the assessment of joints

For subjects with at least 8 swollen and at least 8 tender joints at baseline, the same CMH approach as described in Section 4.2.1 for the primary endpoint will be used to estimate the treatment difference between anifrolumab and placebo in the proportions of subjects achieving an at least 20% reduction and at least 50% reduction in both swollen and tender joints, respectively.

The change from baseline in the number of active, swollen and tender joints, respectively, will be analysed using the same repeated measures models as described for the analysis of SLEDAI-2K and PGA above. Thereby, an unstructured covariance matrix will be used. In case of convergence issues, the following alternative structures will be used for fitting (in that order): Heterogeneous Toeplitz, heterogeneous AR(1), Heterogeneous CS, Homogeneous CS.

Supportive outcome variables for the assessment of flares

The analysis of flares using a negative binomial regression model as described in Section 4.2.2.4 will be repeated for flares versus baseline.

A summary of the annualized flare rate by descriptive statistics for flares versus baseline as well as a summary of the number and percentage of subjects with no flares, at least one flare, 1 flare, 2 flares, and 3 or more flares, respectively, will be presented by treatment group.

The time to first flare will be analysed as a supportive analysis to the assessment of reduction of flares to explore the extent to which treatment with anifrolumab delays the time to first flare compared to placebo. The analyses of time to first flare will be provided for the key secondary outcome variable and flares versus baseline.

Cox proportional hazard models (using a profile likelihood approach with ties=Efron) including the covariates of treatment and the stratification factors will be used to estimate the treatment effect. The estimated hazard ratios and corresponding CIs will be presented for the effect of the treatment group.

Furthermore, the time to first flare (key secondary outcome variable only) will be presented as Kaplan-Meier plot including the number of subjects at risk at each visit.

[redacted]

4.2.4 Presentation of study population

4.2.4.1 Subject disposition

The number and percentage of subjects completing the study and completing the study up to and including Week 52 (Visit 14/EDV) and the number and percentage of subjects withdrawing from the study including reason for withdrawal, will be summarized by treatment group for the full analysis set. Additionally, the number and percentage of subjects enrolled to the LTE study will be presented.

The number of subjects completing treatment with investigational product up to and including Week 48 (ie, with last administration of investigational product at Visit 13) and the number of subjects permanently discontinuing the treatment with investigational product including reason for withdrawal, will be summarized by treatment group for the full analysis set.

Furthermore, the number and percentage of subjects remaining on investigational product, discontinued investigational product but remain on study and withdrawn from study will be summarized by visit up to Week 48 for the full analysis set. The number and percentage of subjects withdrawn from study at Week 52 and the number of subjects still in study at weeks 56 and 60 will also be presented.

A summary of number and percentage of subjects in each region, each country and each site by treatment group and overall will be provided for the full analysis set.

A summary of number of subjects in each population will be provided for each analysis set.

Important protocol deviations will be summarised for the full analysis set.

4.2.4.2 Demographic and baseline characteristic

Demography and baseline characteristics will be presented by descriptive statistics by treatment group as well as overall for the full analysis set. Additionally, the stratification factors (as calculated from the data for SLEDAI-2K score at screening and Week 0 [Day 1] OCS dose and as recorded at randomisation by IXRS for the type 1 IFN test) and the cardiovascular risk will be presented by descriptive statistics for the full analysis set.

An additional table will be prepared summarising miss-stratifications as per the IXRS at randomisation for the SLEDAI-2K score at screening and Week 0 (Day 1) OCS dose.

Past and current medical history will be summarized separately by MedDRA primary 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 summarized separately by WHO-DD Anatomical Main Group (ATC level 1), and preferred term. Disease related treatments at baseline will be summarized by the categories given in Section 3.4.3.

4.2.4.3 Restricted medications

Concomitant medications beyond the protocol allowed threshold (restricted medications) that are considered in the evaluation of the efficacy endpoints will be summarized by preferred term and on-IP/off-IP and listed. On-IP/off-IP will be determined based on the medication start date. Subjects treated with restricted medications before the assessment of interest will be treated as non-responders for the primary and secondary efficacy endpoints; including BICLA, OCS reduction, CLASI, joints [redacted] in accordance with the rules defined in Section 1.2.1 and [redacted]

4.2.4.4 Exposure

Exposure will be summarized by treatment group for the full analysis set.

Summary statistics will be provided for the duration of exposure. The number and percentage of subjects treated ≥4 weeks, ≥8 weeks, and up to ≥52 weeks in 4-weekly intervals will be provided. Furthermore, the total subject years of exposure will be presented.

The number and percentage of subjects with infusions will be presented by total number of infusion (ie, 1, 2, …, 13) and by visit (ie, Day 1, Week 4, Week 8, Week 12, …, Week 48).

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).

4.2.5 Analysis methods for safety variables

Safety variables will be summarised by treatment group for the full analysis set.

4.2.5.1 Adverse events

If not stated otherwise, all summaries described below will be presented separately for

- AEs during treatment
- AEs during follow-up
- AEs during treatment and follow-up.

For summaries during follow-up, only subjects with any study documentation after the date of last dose of investigational product + 28 days will be considered.

An overall summary of subjects with at least one AE in the following categories will be presented:

- 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
  - Any AESI of major adverse cardiovascular events
- Any other significant AE

The number and percentage of subjects with at least one AE (ie, multiple occurrences of an AE in 1 subject will only be counted once) will be summarised by MedDRA primary system organ class and preferred term for the following AE categories. These summaries will also include the event rate per 100 subject years, unless otherwise specified. Event rates will generally not be included in summaries presented for AEs during treatment and follow-up.

- Any AE
- Any AE above reporting threshold of 2%
  This summary will be presented by preferred term only for AEs during treatment only.

- Any AE with outcome = death
  This summary will be presented for AEs during treatment and follow-up only.
- Any SAE (including events with outcome = death)
  This summary will not be presented for AEs during follow-up. This summary will also be presented by preferred term for SAEs during treatment only.
- Any AE leading to discontinuation of investigational product
  This summary will be presented for all AEs irrespective of the study period. The end of exposure for the calculation of event rates is defined as the maximum of date of last dose of investigational product + 28 days and the date of the AE leading to discontinuation. AEs with (partially) missing start date information will be considered on-treatment unless the available information indicates otherwise and will be imputed with the earliest on-treatment date possible given the available start and stop date information for this analysis. This summary will also be presented by preferred term.
- Any AE by relationship to investigational product (yes, no)
  (multiple occurrences of an AE in 1 subject will only be counted once as related if at least one AE is related and as not related if all occurrences are not related)
  This summary will not be presented for AEs during treatment and follow-up.
  This summary will not include the event rate per 100 subject years.
- Any AE by maximum intensity (mild, moderate, severe)
  (multiple occurrences of an AE in 1 subject will only be counted once with the maximum intensity in this AE)
  This summary will not be presented for AEs during treatment and follow-up.
  This summary will not include the event rate per 100 subject years.
- Any AESI
  This summary will not be presented by system organ class but by AESI category (non-opportunistic serious infections, opportunistic infections, anaphylaxis, malignancy, herpes zoster, tuberculosis, influenza, vasculitis, and MACEs).
  This summary will not be presented for AEs during follow-up.
- Any other significant AE
  This summary will be presented for AEs during treatment and follow-up only.
- Any AE by time interval for the first onset of event
  This summary will be presented for AEs during treatment only.

Cardiovascular outcome events (during treatment and during treatment and follow-up) as determined by the Cardiovascular Event Adjudication Committee 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 a non-opportunistic serious infection during treatment and time to first onset of herpes zoster during treatment will be presented as Kaplan-Meier plots including the number of subjects at risk at each visit.

Furthermore, the alternative event rates per 100 subject years for herpes zoster (and possible other AESIs) will be summarized for events during treatment and follow-up, during treatment (overall and by time intervals), and during follow-up. The following subcategories will also be considered in this summary: SAE (including events with outcome of death), AE leading to discontinuation of investigational product, and AE by maximum intensity (mild, moderate, and severe).

The number and percentage of subjects with at least one anaphylaxis, hypersensitivity, and infusion-related reaction (as reported by the 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 of investigational product, 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 3.5.1.

Infections, opportunistic infections and non-opportunistic infections, will be summarised with the same subcategories as given above.

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, and subjects with a cardiovascular event, respectively, will be provided (all for AEs occurring during treatment and follow-up only).

4.2.5.2 Laboratory variables

Observed values and changes from baseline of laboratory data for haematology, clinical chemistry, continuous urinalysis, 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 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 summarized by visit. Additionally the number and percentage of subjects with at least one 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 (see [redacted] will be presented as shift tables from baseline to maximum and minimum on-treatment value, respectively.

Urinalysis will be summarized as shift tables from baseline to the last post-baseline value for each parameter. Furthermore, the number and percentage of subjects with treatment-emergent changes will be summarized 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 (at the respective visit).

In order to identify potential Hy's Law cases, maximum post baseline total bilirubin will be plotted against maximum post baseline ALT, expressed as multiples of ULN. This plot will be repeated to show maximum post baseline total bilirubin against maximum post baseline AST, expressed as multiples of ULN. These plots will be produced on a log scale and reference lines will be included at 2xULN for total bilirubin and at 3xULN for ALT/AST.

4.2.5.3 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 Week 52.

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 Clinical Significant post-baseline values and Potentially Clinical Significant changes from baseline, respectively, will be presented by parameter and criterion.

4.2.5.4 Modified SELENA Flare Index based flares

The number and percentage of subjects with at least one flare after Day 1 will be presented for mild/moderate flares, severe flares, and any flares.

4.2.5.5 Physical examination

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

4.2.5.6 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 summarized by visit. Additionally, the number and percentage of subjects with at least one 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).

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 each post-baseline visit.

4.2.5.7 Cushingoid features

The number and percentage of subjects will be explored for each feature by visit. For subjects with baseline OCS ≥10 mg/day prednisone or equivalent, the summary will be repeated by maintained OCS reduction at Week 52 (yes versus no) as defined in Section 3.2.2).

