16.1.9 Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

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Table of Abbreviations

Abbreviation	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CDAI	Clinical disease activity index
eCRF	Electronic case report form
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
DAS28-CRP	Disease activity score (28 joint) calculated using the C-reactive protein formula
DAS28-ESR	Disease activity score (28 joint) calculated using the erythrocyte sedimentation rate formula
DW	Disease-Worsening
EOS	End of Study
EOT	End of Treatment
ESR	Erythrocyte Sedimentation Rate
ET	Early termination
ETN	Etanercept
HAQ-DI	Disability Index of the Health Assessment Questionnaire
ICH	International Conference on Harmonisation
IP	Investigational product
IPD	Important protocol deviation
IXRS	Interactive Voice and Web Response System
LDA	Low Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NRI	Non-responder Imputation
PhGA	physician global assessment of arthritis disease activity
PtGA	patient global assessment of arthritis disease activity
PRO	Patient reported outcomes
QW	Once weekly
RA	Rheumatoid arthritis
SAP	Statistical analysis plan

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Abbreviation	Definition/Explanation
SDAI	Simplified Disease Activity Index
SF-36	Medical Outcomes Short Form-36 Questionnaire
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cells
WHODRUG	World Health Organization Drug

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for etanercept Study 20110186 dated 17 October 2017. The scope of this plan includes the final analysis that is planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary Objective

To evaluate the efficacy of etanercept monotherapy compared to methotrexate monotherapy on maintenance of remission in subjects with rheumatoid arthritis (RA) who were on etanercept plus methotrexate combination therapy.

2.2 Secondary Objectives

To evaluate the efficacy of etanercept plus methotrexate therapy compared to methotrexate monotherapy on maintenance of remission.

To evaluate the efficacy of 1) etanercept monotherapy compared to methotrexate monotherapy and 2) etanercept plus methotrexate therapy compared to methotrexate monotherapy on:

- disease activity
- disease-worsening and time to disease-worsening
- remission and time to recapture remission after rescue treatment

2.3 Safety Objective

To evaluate the safety of etanercept and methotrexate

2.4 Exploratory Objectives

- To evaluate Patient Reported Outcomes (PRO)
- To investigate potential biomarkers of disease activity and response to etanercept.
- To investigate the effects of genetic variation in disease genes and drug target genes on RA and/or subject response to etanercept.

3. Study Overview

3.1 Study Design

This is a Phase 3, multicenter, randomized withdrawal, double-blind controlled study in subjects with RA on etanercept plus methotrexate who are in very good disease control for 6 months prior to study entry. The study will consist of a 30-day screening period, a

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24-week open-label run-in period, a 48-week double-blind treatment period and a 30-day safety follow-up period.

The study will enroll approximately 358 subjects. During the run-in period subjects will receive open-label etanercept and methotrexate at the same dose they were receiving during screening. It is expected that approximately 30% of subjects will early terminate the run-in period. Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately 250 subjects are randomized to treatment.

Approximately 250 subjects will be randomly assigned in a 2:2:1 ratio to one of three treatment groups:

- Etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate (n = 100)
- Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept (n = 100)
- Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly (n = 50)

Subjects randomized to the etanercept plus methotrexate group and the methotrexate monotherapy group will receive methotrexate at the same dose they were receiving at screening and during the run-in period.

3.2 Sample Size

The sample size was determined from a hypothesis of superiority of etanercept monotherapy over methotrexate monotherapy. The proportion of subjects achieving SDAI remission after 52 weeks of double-blind treatment in the PRESERVE and COMET studies was used to estimate the treatment effects. PRESERVE was a two-period study conducted in subjects with RA who had moderate disease activity despite a stable dose of oral methotrexate for a minimum of 8 weeks at the time of screening. Among all subjects who were in SDAI remission at both week 28 and week 36 (the last two visits of the open-label run-in period), the proportion of subjects who were still in remission after the 52-week double-blind period was 86.1% and 38.1% for the etanercept plus methotrexate therapy and methotrexate monotherapy treatment groups, respectively. COMET was a two-period study conducted in subjects with active early RA. Among all subjects who received etanercept plus methotrexate therapy in Period 1 and were in SDAI remission at week 52, the last visit of Period 1, the proportion of subjects who were in still in remission after the 52-week double-blind Period 2 was 78.3% and 72.4%, respectively, for the etanercept plus methotrexate therapy and etanercept monotherapy treatment groups. Given key differences noted in this study, including the sustained period of remission prior to withdrawal, the response rate in the methotrexate monotherapy arm is approximated to be higher at 50%, with the response

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rate in the etanercept monotherapy arm at approximately 72%. It is expected that compared to PRESERVE, subjects in the current study will have more stable disease at the time of randomization. Namely, subjects must be in very good disease control for 6 months prior to study entry and must be in SDAI remission at the end of a 24-week open-label run-in period.

The sample size is based on the adequacy to evaluate the efficacy of etanercept monotherapy compared to methotrexate monotherapy as measured by the primary endpoint of SDAI remission at week 48 at a significance level of 0.05. The sample size was also ensured to be sufficient to evaluate the efficacy of the etanercept plus methotrexate treatment arm compared to methotrexate monotherapy. Based on a two-sided chi-square test with 90% power, 100 subjects per arm are required at randomization.

Using an assumed attrition rate of 30% in the open-label run-in period, due to exclusion of subjects with Disease-Worsening during the run-in period, or other reasons, approximately 358 subjects will be enrolled in order to have approximately 250 subjects randomized in a 2:2:1 ratio to one of three treatment groups: etanercept monotherapy (n = 100), methotrexate monotherapy (n = 100) and etanercept plus methotrexate combination therapy (n = 50). Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately 250 subjects are randomized to treatment.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

- SDAI remission (≤ 3.3) at week 48

The primary estimand consists of:

- Target population – patients with a history of moderate to severe rheumatoid arthritis (RA) who are on etanercept and methotrexate combination therapy and who are in very good disease control.
- Endpoint – SDAI remission (SDAI<=3.3) at week 48
- Intercurrent events – there are 2 intercurrent events: first, discontinuation of IP before week 48; second, disease-worsening after randomization which triggers initiation of rescue therapy. Treatment effects will be estimated for subjects regardless of whether subjects complete 48 weeks of IP.
- Summary measure – difference in the proportion of subjects achieving SDAI<=3.3 *(yes/no)* at Week 48 on etanercept monotherapy and that of subjects achieving SDAI<=3.3 *(yes/no)* at Week 48 on methotrexate monotherapy.

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In summary, the primary estimand is the difference in proportions of subjects in etanercept monotherapy and methotrexate monotherapy maintaining SDAI remission at Week 48 without experiencing disease-worsening on study in adults with a history of moderate to severe RA who have been on etanercept and methotrexate combination therapy and in very good RA disease control, regardless of adherence to treatment and completion of 48 weeks of IP.

4.1.2 Secondary Endpoints

- SDAI score and change from baseline at all measured timepoints
- DAS-28-ESR and change from baseline at all measured timepoints
- DAS-28-CRP and change from baseline at all measured timepoints
- CDAI and change from baseline at all measured timepoints
- SDAI remission (≤ 3.3) at all measured timepoints
- Boolean remission at all measured timepoints
- Disease-Worsening defined as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization
- Time to Disease-Worsening as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization

In subjects that receive rescue treatment during the double-blind treatment period

- Time to recapture SDAI remission after starting rescue treatment
- SDAI remission at week 48

4.1.3 Safety Endpoints

- Adverse events
- Serious adverse events
- Laboratory parameters

4.1.4 Exploratory Endpoints

- Components of SDAI at all measured timepoints
- HAQ-DI at all measured timepoints
- SF-36 domains, physical component summary, and mental component summary at all measured timepoints

Additional exploratory endpoints pertaining to the Run-In Period are:

- SDAI score at run-in visits
- Time to run-in failure
- Time to randomization failure

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Additional exploratory endpoints pertaining to the Double-Blind Period are:

- Observed SDAI Remission (<= 3.3) at all timepoints
- Patient Global Assessment of Joint Pain at all timepoints
- SDAI LDA at all timepoints
- DAS28-ESR remission at all timepoints
- DAS28-ESR LDA at all timepoints
- DAS28-CRP remission at all timepoints
- Reason for Disease-Worsening
- SDAI score at Disease-Worsening
- Disease Activity at Disease-Worsening

In subjects that receive rescue treatment and in subjects that fulfill disease-worsening criteria during the double-blind treatment period:

- Observed SDAI remission (yes/no) at visits following rescue
- SDAI LDA (yes/no) at visits following rescue
- Time to SDAI LDA
- SDAI score on Disease-Worsening Date and at subsequent visits
- Change in SDAI from Disease-Worsening Date and at subsequent visits
- DAS28-ESR remission (yes/no) at visits following rescue
- Time to DAS28-ESR remission
- DAS28-ESR LDA (yes/no) at visits following rescue
- DAS28-CRP remission (yes/no) at visits following rescue
- Time to DAS28-CRP remission.

4.2 Planned Covariates

The following baseline covariates will be considered to assess their influence on the primary and secondary endpoints:

- age (years) (continuous)
- sex (male, female)
- race (Caucasian, non-Caucasian)
- ethnicity (Hispanic or Latino vs Non-Hispanic or Latino)
- disease duration (in years)
- baseline methotrexate dose (continuous)
- additional covariates will be evaluated (baseline methotrexate dose [<15 mg / ≥15 mg], smoking [never, former, current])

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The rationale for inclusion of baseline methotrexate dose [<15 mg / ≥15 mg] and smoking status is provided in Section 12.

Subgroup analyses, which would be considered exploratory, may be performed if an examination of the above covariates suggests that any treatment difference for the primary and secondary endpoints depends on any baseline covariates.

5. Hypotheses and/or Estimations

There are two clinical hypotheses. First,

> Etanercept monotherapy is superior to methotrexate monotherapy for maintaining remission in subjects with RA who were on etanercept plus methotrexate therapy as measured by the proportion of subjects who maintain SDAI remission (SDAI ≤ 3.3) at week 48.

Specifically, the null (H_0) and alternative (H_1) hypotheses are defined as follows:

H_0: The difference in proportion of subjects who maintain SDAI remission at week 48 in the etanercept monotherapy arm and in that of the methotrexate monotherapy arm = 0

H_1: The difference in proportion of subjects who maintain SDAI remission at week 48 in the etanercept monotherapy arm and in that of the methotrexate monotherapy arm ≠ 0.

Second,

> Etanercept and Methotrexate combination therapy is superior to methotrexate monotherapy for maintaining remission in subjects with RA who were on etanercept plus methotrexate therapy as measured by the proportion of subjects who maintain SDAI remission (SDAI ≤ 3.3) at week 48.

Specifically, the null (H_0) and alternative (H_1) hypotheses are defined as follows:

H_0: The difference in proportion of subjects who maintain SDAI remission at week 48 in the etanercept and methotrexate combination arm and in that of the methotrexate monotherapy arm = 0

H_1: The difference in proportion of subjects who maintain SDAI remission at week 48 in the etanercept and methotrexate combination arm and in that of the methotrexate monotherapy
arm ≠ 0.

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6. Definitions

6.1 Study Time Points

Enrollment Date

A subject's Enrollment Date is defined as the date he or she has met all Part 1 eligibility criteria and the enrollment call in the IXRS system has been completed.

Part 1/Run-in Period

The 24-week period after enrollment and prior to randomization. Specifically, the period begins when a subject initiates treatment with open-label run-in etanercept and/or open-label run-in methotrexate per the eCRF at the same dose he or she was receiving at screening. There are three visits associated with the Run-in Period: Run-in Visit 1, Run-in Visit 2, and Run-in Visit 3.