4.2.5.8 C-SSRS

The number and percentage of subjects with suicidal ideation (overall and by maximum category), suicidal behaviour (overall and by maximum category), and no suicidal ideation or behaviour will be given for assessments during screening, during treatment, and during follow-up, respectively.

Furthermore, descriptive statistics on the total number of attempts, total number of interrupted attempts, and total number of aborted attempts will be summarized for attempts during screening, during treatment and during follow-up, respectively.

Subjects with a suicidal ideation or behaviour at any time will be presented in a listing.

4.2.5.9 Personal Health Questionnaire Depression Scale-8

Observed values and changes from baseline in PHQ-8 total score will be presented longitudinally with descriptive statistics.

[redacted]

[redacted]

4.3 Subgroup analysis

To explore the uniformity of the detected overall treatment effect, subgroup analyses on the primary, key secondary endpoints, [redacted] will be performed for the following factors:

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
- OCS dose at baseline (<10 mg/day versus ≥10 mg/day prednisone or equivalent)
- IFN test (IFN test [high versus low])
- Sex (male versus female)
- Age (≥18 to 65 versus ≥65 years)
- Onset of disease (adult versus paediatric onset)
- BMI (≤30 versus >30 kg/m^2)
- Race (white; black or African American; Asian, native Hawaiian or other Pacific Islander; American Indian or Alaska native; other)
- Ethnicity (Hispanic/Latino versus no Hispanic/Latino)
- [redacted]
- [redacted]

Table 5 gives an overview of subgroup analyses to be performed. Where necessary (eg, for subgroup analysis based on stratification factors), the model factors will be reduced. If not stated otherwise, the subgroup analysis will be supressed if any of the sub-populations in any treatment group will consist of less than 25 subjects.

For the primary endpoint BICLA at Week 52, a forest plot will be used to summarise the estimates of the treatment effect for the applicable subgroups.

A listing of adverse events in [redacted] (at any time) subjects will also be presented.

Table 5 Overview of subgroup analyses

Analysis	SLEDAI-2K	OCS at baseline	IFN test	Sex	Age	Disease Onset	BMI	Race	Ethnicity	[redacted]
BICLA – CMH [a]	X	X	X	X	X	X	X	X	X	
BICLA in IFN test-high – CMH	X	X								
Maintained OCS reduction – CMH	X		X							
CLASI activity reduction – CMH	X	X	X							
Flare rate – binominal regression	X	X	X							
Joints reduction - CMH	X	X	X							
[redacted]										
[redacted]										
AE overview										
SAE summary by SOC and PT										

[a] Subgroup analysis will also be conducted if resulting in a sub-population of <25 subjects.

5. INTERIM ANALYSES

No interim analysis is planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

No changes of analysis from the protocol are planned for this study.

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8. APPENDIX

Appendix A: Supplemental Process Description: Restricted medications

Appendix B: Supplemental Process Description: Oral Corticosteroids

Appendix C: Derivation rules for imputation of partial or missing dates

Appendix D: Reference ranges and TELVC for laboratory values

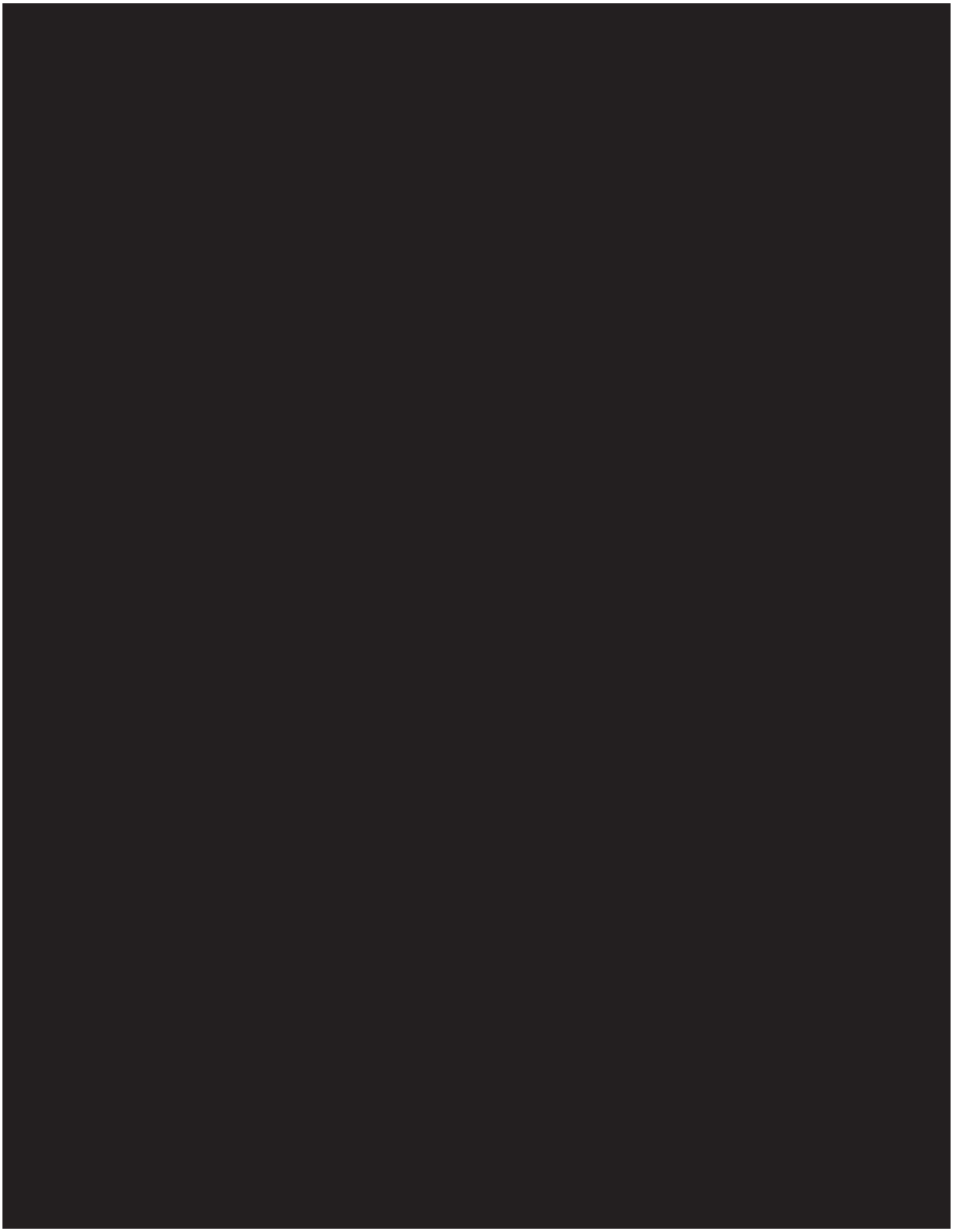
Appendix E: ECG: Potentially Clinically Significant post baseline values

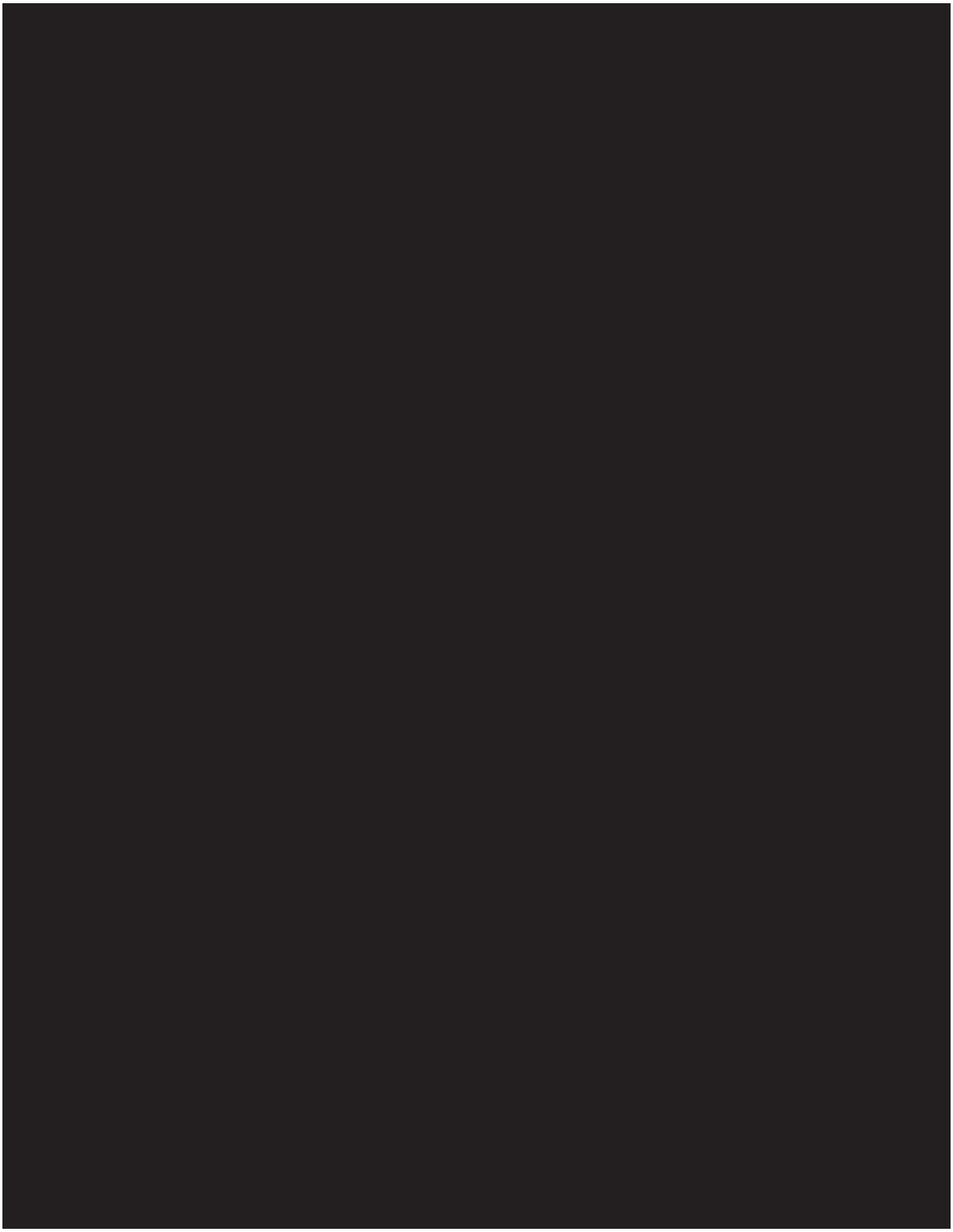
Appendix F: Reference ranges and TELVC for vital signs