Run-In Day 1

A subject's Run-In Day 1 is defined as the date of the first dose of IP administration during Part 1.

Run-In Day

A subject's Run-In Day = (Visit Date – Run-In Day 1 date) + 1.

Run-In Failure Date

A subject's Run-In Failure Date is the date the subject ended run-in due to protocol specified criteria per the eCRF.

Randomization Failure Date

A subject's Randomization Failure Date is the date the subject ended run-in due to any reason and was not randomized.

End-of Run-In Date

A subject's End-of Run-In Date is the date subject ends the run-in period per the CRF.

Randomization Date

A subject's Randomization Date is the date when a randomization number is assigned to him or her through the Interactive Voice/Web Response System (IXRS).

Study Day 1

A subject's Study Day 1 is defined as the date of the first dose of IP administration after randomization, or the randomization date if the subject is not dosed.

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Baseline

The last measurement for the endpoint of interest taken on or prior to Study Day 1 and after Run-In Visit 3. Hematology and chemistry profiles were not assessed on Day 1; their Run-in Visit 3 values will be used when reporting baseline.

Baseline for Concomitant Medications

Run-In Period Baseline for Concomitant Medications is enrollment date, and Post-Run-In Period Baseline for Concomitant Medications is randomization date.

Study Day

For a given study visit, the study day for a subject is defined as:
Study Day = (Visit Date – Study Day 1 date) + 1.

Part 2/Treatment Period

The up-to 48-week double-blind period beginning with Study Day 1 and ending with the End of Study date.

SDAI Assessment Datea

The SDAI Assessment Date is the latest date of the assessments for Tender Joint Count, Swollen Joint Count, Physician Global Assessment, Patient Global Assessment, and CRP for a given SDAI score.

Disease-Worsening Date (DW Date)

A subject's Disease-Worsening Date is the first Visit Date in which the subject meets the definition for Disease-Worsening. With the exception of analysis using multiple imputation method, Disease-Worsening classification is based on observed SDAI values only. Each subject will have at most one DW Date. A subject's disease-worsening date is used to define his/her Disease-Worsening Baseline.

Rescue Date

A subject's rescue date is the Visit Date in which he or she first receives rescue therapy as identified by the Investigational Product Administration (Rescue Therapy Etanercept) or Investigational Product Administration (Rescue Therapy Methotrexate) form.

Rescue Therapy Period

For the Rescue Analysis Set as defined in Section 7.4, the Rescue Therapy Period begins with the Rescue Date through the EOS Date.

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Disease-Worsening Analysis Visit (DW_visit)

The DW_visit defines the analysis visit after a subject fulfills disease-worsening criteria. Details of DW_visit derivation are in Appendix A.

Rescue Analysis Visit (Rescue_visit)

Rescue_visits define the analysis visits after a subject initiates rescue therapy. Details of Rescue_Visit derivation are in Appendix A.

End of Treatment (EOT)

The End of Treatment for a subject is the subject's last assessment for the protocol-specified treatment phase of the study.

End of Study Date

The End of Study Date for a subject is the date the subject completes the safety follow-up phone call, or the date of the Early Termination (ET) visit if no safety follow-up phone call is completed. The date the subject has ended the study is recorded on the End of Study Electronic Case Report Form (eCRF).

End of Study

The End of Study is the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

6.2 Primary Endpoint

Primary Endpoint - SDAI remission at week 48

The primary endpoint of SDAI remission is defined as achievement of SDAI ≤ 3.3 at Week 48 without fulfilling the definition of disease-worsening during the study.

Primary endpoint of SDAI remission will be defined as follows:

- SDAI_remission_maintenance (<= 3.3) at Week 48 = 1,
  if SDAI ≤ 3.3 at Week 48 AND subject did not fulfill the definition of disease-worsening during the study;
- SDAI_remission_maintenance (<= 3.3) at Week 48 = missing,
  if subject has no Week 48 SDAI value AND subject did not fulfill the definition of disease-worsening during the study;
- SDAI_remission_maintenance (<= 3.3) at Week 48 = 0,
  otherwise.

Different statistical methods for addressing missing SDAI remission status are addressed in Section 11.5.

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6.3 Basic Definitions

Age

Number of years at time of enrollment as recorded on the electronic case report form.

Investigational Product (IP)

Etanercept (or placebo for etanercept) and methotrexate (or placebo for methotrexate).

Adverse Event

In addition to the International Conference on Harmonisation (ICH) Guidance definition, an adverse event also includes any occurrence or worsening of a pre-existing medical condition.

Treatment-Emergent Adverse Event (TEAE)

TEAE during the run-in period is an adverse event that occurs on or after Run-In Day 1 (as determined by adverse event start date and pre-treatment flag NE 'Y' on the Events CRF) and up to Study Day 1. TEAE during the double-blind period is an adverse event that occurs on or after Study Day 1 (as determined by adverse event start date and pre-treatment flag NE 'Y' on the Events CRF) and up to 30 days after the last dose of IP.

Subject Incidence Rate

The subject incidence rate for a given event in a given time period is defined as the number of subjects with a first reported occurrence of the event divided by the number of subjects who entered the time period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

Actual treatment received

Safety analyses will be performed on the Safety Analysis Sets, which analyzes subjects by actual treatment received. Actual treatment is defined below:

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Actual Treatment In the Open-Label Run-In Period
• **Actual Treatment = Etanercept + Methotrexate**
Actual Treatment In the Double-Blind Treatment Period
If a subject receives - any active methotrexate and no active etanercept, then his/her actual treatment assignment is methotrexate - any active etanercept and no active methotrexate, then his/her actual treatment assignment is etanercept - any active etanercept and any active methotrexate, then his/her actual treatment assignment is etanercept + methotrexate - no active etanercept and no active methotrexate, then he/she received no actual treatment and will not be included in the safety analysis set
Actual Treatment In the Rescue Therapy Period
• **Actual Treatment = Etanercept + Methotrexate**

Run-in Failure

The subjects who participate in the run-in period but fulfill *any* of the below criteria are deemed not eligible for randomization and are considered run-in failures.

- SDAI > 3.3 at run-in visit 3
- if female and not at least 2 years postmenopausal or having a history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, does *not* have a negative urine pregnancy test at baseline
- has any clinically significant change in the Part 1 eligibility criteria during the run-in period
- SDAI > 3.3 and ≤ 11 on two consecutive visits at least two weeks apart
  OR
  SDAI > 3.3 and ≤ 11 on two or more separate visits
  OR
  SDAI > 11 at any time during the run-in period
- Clinically significant laboratory abnormality in run-in which per investigator poses a safety risk, will prevent the subject from completing the study, or will interfere with the interpretation of the study results during the run-in period.

Rescue Therapy

After randomization, if a subject experiences Disease-Worsening as defined in Section 6.3, he/she will initiate rescue treatment with etanercept 50 mg once weekly (QW) plus methotrexate (10 to 25 mg). Those assigned to the etanercept plus

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methotrexate arm will continue on the assigned treatments, but are still considered to be on rescue therapy once the open-label rescue etanercept or open-label methotrexate eCRF forms are used. Subjects will receive methotrexate at the same dose that they were receiving at screening.

Original treatment assignments will remain blinded. Dispensing of etanercept plus methotrexate rescue therapy will be managed via the Interactive Voice and Web Response System (IXRS).

6.4 Derived Variables

Duration of Rheumatoid Arthritis

The number of years between the date of diagnosis (DXDT) and Run-in Day 1, rounded to one decimal place, is given by formula below to calculate the duration:

Observed portion	Missing portion	Formula to Calculate Duration
Year, Month, Day		(Run-in Day 1 – DXDT + 1)/365.25
Year, Month	Day	[Year(Run-in Day 1)-Year(DXDT)]+ [Month(Run-in Day 1)-Month(DXDT)]/12 *if duration equals 0, add 1 month or 1/12 years (to avoid a disease duration of 0)
Year	Month, Day	[Year(Run-in Day 1)-Year(DXDT)] *if duration equals 0, add 1 month or 1/12 years (to avoid a disease duration of 0)

Time to Disease-Worsening

Time to Disease-Worsening = DW Date – Study Day 1 + 1

The subjects without Disease-Worsening will be censored at their last SDAI assessment date.

Only time to subject's *first* instance of disease-worsening will be evaluated.

Time-to-Event (for Rescue Analysis Set)

Time-to-Event = Earliest Date of Achievement of Event of Interest During the Rescue Therapy Period – Rescue Date + 1

For example, for subjects who recapture SDAI remission:
Time-to-Recapture SDAI remission = Earliest Date of Achievement of Observed SDAI remission During the Rescue Therapy Period – Rescue Date + 1

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The subjects who do not experience the event of interest will be censored at their last SDAI assessment date.

Only time to subject's *first* instance of each event of interest will be evaluated.

Time-to-Event (for Disease-Worsening Analysis Set)

Time-to-Event = Earliest Date of Achievement of Event of Interest After Disease-Worsening – DW Date + 1

For example, for subjects who recapture SDAI remission:
Time-to-Recapture SDAI remission = Earliest Date of Achievement of Observed SDAI remission After Disease-Worsening – DW Date + 1

The subjects who do not experience the event of interest will be censored at their last SDAI assessment date.

Only time to subject's *first* instance of each event of interest will be evaluated.

6.5 Study Endpoints

Patient Global Assessment of Joint Pain (PtGAJP)

An assessment of the severity of the subject's joint pain (0=no pain at all, 100=worst pain imaginable) completed by the patient using a visual analog scale (VAS) in mm.

Patient Global Assessment of Disease Activity (PtGA)

A global assessment of the subject's arthritis (0=no arthritis activity at all, 100=worst arthritis activity imaginable) completed by the patient using a visual analog scale (VAS).

Physician Global Assessment of Disease Activity (PhGA)

A global assessment of the subject's arthritis (0=no activity at all, 100=worst activity imaginable) completed by the physician using a visual analog scale (VAS).

Swollen Joint Count

A score that assesses the presence or absence of swelling in 66 joints. There are also a 28-joint Swollen Joint Count and a 28-joint Plus Feet and Ankles Swollen Joint Count. Details of the scoring algorithm are described in Appendix A.

Tender Joint Count

A score that assesses the presence or absence of tenderness in 68 joints. There are also a 28-joint Tender Joint Count and a 28-joint Plus Feet and Ankles Tender Joint Count. Details of the scoring algorithm are described in Appendix A.

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Simplified Disease Activity Index (SDAI)

A composite score that is based on the number of tender and swollen joints using a 28-joint count, PhGA (0-10 visual analog scale), PtGA (0-10 visual analog scale), and CRP in mg/dL. A higher score represents worse disease.

Details of the scoring algorithm are described in Appendix A.

SDAI Remission at Analysis Visit *k*

For Analysis Visits other than Week 48, SDAI Remission at a given Visit will be derived using the same approach as in Section 6.2, replacing Week 48 with the Analysis Visit Week *k*, and replacing "subject did not fulfill the definition of disease-worsening during the study" with "subject did not *previously* fulfill the definition of disease-worsening". Specifically,

- SDAI_remission_maintenance (<= 3.3) at Week *k* = 1,
  if SDAI ≤ 3.3 at Week k AND subject did not previously fulfill the definition of disease-worsening;
- SDAI_remission_maintenance (<= 3.3) at Week *k* = missing,
  if subject has no Week k SDAI value AND subject did not previously fulfill the definition of disease-worsening;
- SDAI_remission_maintenance (<= 3.3) at Week *k* = 0,
  otherwise.