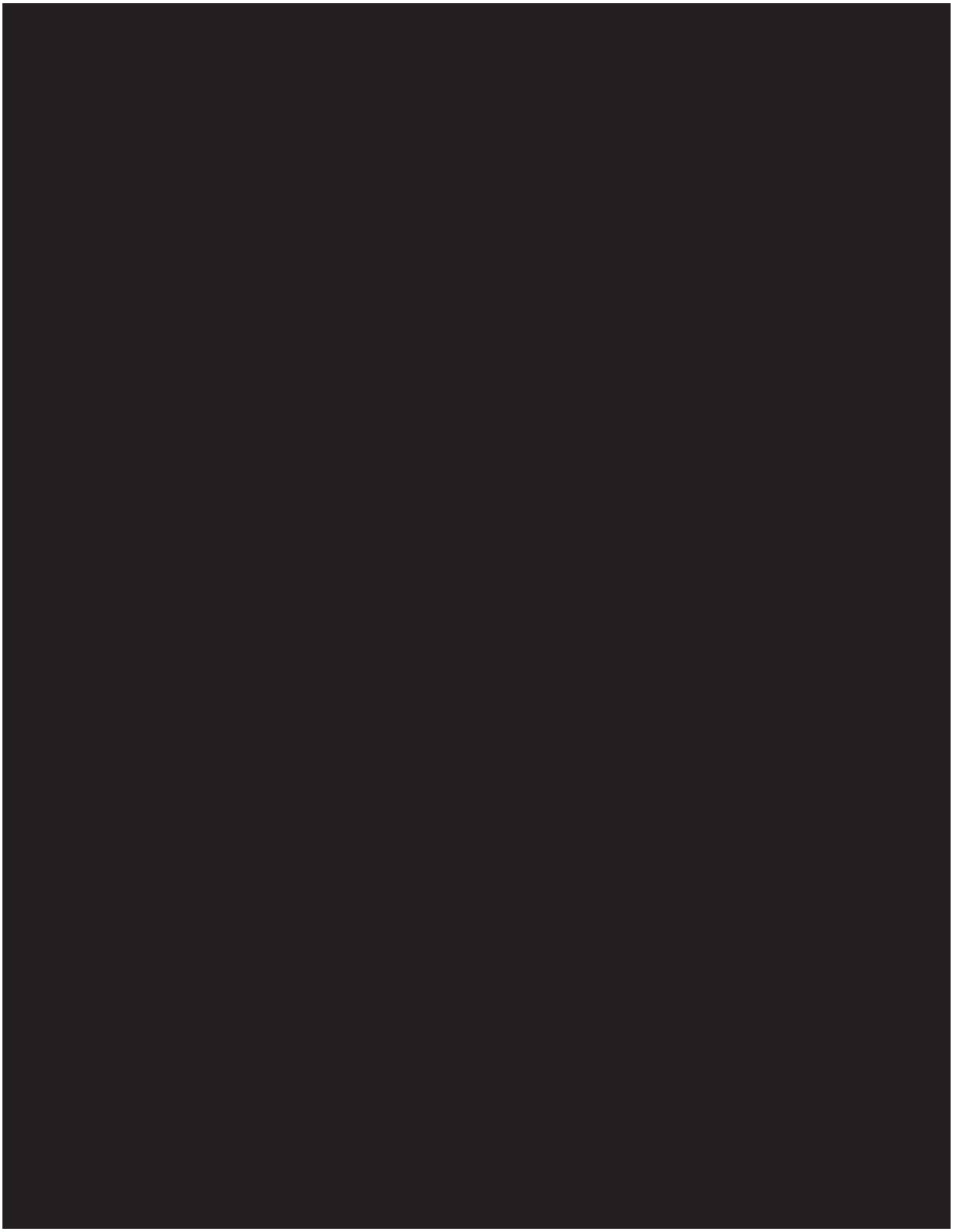
Appendix G Derivation of IFN21 Parameters