Observed SDAI Remission at Analysis Visit *k*

- Observed_SDAI_Remission at Analysis Visit *k* =1,
  if SDAI ≤ 3.3 at Analysis Visit *k*;
- Observed_SDAI_remission (<= 3.3) at Analysis Visit *k* = missing,
  if subject has no SDAI value at Analysis Visit *k*;
- Observed_SDAI_remission (<= 3.3) at Analysis Visit *k* = 0,
  if SDAI > 3.3 at Analysis Visit *k*.

Observed SDAI Remission at DW Visit (or Rescue Visit) *k*

- Observed_SDAI_Remission at DW Visit (or Rescue Visit) *k* = 1,
  if SDAI ≤ 3.3 at DW Visit *k*;
- Observed_SDAI_remission (<= 3.3) at DW Visit (or Rescue Visit) *k* = missing,
  if subject has no SDAI value at DW Visit *k*;
- Observed_SDAI_remission (<= 3.3) at DW Visit (or Rescue Visit) *k* = 0,
  if SDAI > 3.3 at DW Visit *k*.

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Disease Activity

For a specific timepoint, subjects are classified as having

- SDAI Low Disease Activity (LDA): 3.3 < SDAI ≤ 11
- SDAI Moderate Disease Activity (MDA): 11 < SDAI ≤ 26
- SDAI High Disease Activity (HDA): SDAI > 26

Disease-Worsening

During the double-blind treatment period, disease-worsening for the study is defined as:

- SDAI > 3.3 and ≤ 11 on two consecutive visits at least two weeks apart OR
- SDAI > 3.3 and ≤ 11 on three or more separate visits OR
- SDAI > 11 at anytime

Disease-Worsening may be assessed at a regularly scheduled visit or at an unscheduled Disease Assessment visit. Subjects will remain on study and complete all study visits.

Disease Activity Score using the erythrocyte sedimentation rate formula (DAS28-ESR)

A modified composite index that was designed to measure disease activity in subjects using the number of tender and swollen joints based upon a 28-joint count, ESR in mm/hr, and a 100 mm visual analog scale measuring the subject's general health. A higher score represents worse disease.

Details of the scoring algorithm are described in Appendix A.

Disease Activity Score using the C-reactive protein formula (DAS28-CRP)

A composite index that was designed to measure disease activity in subjects using the number of tender and swollen joints based upon a 28-joint count, CRP in mg/L, and a 100 mm visual analog scale measuring the subject's general health. A higher score represents worse disease.

Details of the scoring algorithm are described in Appendix A.

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DAS28-ESR remission

Subjects are classified as achieving DAS28-ESR remission at a specific timepoint if their DAS28-ESR < 2.6 at that timepoint. Specifically, let DAS28ESR_remission be defined as follows:

- DAS28ESR_remission (< 2.6) = 1,
  if DAS28-ESR < 2.6;
- DAS28ESR_remission (< 2.6) = missing,
  if subject has no DAS28-ESR value;
- DAS28ESR_remission (<2.6) = 0,
  otherwise.

DAS28-ESR LDA

Subjects are classified as achieving DAS28-ESR LDA at a specific timepoint if their DAS28-ESR >= 2.6 and < 3.2 at that timepoint. Specifically, let DAS28ESR_LDA be defined as follows:

- DAS28ESR_LDA = 1,
  if DAS28-ESR >= 2.6 and < 3.2;
- DAS28ESR_LDA = missing,
  if subject has no DAS28-ESR value;
- DAS28ESR_LDA = 0,
  otherwise.

DAS28-CRP remission

Subjects are classified as achieving DAS28-CRP remission at a specific timepoint if their DAS28-CRP < 2.6 at that timepoint. Specifically, let DAS28CRP_remission be defined as follows:

- DAS28CRP_remission (< 2.6) = 1,
  if DAS28-CRP < 2.6;
- DAS28CRP_remission (< 2.6) = missing,
  if subject has no DAS28-CRP value;
- DAS28CRP_remission (<2.6) = 0,
  otherwise.

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DAS28-CRP LDA

Subjects are classified as achieving DAS28-CRP LDA at a specific timepoint if their DAS28-CRP >= 2.6 and < 3.2 at that timepoint. Specifically, let DAS28CRP_LDA be defined as follows:

- DAS28CRP_LDA = 1,
  if DAS28-CRP >= 2.6 and < 3.2;
- DAS28CRP_LDA = missing,
  if subject has no DAS28-CRP value;
- DAS28CRP_LDA = 0,
  otherwise.

Clinical Disease Activity Index (CDAI)

A composite score that is based on the number of tender and swollen joints using a 28-joint count, PhGA (0-10 visual analog scale), and PtGA (0-10 visual analog scale). A higher score represents worse disease.

Details of the scoring algorithm are described in Appendix A.

Boolean remission status (28-joint count)

A subject achieves Boolean remission (28-joint count) if all of the following criteria are met:

- 28-joint tender joint count ≤ 1,
- 28-joint swollen joint count ≤ 1,
- CRP (mg/dL) ≤ 1, and
- patient global assessment ≤ 1 (on a 0-10 scale).

Specifically, let Boolean_28 be defined as follows:

- Boolean_28 = 1,
  if a subject fulfills the definition of Boolean remission (28-joint count);
- Boolean_28 = missing,
  if any components of the Boolean remission definition are missing;
- Boolean_28 = 0,
  otherwise.

Boolean remission (28 joints plus feet/ankles)

A subject achieves Boolean remission (28-joint count plus feet/ankles) if all of the following criteria are met:

- 28-joint plus feet and ankles tender joint count ≤ 1,
- 28-joint plus feet and ankles swollen joint count ≤ 1,

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- CRP (mg/dL) ≤ 1, and
- patient global assessment ≤ 1 (on a 0-10 scale).