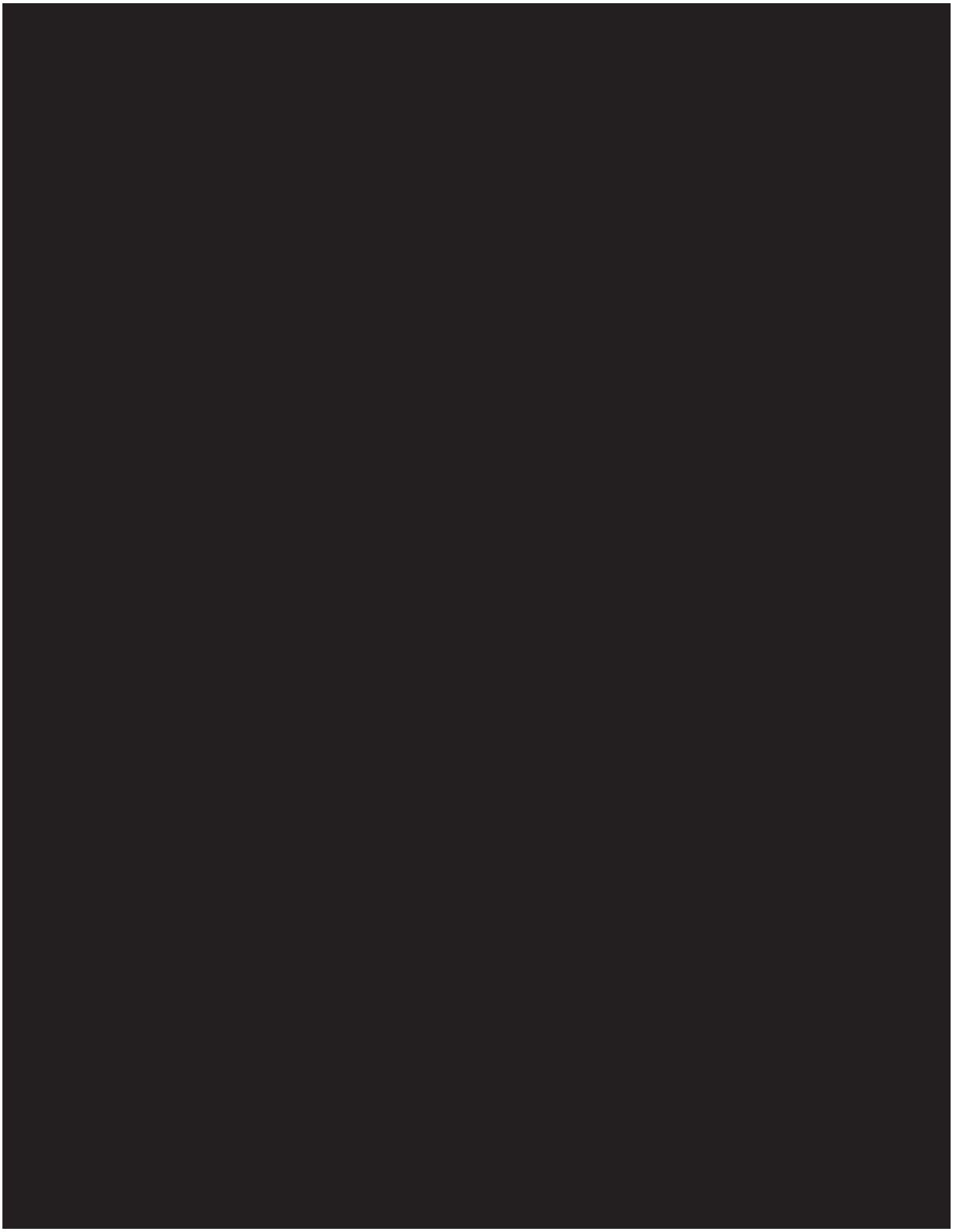
Appendix A

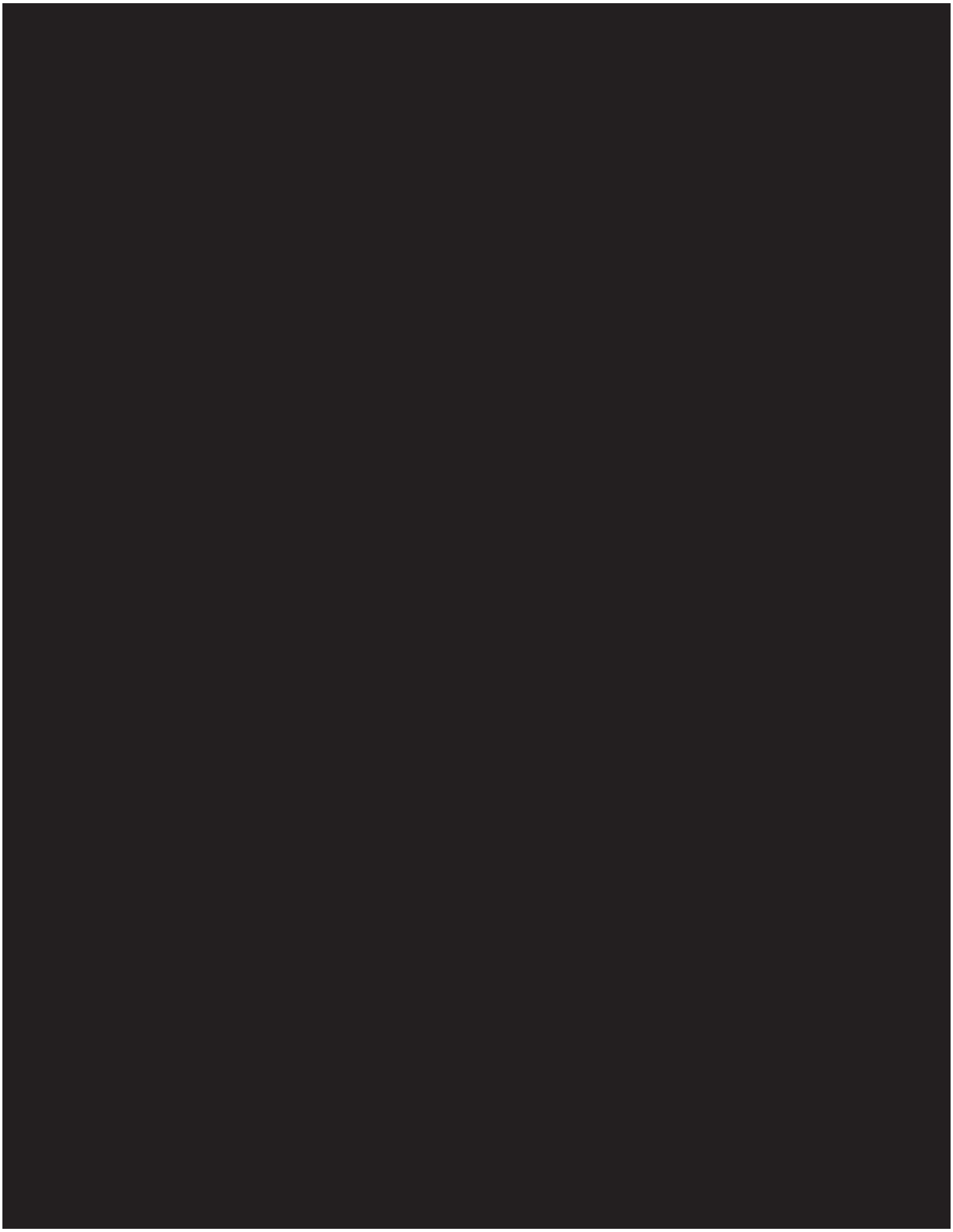
APPENDIX A - SUPPLEMENTAL PROCESS DESCRIPTION: RESTRICTED MEDICATIONS

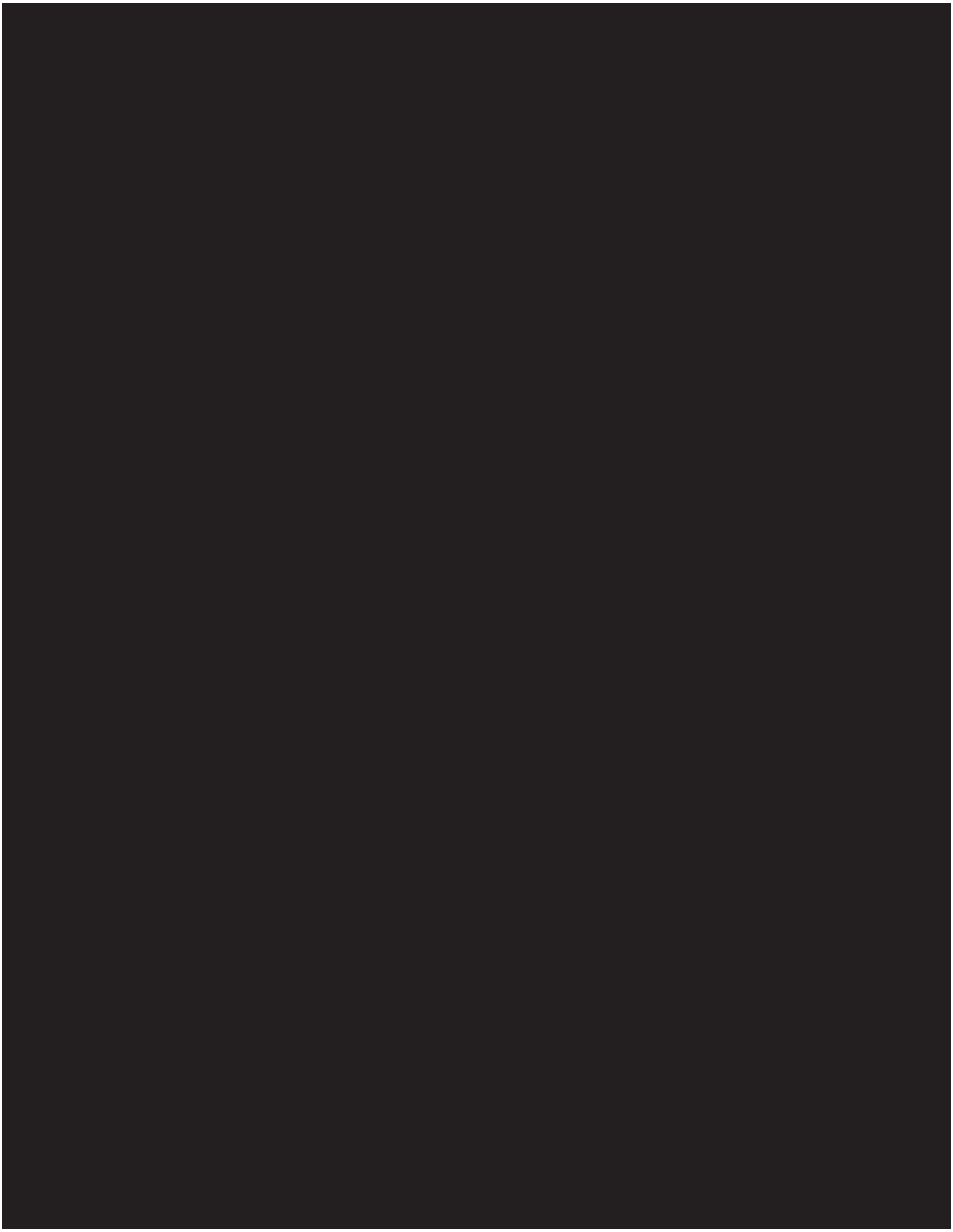


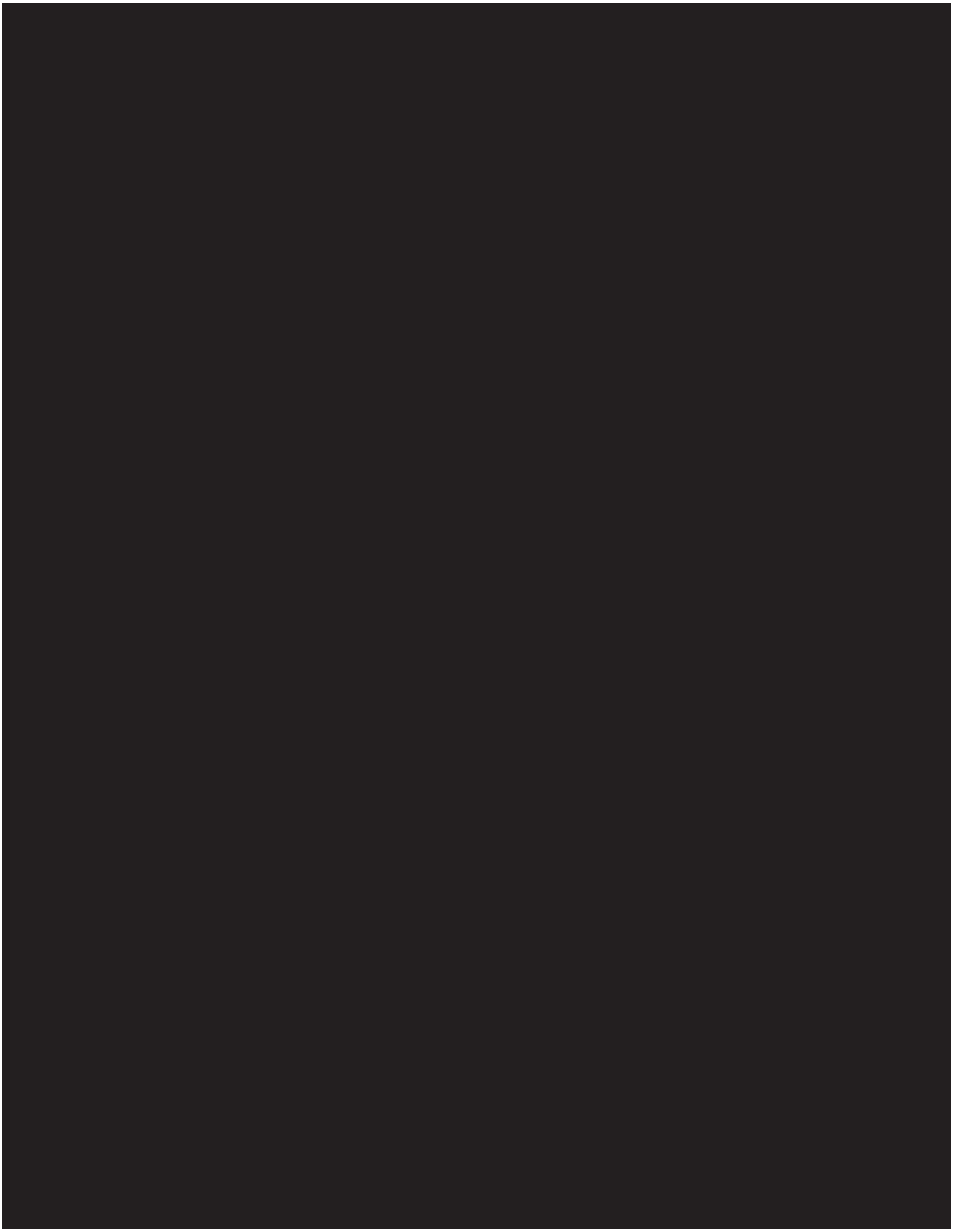


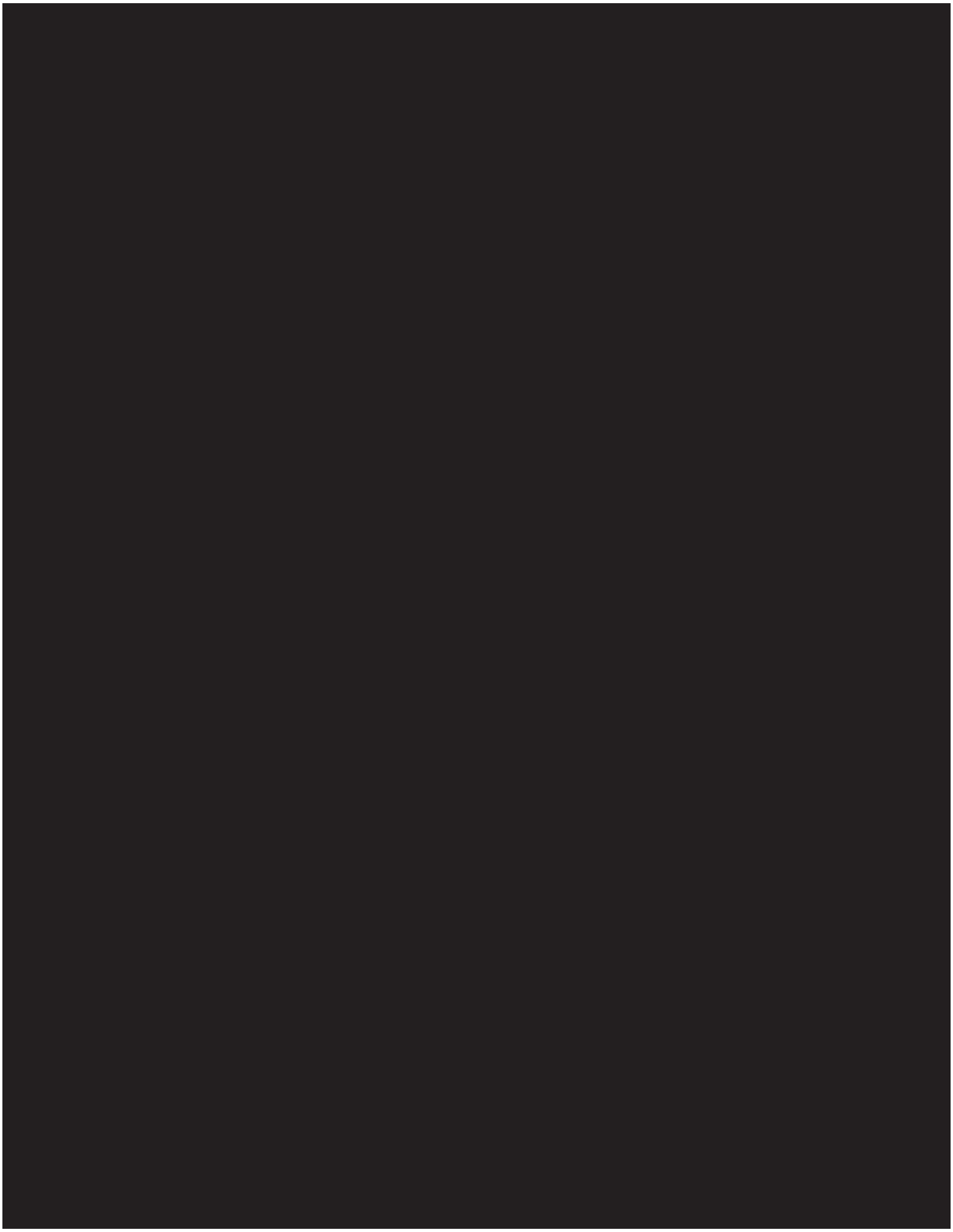


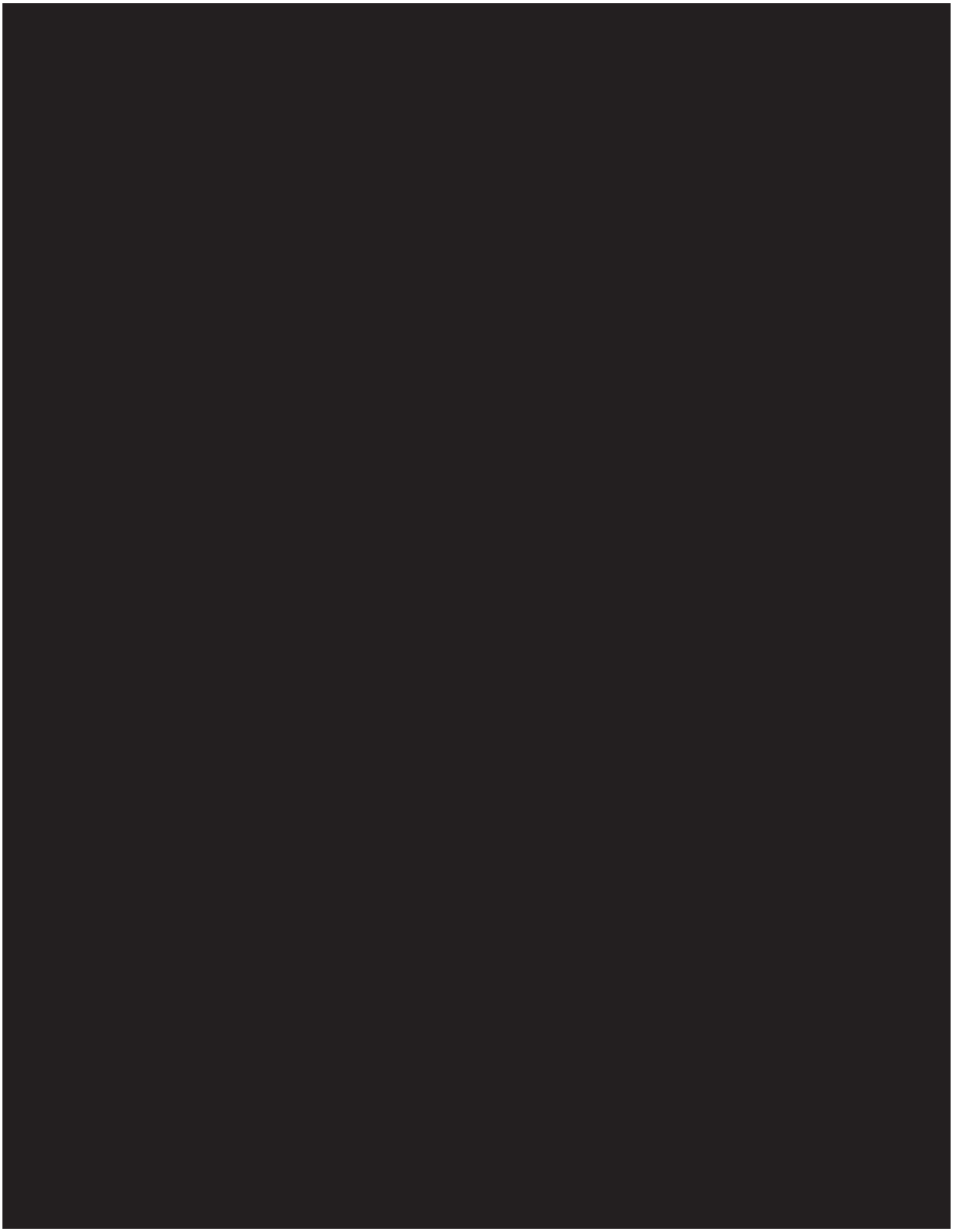


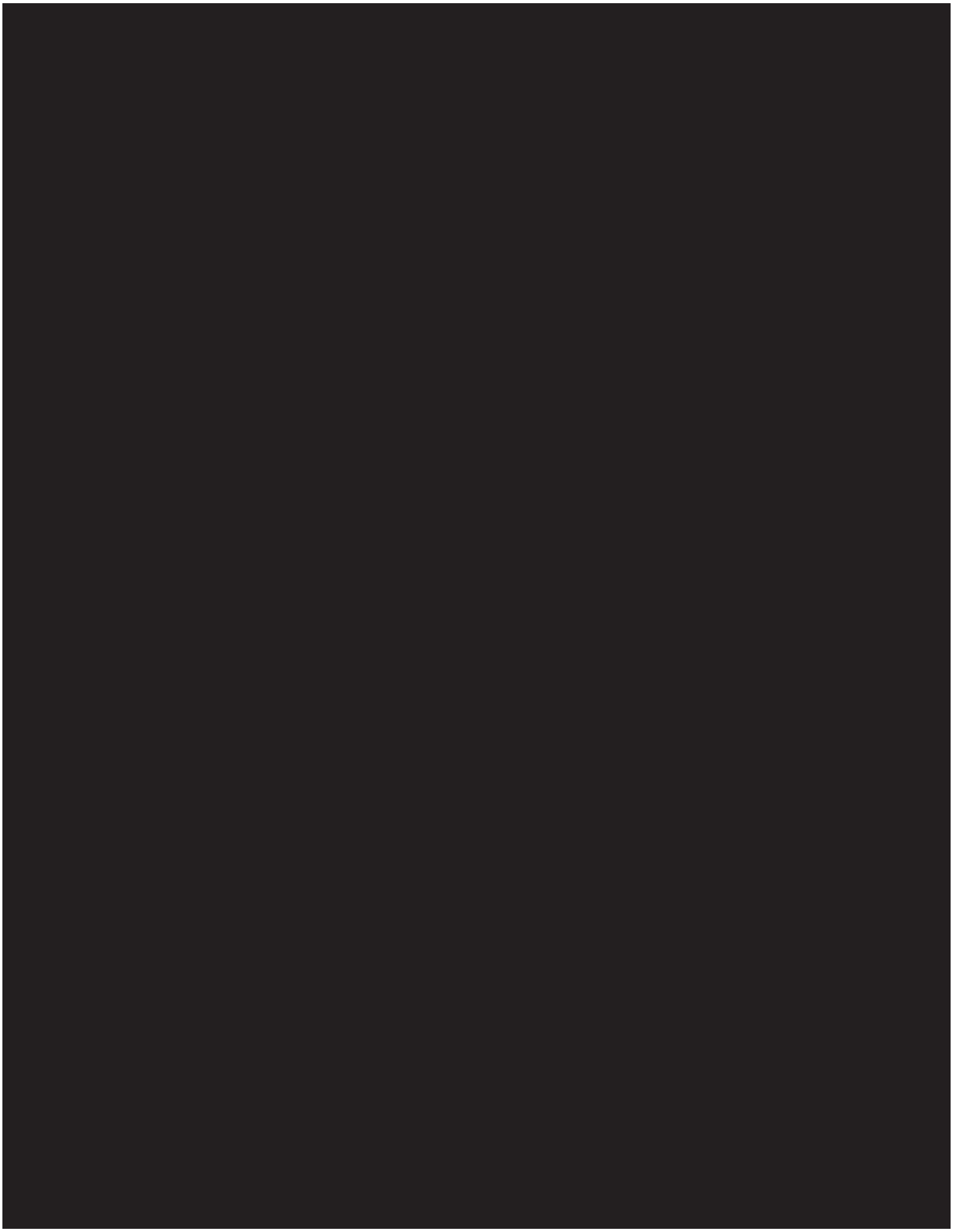


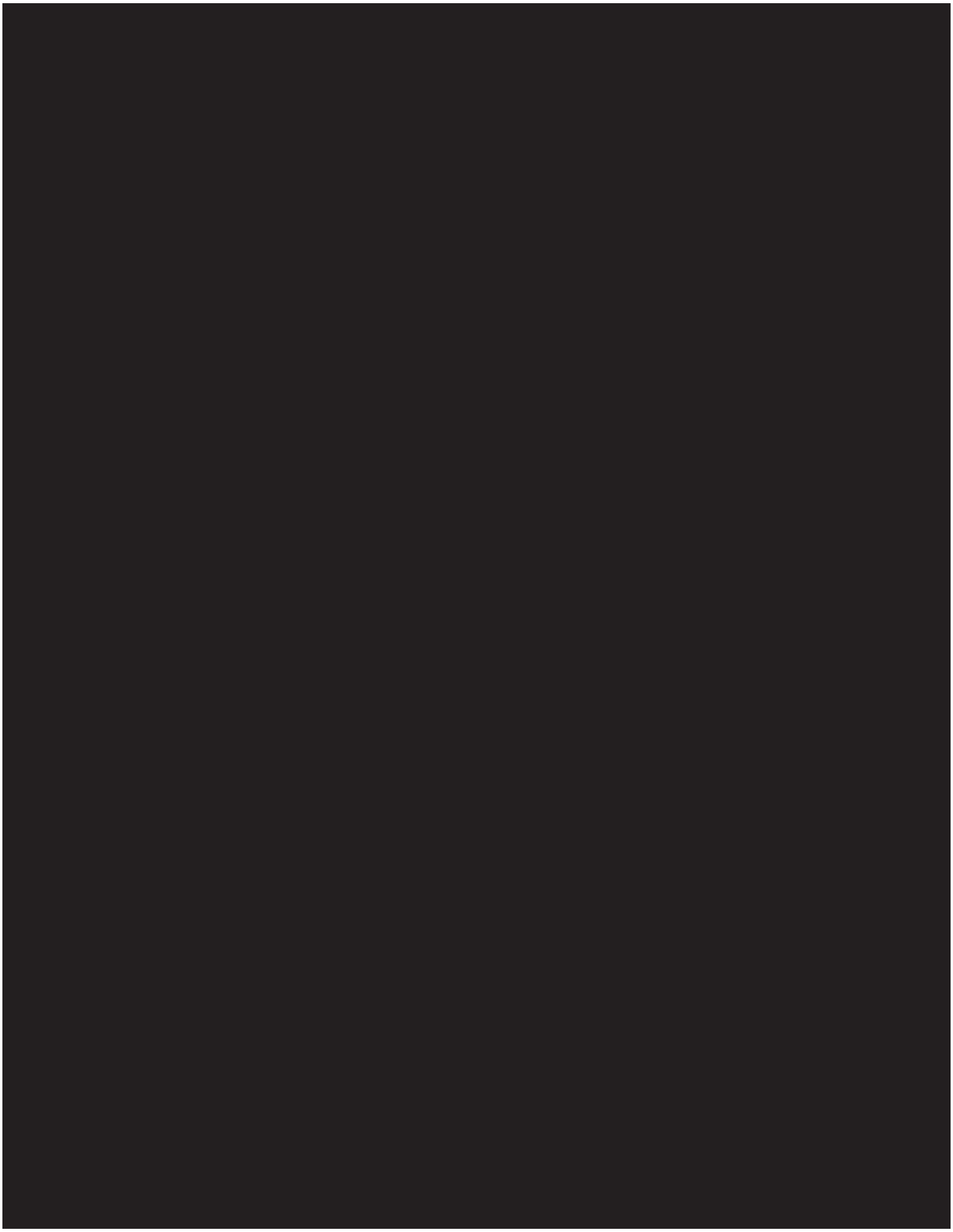


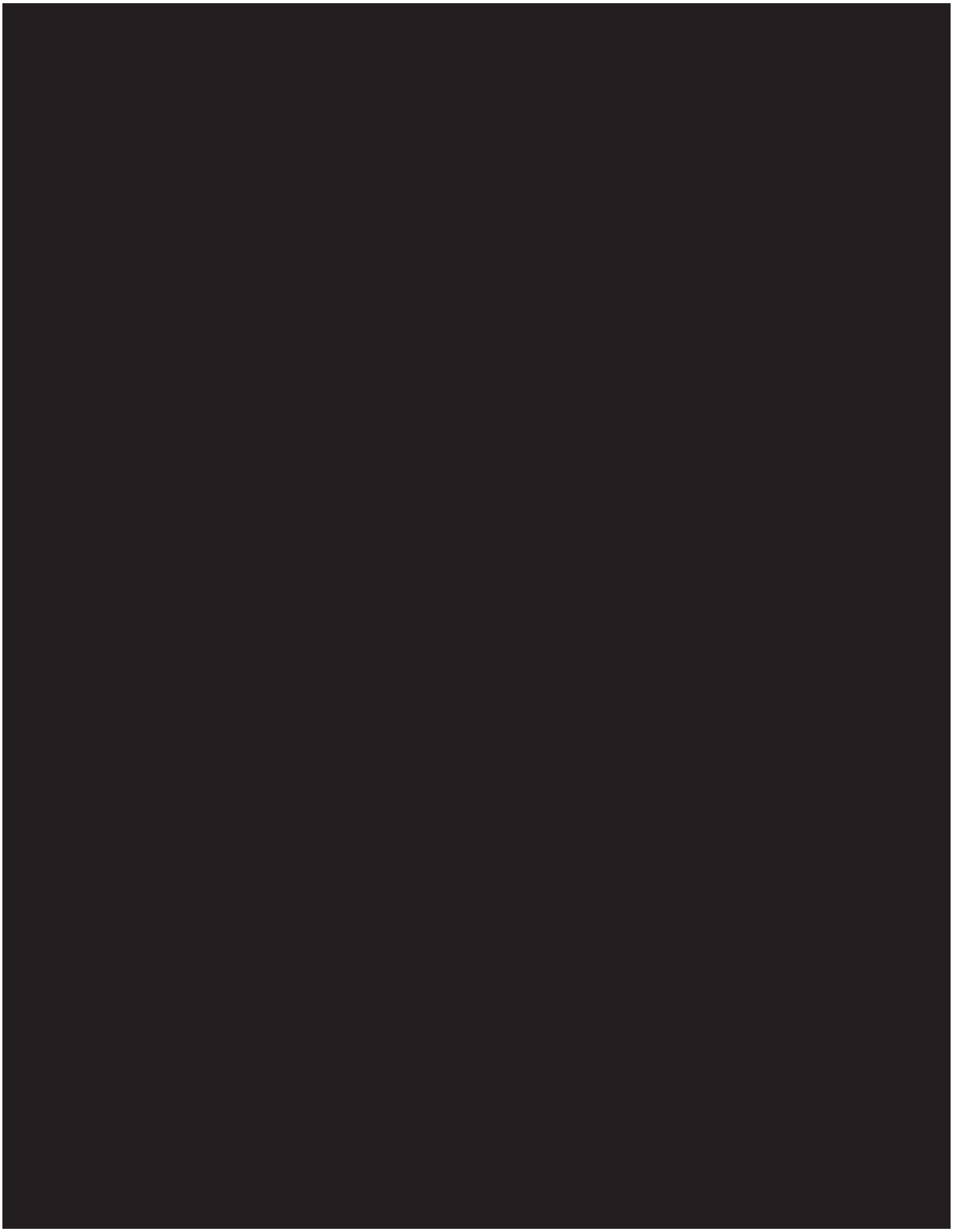