Boolean remission (66/68 joint count)

A subject achieves Boolean remission (66/68-joint count) if all of the following criteria are met:

- 68-joint tender joint count ≤ 1,
- 66-joint swollen joint count ≤ 1,
- CRP (mg/dL) ≤ 1, and
- patient global assessment ≤ 1 (on a 0-10 scale).

Let Boolean_68 be defined in a manner similar to that of Boolean_28.

C-Reactive Protein (CRP)

A specific measure of inflammatory activity measured in mg/dL.

Disability Index of the Health Assessment Questionnaire (HAQ-DI)

The HAQ-DI assesses the subject's physical function or disability. The questionnaire asks about the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities). Responses in each functional area are scored from 0 indicating no difficulty to 3 indicating inability to perform a task in that area.

Details of the scoring algorithm are described in Appendix D.

Medical Outcomes Health Survey Short Form 36 Items Version 2 (SF-36 v2)

The SF-36 v2 is a 36-item instrument that measures general health status and will be scored using the QualityMetric Health Outcomes Scoring Software. It includes 8 multi-item scales, each of which assesses one of the following 8 health concepts over the previous month: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. SF-36 v2 includes the Physical Component Summary and Mental Component Summary measures. A higher score represents less disability.

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7. Analysis Subsets

7.1 Primary Analysis Set

The Primary Analysis Set (PAS) will include all randomized subjects. The analysis will be conducted according to the original randomization assignment regardless of the actual treatment received during the study (as per intent-to-treat principle). All the primary, secondary, and exploratory efficacy endpoints will be evaluated on the Primary Analysis Set, unless otherwise specified.

7.2 Full Analysis Set

The Full Analysis Set (FAS) includes all the subjects who have enrolled in the run-in period.

7.3 Disease-Worsening Analysis Set

The Disease-Worsening Analysis Set includes randomized subjects who meet the definition of Disease-Worsening at any point after randomization.

7.4 Rescue Analysis Set

This includes randomized subjects who meet the definition of Disease-Worsening and have received both at least one dose of active rescue therapy etanercept and at least one dose active rescue therapy methoxrexate as recorded in the eCRF.

7.5 Run-In Failure Analysis Set

The Run-In Failure Analysis Set includes all enrolled subjects who do not complete run-in due to failing to meet Part 2 Inclusion Criteria or due to fulfilling Part 2 Exclusion Criteria per Sections 4.2.1 and 4.2.2, respectively, in the protocol.

7.6 Run-In Safety Analysis Set

The Run-In Safety Analysis Set includes all enrolled subjects who received at least one dose of open label run-in etanercept and/or at least one dose of open label run-in methotrexate (as specified in the eCRF).

7.7 Post-Run-In Safety Analysis Set

The Post-Run-In Safety Analysis Set includes all subjects who received at least one dose of any investigational product after randomization.

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8. Subgroup Analyses

Subgroup analyses, which would be considered exploratory, may be performed if an examination of the covariates in Section 4.2 suggests that any treatment difference for the primary and secondary endpoints depends on any baseline covariates.

9. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

10. Data Screening and Acceptance

10.1 General Principles

The objective of the data screening is to assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses.

10.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses.

10.3 Handling of Missing and Incomplete Data

Subjects may be missing specific data points for a variety of reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. The general procedures outlined below describe what will be done when a data point is missing.

10.3.1 Missing Baseline Evaluation

Missing baseline evaluations will not be imputed.

10.3.2 Missing Post-Baseline Evaluation

See Section 11.5.

10.3.3 Missing Components of Composite Endpoints

Missing components of composite endpoints will not be imputed.

10.3.4 Missing and Incomplete Dates

For any listings, missing or incomplete dates will be listed as is. No imputation will be done on incomplete stop date of an adverse event unless specified otherwise.

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In the case where the start or stop date of an event or medication is missing or incomplete, the following rule will be applied:

	Missing	Imputation	Exception
Start date (AE, concomitant medication)	Day	01	Default to Study Day 1 if an event starts the same year and month as Study Day 1 and Stop date is after Study Day 1
	Day/Month	01JAN	Default to Study Day 1 if an event started the same year as Day1 and Stop date is after Study Day 1
	Day/Month/Year	No imputation	
Stop date (concomitant medication)	Day	Last day of the month	Default to the End of Study Date or the primary analysis cut-off date for ongoing subjects if the concomitant medication stopped the same year and month as the End of Study Date or primary analysis cut-off date
	Day/Month	31DEC	Default to the End of Study Date or the primary analysis cut-off date for ongoing subjects if the concomitant medication stopped the same year as the End of Study Date or primary analysis cut-off date
	Day/Month/Year	No imputation	

In case a subject dies during the study, impute the missing AE and CM end dates using the subject's date of death.

10.4 Detection of Bias

Subject selection and treatment group allocation were performed in a manner minimizing potential bias. Assessing endpoints and handling withdrawals were done without knowledge of treatment group. Other factors that may introduce bias include:

- Important protocol deviations likely to impact the analysis or interpretation of results;
- Breaking blind before database lock and formal unblinding;
- IP dosing non-compliance;
- Reasons for early withdrawal from treatment or from study.

The incidence of these factors will be assessed. Important protocol deviations likely to impact the analysis and interpretation of results will be listed and/or tabulated in the

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Clinical Study Report (CSR). If a significant number of major protocol deviations are observed, an additional sensitivity analysis may be performed on the efficacy data excluding subjects with major protocol deviations.

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR, including the timing and reason for unblinding. The impact of such unblinding on the results will be assessed.

Tabulations of important protocol deviations (IPDs) related to IP dosing non-compliance by treatment group will be provided.

Reasons for early withdrawals from treatment and from study will be summarized. If a significant pattern is observed, additional sensitivity analyses may be performed on efficacy data adjusting for reasons for early withdrawal.

10.5 Outliers

Descriptive summaries will be examined to identify unexpected values. Outliers due to data entry errors will be corrected by the study team before data lock. Outliers that are not due to data entry will be included in the analysis. If it is deemed necessary after the team reviews the output from the planned analyses after data lock, a post-hoc sensitivity analysis excluding subjects with outliers may be performed.