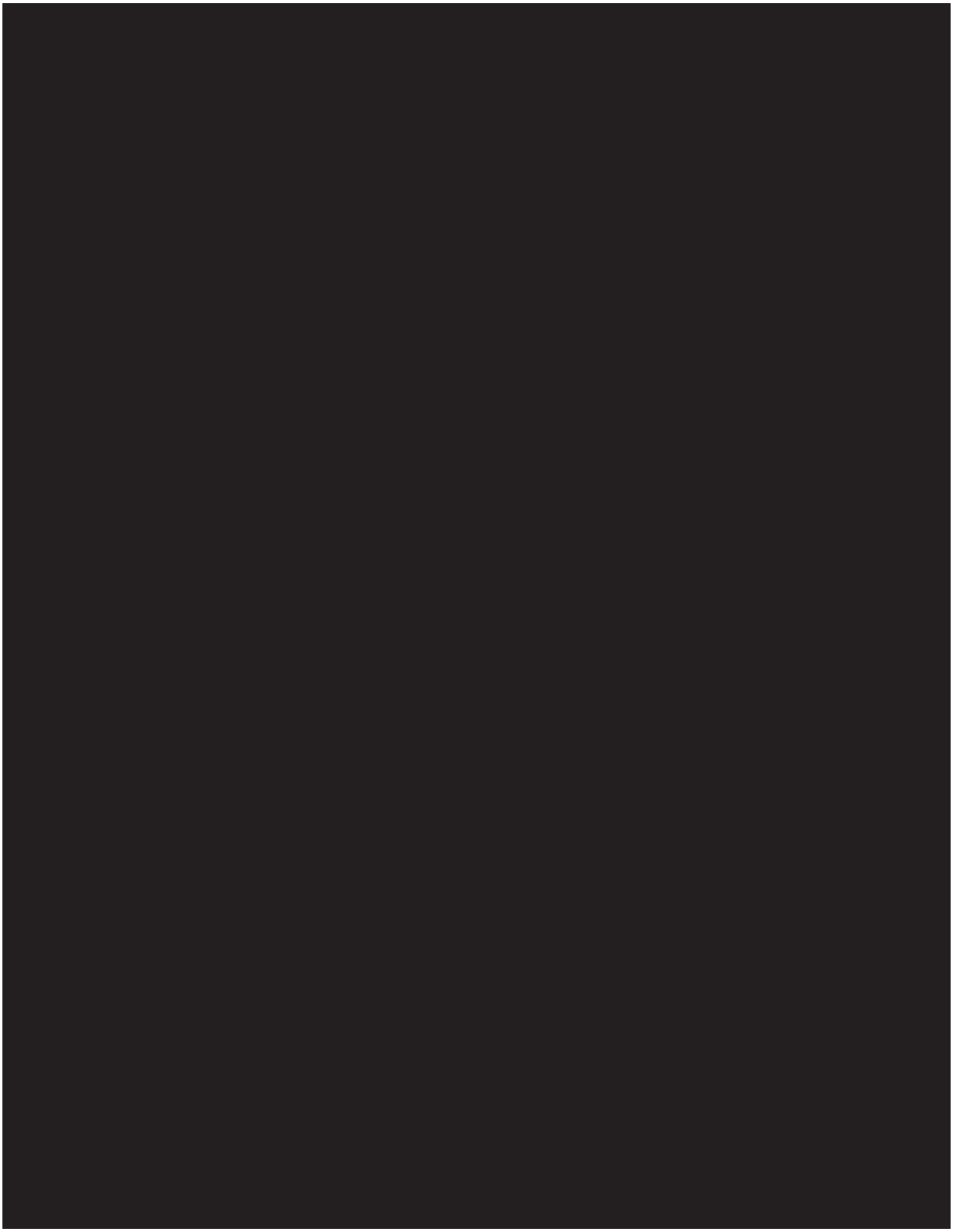


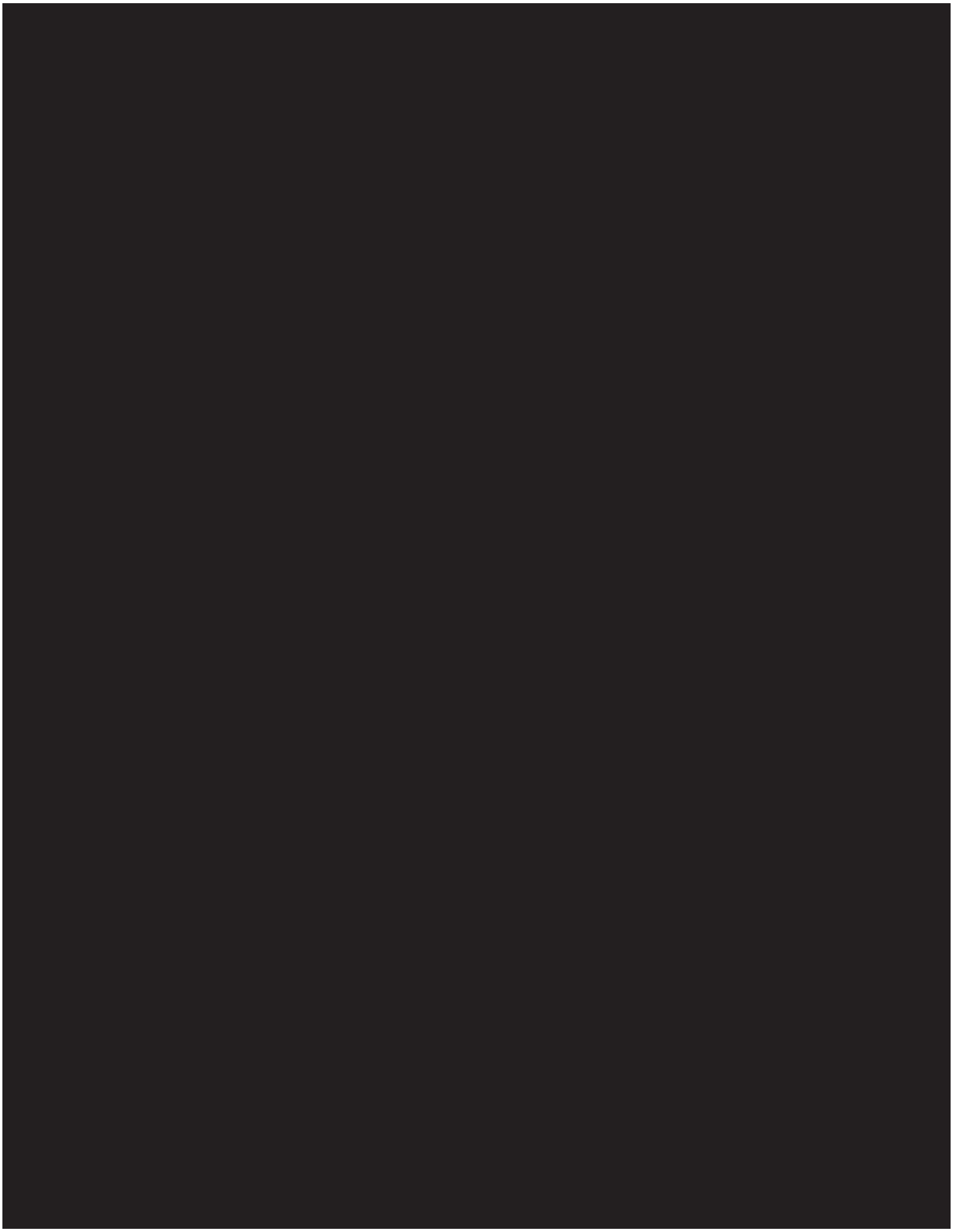












Appendix B

APPENDIX B - SUPPLEMENTAL PROCESS DESCRIPTION: ORAL CORTICOSTEROIDS

Supplemental Process Description: Oral Corticosteroids

Sponsor:	Astra Zeneca
Protocol No:	TULIP Studies 1, 2 and LTE: D3461C00005, D3461C00004, and D3461C00009
PRA Project Id:	AZULUP54-LUP545, AZU545BX-LP545B, and AZU545OL-545OLE
Version Date:	18-Feb-2019

1.0 Table of Contents

1.0 Table of Contents 1
2.0 Purpose 2
3.0 Background 2
4.0 OCS medication 2
4.1 Definition of OCS medication 2
4.2 Derivation of prednisone equivalent dose 2
5.0 Quality Control 3
6.0 Timing and documentation 4
6.1 Timing 4
6.2 Documentation 4
7.0 Approvals: 4
8.0 Document History 5

2.0 Purpose

This document describes the steps required to identify oral corticosteroids (OCS) and derive the prednisone equivalent dose.

3.0 Background

The proportion of subjects who achieve an OCS dose ≤7.5 mg/day at Week 40, which is maintained through Week 52 in the sub-group of subjects with baseline OCS ≥10 mg/day is a key secondary endpoint in the pivotal phase 3 studies (Study 1 and Study 2). The use of OCS over time will be analyzed and summarized in Tables, Figures and Listings (TFLs) in all 3 TULIP studies (Study 1, Study 2, and long-term extension study [LTE]).

4.0 OCS medication

4.1 Definition of OCS medication

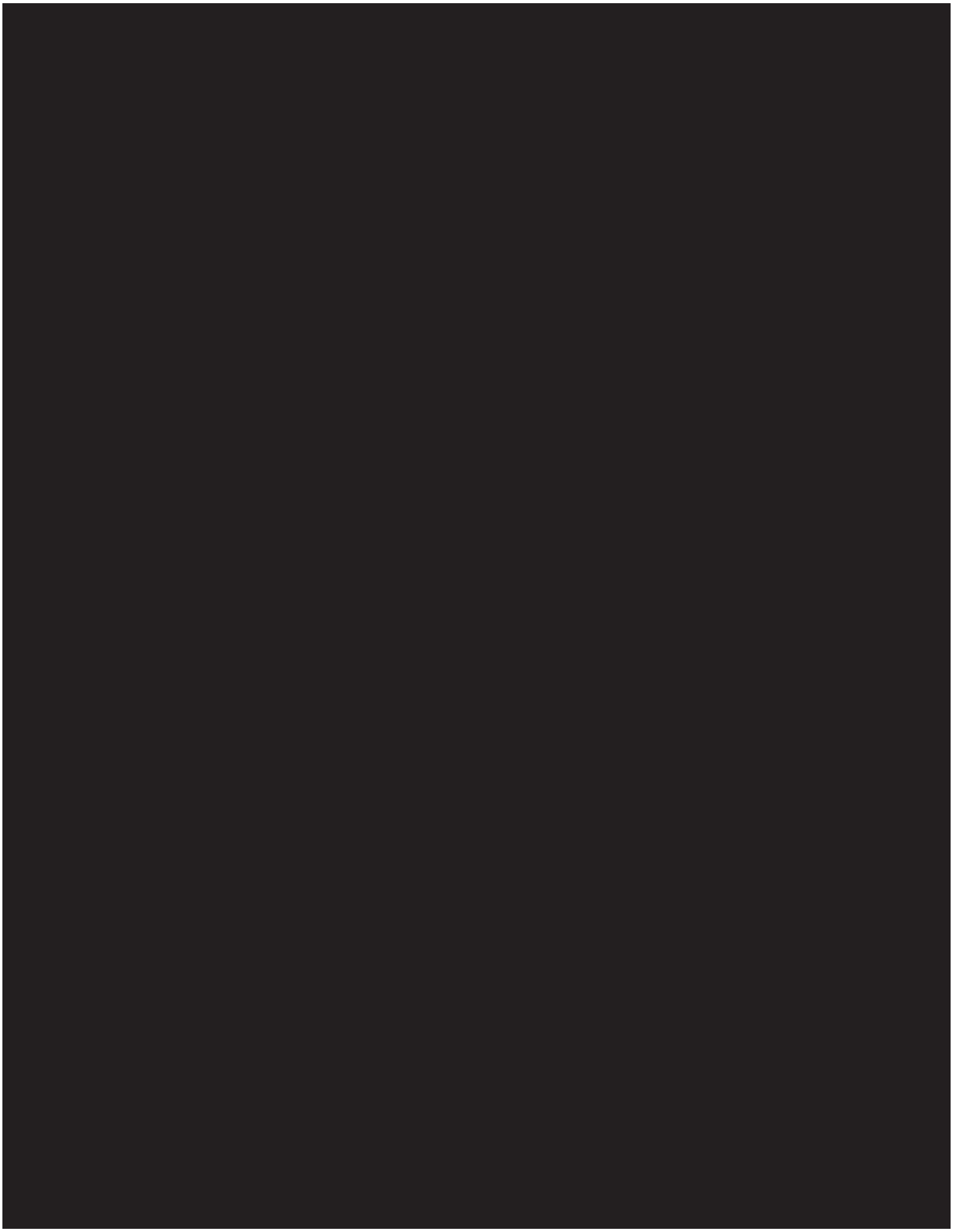
A medication with route = oral listed in the WHO DD Standardised Drug Grouping (SDG) "Corticosteroids" of the version used for coding except preferred term Fludrocortisone will be classified as OCS. Fludrocortisone will not be included as it's a mineralocorticoid and the focus of the study is on glucocorticoids.

4.2 Derivation of prednisone equivalent dose

All OCS medication (as defined in Section 4.1) taken at the respective day (ie, at the date of the respective visit) will be considered for the derivation of the daily dose.

If the medication is taken less than daily the documented total daily dose reflects the dose at the day the medication is taken. To calculate the total daily dose to be used for statistical analyses, the documented total daily dose needs to be divided according to the given medication dose frequency (eg, for medication given every week the documented daily dose needs to be divided by 7). If the total daily dose is missing for a corticosteroid, the available data of this medication will be reviewed by the medical team. If possible, the total daily dose will be derived manually from the available information. OCS administered PRN are not considered in the calculation of the daily dose. Any other routes other than oral will consider doses with frequency of PRN to be given once, at the medication start date.

The conversion factors given in the following table will be used for the calculation of prednisone equivalent doses.



Appendix C

APPENDIX C - DERIVATION RULES FOR IMPUTATION OF PARTIAL OR MISSING DATES

If any medications reported are not able to be determined as prior or concomitant due to missing or partial start dates and/or stop dates, the following imputation rules will be implemented:

- If the year is present but the month and day are missing, then 01JAN will be imputed for the start date and 31DEC for the stop date.
- If the year and month are present but the day is missing, then 01 will be imputed for the start date and the last day of the month for the stop date.
- If the start date is completely missing and the end date is prior to the first dose date of investigational product the medication will be considered prior.
- If the start date is completely missing and the end date is missing or on or after the first dose of investigational product the medication will be considered prior and concomitant.
- If the end date is completely missing and the start date is on or after the first dose of investigational product the medication will be treated as concomitant.
- If the end date is completely missing and the start date is prior to the first dose date of investigational product the medication will be considered prior and concomitant.

Appendix D

APPENDIX D - REFERENCE RANGES AND TELVC FOR LABORATORY VALUES

Parameter	Unit	Low value	Low decrease	High value	High increase
Haematology					
Haemoglobin	g/L	≤60	NA	≥200	NA
		≤70 and decrease from BL ≥15			
Haematocrit	V/V	≤0.18	NA	≥0.64	NA
		≤0.21 and decrease from BL ≥15%			
WBC	10E9/L	≤2, <1	NA	≥20	NA
Neutrophils	10E9/L	<0.5	NA	≥20	NA
		<1.0 and decrease from BL ≥0.5			
Lymphocyte	10E9/L	≤0.5, ≤0.25	NA	≥10.0	NA
Monocytes	10E9/L	NA	NA	≥1.4, ≥5.0	NA
Eosinophils	10E9/L	NA	NA	≥1.5, ≥5.0	NA
Basophils	10E9/L	NA	NA	≥1.0, ≥2.0	NA
Platelet Count	10E9/L	≤20		≥600	NA
		≤50 and decrease from BL ≥25			
INR		NA	NA	≥4.5	NA
Biochemistry					
ALT	IU/L	NA	NA	≥3 x ULN, ≥5 x ULN	NA
AST	IU/L	NA	NA	≥3 x ULN, ≥5 x ULN	NA
ALP	IU/L	NA	NA	≥3 x ULN	NA
CK	IU/L	NA	NA	≥500, ≥2000	NA
GGT	IU/L	NA	NA	≥5 x ULN	NA
Total Bilirubin	µmol/L	NA	NA	≥2 x ULN	NA

Parameter	Unit	Low value	Low decrease	High value	High increase
Albumin	g/L	≤20	NA	≥100	NA
		≤25 and decrease from BL ≥10		≥70 and increase from BL ≥10	
BUN	mmol/L	NA	NA	≥18	NA
Creatinine	umol/L	NA	NA	≥140, ≥190	NA
Sodium	mmol/L	≤132	NA	≥152	NA
Potassium	mmol/L	≤3	NA	≥5.5	NA
Chloride	mmol/L	≤90	NA	≥120	NA
Fasting Glucose	mmol/L	≤2.5	NA	≥7.0, ≥11.1	NA
Total Cholesterol	mmol/L	NA	NA	≥7.25	NA
Urinalysis					
Urine protein/ creatinine ratio	g/mmol	NA	NA	≥0.395	NA
Fasting lipid profile					
HDL	mmol/L	≤0.8	NA	NA	NA
LDL	mmol/L	NA	NA	≥5.2	NA
Triglycerides	mmol/L	NA	NA	≥3.6, ≥5.4	NA

Appendix E

APPENDIX E - ECG: POTENTIALLY CLINICALLY SIGNIFICANT POST BASELINE VALUES

ECG parameter	Unit	Low value	Low decrease	High value	High increase
RR interval	ms	<500	NA	>1500	NA
PR interval	ms	NA	NA	≥240	NA
QRS duration	ms	≤60	NA	≥140	NA
QT	ms	≤300	NA	≥500	≥60
QTcF	ms	≤300	NA	≥500	≥30, ≥60
				≥500 and increase from baseline ≥30,	
				≥500 and increase from baseline ≥60	
QTcB	ms	≤300	NA	≥500	≥30, ≥60
				≥500 and increase from baseline ≥30,	
				≥500 and increase from baseline ≥60	

Appendix F

APPENDIX F - REFERENCE RANGES AND TELVC FOR VITAL SIGNS

Parameter	Unit	Low value	Low decrease	High value	High increase
Pulse	Beats per minute	≤50	NA	≥120	NA
		≤50 and decrease from BL ≥20		≥120 and increase from BL ≥20	
Systolic blood pressure	mmHg	≤90	NA	≥160	NA
		≤90 and decrease from BL ≥20		≥160 and increase from BL ≥20	
Diastolic blood pressure	mmHg	≤50	NA	≥100	NA
		≤50 and decrease from BL ≥10		≥100 and increase from BL ≥10	

Appendix G

APPENDIX G - DERIVATION OF IFN21 PARAMETERS

There are two IFN parameters to be calculated during the study; percent neutralization and the gene signature fold change.

The following steps should be implemented in the derivation of these parameters.

1. Calculate the mean Ct values for each gene and the three housekeeper genes (18S, ATCB and GAPDH) on the ThermoFisher TLDA platform (test and normal control samples) within a particular subject.

2. Calculate the mean Ct value of the three housekeeper genes;
$$HK_{mean} = mean(Ct_{18S}, Ct_{ATCB}, Ct_{GAPDH})$$

3. Calculate ΔCt values by subtracting the mean Ct value of the three housekeeper genes from each test gene:
$$\Delta Ct_{gene} = Ct_{test\ gene} - HK_{mean}$$

4. Calculate the ΔCt values for the normal control genes, as in Step 3.

5. Calculate -ΔΔCt values as:
$$-\Delta\Delta Ct_{gene} = \Delta Ct_{normal\ control} - \Delta Ct_{test\ gene}$$

6. Linearize the -ΔΔCt values for each gene as follows:
$$linearized_{gene} = 2^{-\Delta\Delta Ct}$$

7. Calculate the percent neutralization values for each gene for each post-Visit 1 visit (Visit X) as:
$$\%neutralization_{gene} = 100 - \left(\left(\frac{2^{-\Delta\Delta Ct_{Visit\ 1}} - 2^{-\Delta\Delta Ct_{visit\ x}}}{2^{-\Delta\Delta Ct_{Visit\ 1}}}\right) \times 100\right)\#$$

The final percent neutralization score for each timepoint, for each subject, is the median of the individual gene % neutralization values calculated in Step 7. There will be one value per subject per post-Visit 1 visit:
$$Overall\ \%neutralization = median(\%neutralization_{gene})$$

The fold change for each timepoint and each subject is the median of the linearized values for each gene, calculated in Step 6:

$$Fold\ Change = median(2^{-\Delta\Delta Ct})$$