10.6 Distributional Characteristics

The Chi-squared test with contuinity correction allows for analysis of categorical endpoints even when some or all contingency cells have less than 5 subjects. The t-test used for continuous endpoints assumes that the means of two independent populations follow normal distributions. With all three treatment arms having more than 30 subjects, this assumption is fair per the central limit theorem. When standard deviations are statistically significantly different as identified by an F-test with p-value less than or equal to 0.05, the Satterthwaite approximation is used.

10.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs to produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example SAS System version 9.4 or later.

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11. Statistical Methods of Analysis

11.1 General Considerations

The primary analysis will be performed after all subjects have completed the Week 48/ET assessment and the 30-day safety follow-up period and all data have been finalized.

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively by randomized treatment group.

For categorical endpoints, descriptive statistics will report frequency and percentage. For continuous endpoints, descriptive statistics will include the number of observations, mean, standard error or standard deviation, median, minimum, and maximum.

The statistical test for the primary efficacy endpoint will have a significance level of 0.05. Non-responder imputation will be employed for the missing values of the primary endpoint.

For continuous secondary endpoints, t-tests will compare 1) etanercept monotherapy vs methotrexate monotherapy, and 2) etanercept and methotrexate combination therapy vs methotrexate monotherapy. No multiplicity adjustments will be made.

For binary secondary endpoints, Chi-squared tests with continuity correction will compare 1) etanercept monotherapy vs methotrexate monotherapy, and 2) etanercept and methotrexate combination therapy vs methotrexate monotherapy. No multiplicity adjustments will be made.

For time-to-event secondary endpoints, the number of subjects achieving the event and the number of subjects censored as defined in Section 6.4 will be provided. Kaplan-Meier (KM) curves, estimates, and 95% CIs will be provided by treatment group. A two-sided log-rank test incorporating treatment group will evaluate 1) etanercept monotherapy vs methotrexate monotherapy, and 2) etanercept and methotrexate combination therapy vs methotrexate monotherapy. Median time-to-event will be provided for each of the treatment arms.

11.2 Subject Accountability

Analysis Set Disposition

The number (percent) of subjects in each of the Analysis Subsets detailed in Section 7 will be summarized.

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During the Run-In Period

The subject disposition for the run-in period will be summarized descriptively for all subjects enrolled in the run-in period, and will include the number (percent) of subjects who

- are enrolled
- are dosed with open-label etanercept and methotrexate
- complete the 24-week open-label run-in period
- discontinued prematurely and their reasons for discontinuation.

After Randomization

The subject disposition will be summarized descriptively for all randomized subjects by randomized treatment group, and will include the number (percent) of subjects who

- are randomized
- are dosed with investigational product
- complete investigational product
- complete the study
- discontinued prematurely and their reasons for discontinuation.

11.3 Important Protocol Deviations

Important Protocol Deviation (IPD) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study.

11.4 Demographic and Baseline Characteristics

Subject demographic and disease characteristics at enrollment will be summarized descriptively for all subjects in the run-in period.

Subject demographic and baseline disease characteristics at randomization will be summarized descriptively for all subjects in the double-blind treatment period by randomized treatment group.

11.5 Efficacy Analyses

All efficacy analyses will be conducted using the PAS, unless otherwise specified.

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11.5.1 Primary Efficacy Endpoint

11.5.1.1 Primary Analysis of Primary Estimand

The primary analysis of the primary estimand as defined in Section 4.1.1 will be performed using the PAS. The primary endpoint is defined in Section 6.2. When an endpoint cannot be derived due to missing SDAI assessment, a subject will be assumed to have not achieved the outcome, that is, Non-Responder Imputation (NRI).

The treatment effect for SDAI remission at Week 48 will be tested using a chi-squared test at significance level of 0.05. Difference in proportions and a 95% CI will be provided comparing etanercept monotherapy with methotrexate monotherapy.

11.5.1.2 Sensitivity/Exploratory Analyses of Primary Estimand

SDAI remission at Week 48 will be tested using a chi-squared test at significance level of 0.05 using observed cases only.

In addition, multiple-imputation will be implemented to impute SDAI values when missing for randomized subjects. SDAI values after rescue are also set to missing and imputed in this analysis. The composite SDAI values will be imputed rather than its components. A chi-squared test will compare the resulting values under the etanercept monotherapy arm and the methotrexate monotherapy arm.

11.5.2 Secondary Efficacy Endpoint(s)

For secondary endpoints, unless otherwise noted, the Chi-squared test will be used for categorical endpoints, the t-test for continuous endpoints, and Log-rank test for time-to-event endpoints. In comparison of means, the Satterthwaite t-test may be used when variances between the two groups are different. These tests will evaluate etanercept monotherapy vs methotrexate monotherapy and etanercept and methotrexate combination therapy vs methotrexate monotherapy.

Proportion of subjects achieving SDAI remission at week 48 for the etanercept plus methotrexate treatment arm will be compared to that of the methotrexate monotherapy arm using the chi-squared test and will be presented with nominal p-values only (eg, no adjustment for multiplicity will be done). To parallel the the primary analysis of the primary estimand, the proportion of subjects in the etanercept plus methotrexate treatment arm and the methotrexate monotherapy arm achieving SDAI remission at week 48 will be evaluated using non-responder imputation, as observed data, and multiple imputation.

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The proportion of subjects achieving SDAI remission (≤ 3.3), SDAI continuous score, and SDAI change from baseline at all visits will be summarized by treatment group using the PAS. Subjects with missing SDAI value at week 48 and subjects who disease-worsened are considered non-responders.

DAS28-ESR, DAS28-CRP, and CDAI, and their changes from baseline will also be summarized by visit for each treatment group using the PAS. Missing data will not be imputed for these continuous endpoints. T-tests will compare means between etanercept vs methotrexate and etanercept + methotrexate vs methotrexate.

Proportion of subjects achieving Boolean remission will be tabulated by visit for each treatment group using the PAS. Boolean remission using 28-joint-count, 28-joint-count + feet and ankles, and 66/68 joint count will be assessed.

Proportion of subjects with Disease-Worsening and time-to-disease-worsening will be evaluated by treatment group for the PAS. Time-to-disease-worsening wil be evaluated using Kaplan-Meier (KM) curves, estimates, and 95% CIs by treatment group. For subjects with more than one DW Date, the first DW date will be used. Subjects who do not experience disease-worsening will be censored at last SDAI assessment date. In addition, a two-sided log-rank test will evaluate the etanercept monotherapy vs methotrexate monotherapy arms, and the etanercept plus methotrerxate combination vs methotrexate monotherapy arms.

Time-to-recapture observed SDAI remission from Rescue Date will be evaluated for the Rescue Analysis Set using Kaplan-Meier (KM) curves, estimates, and 95% confidence intervals by treatment group; subjects who do not recapture SDAI remission will be censored at their last SDAI assessment date. This analysis will be repeated for Time-to-recapture SDAI remission from Disease-Worsening Date for the Disease-Worsening Analysis Set. For subjects with more than one recapture of observed SDAI remission, the first recapture date will be used. Additionally, the proportion of subjects who recapture observed SDAI remission at week 48 will be summarized for both the Rescue Analysis Set and the Disease-Worsening Analysis Set.

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Table 1. Primary and Secondary Endpoints Summary Table

Endpoint	Primary Analysis Method	Sensitivity/Exploratory Analysis
Primary Endpoint		
SDAI remission (<= 3.3) at week 48 as defined by SDAI_remission_maintenance detailed in Section 6.2	Count (percentage) of subjects achieving SDAI remission as defined by SDAI_remission_maintenance detailed in Section 6.2 at Week 48 for the PAS. A chi-squared test comparing etanercept monotherapy and methotrexate monotherapy using the PAS. Subjects who have a missing SDAI_remission value will be considered as non-responders.	Observed_SDAI_remission using as observed approach as detailed in Section 6.5 (missing data will be excluded). Multiple imputation method: impute SDAI values when missing and after rescue for randomized subjects. The composite SDAI values will be imputed rather than its components.
Secondary Endpoints		
SDAI remission (<= 3.3) at week 48	Count (percentage) of subjects achieving SDAI remission as defined by SDAI_remission_maintenance detailed in Section 6.2 at Week 48 for the PAS. A chi-squared test comparing etanercept plus methotrexate combination arm and methotrexate monotherapy using the PAS. Subjects who have a missing SDAI_remission value will be considered as non-responders. Nominal p-values will be provided.	Observed_SDAI_remission using as observed approach as detailed in Section 6.5 (missing data will be excluded). Multiple imputation method: impute SDAI values when missing and after rescue for randomized subjects. The composite SDAI values will be imputed rather than its components.
SDAI score and change from baseline at all measured timepoints	Summary statistics for SDAI score and change from baseline at each Analysis Visit for the PAS. T-test comparing etanercept monotherapy vs methotrexate monotherapy T-test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
DAS28-ESR and change from baseline at all measured timepoints	Similar analysis as for SDAI score and change from baseline at all measured timepoints	

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Table 1. Primary and Secondary Endpoints Summary Table

Endpoint	Primary Analysis Method	Sensitivity/Exploratory Analysis
Secondary Endpoints (Continued)		
DAS28-CRP and change from baseline at all measured timepoints	Similar analysis as for SDAI score and change from baseline at all measured timepoints	
CDAI and change from baseline at all measured timepoints	Similar analysis as for SDAI score and change from baseline at all measured timepoints	
SDAI remission (≤ 3.3) at all measured timepoints	Count (percentage) of subjects achieving SDAI remission as defined by SDAI_remission_maintenance detailed in Section 6.5 for the PAS. Chi-squared test comparing etanercept monotherapy vs methotrexate monotherapy Chi-squared test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
Boolean remission at all measured timepoints	Observed count (percentage) of subjects achieving Boolean remission at each Analysis Visit for the PAS. Boolean remission using 28-joint-count, 28-joint-count + feet and ankles, and 66/68 joint count will be assessed. Chi-squared test comparing etanercept monotherapy vs methotrexate monotherapy Chi-squared test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
Disease-Worsening defined as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization	Observed count (percentage) of subjects fulfilling Disease-Worsening criteria at each Analysis Visit for the PAS.	

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Table 1. Primary and Secondary Endpoints Summary Table

Endpoint	Primary Analysis Method	Sensitivity/Exploratory Analysis
Secondary Endpoints (Continued)		
Time to Disease-Worsening as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization	Kaplan-Meier curves, estimates, and 95% CIs assessing Time to Disease-Worsening by treatment group for the PAS. Subjects with more than one DW Date will be analyzed using the first DW Date. Subjects who do not experience disease-worsening will be censored at last SDAI assessment date. Log-rank test comparing etanercept monotherapy versus methotrexate monotherapy. Log-rank test comparing etanercept and methotrexate combination therapy versus methotrexate monotherapy.	
Time to recapture observed SDAI remission after starting rescue treatment	Kaplan-Meier curves assessing Time to recapture observed SDAI remission from Rescue Date for the Rescue Analysis Set. Subjects with more than one recapture of SDAI remission will be analyzed using their first recapture date. Subjects who do not recapture SDAI remission are censored at their last SDAI assessment date. Log-rank test comparing etanercept monotherapy versus methotrexate monotherapy. Log-rank test comparing etanercept and methotrexate combination therapy versus methotrexate monotherapy.	Similar analysis as the Primary Analysis Method but using the Disease-Worsening Analysis Set, looking at time to recapture SDAI remission from DW Date.
Observed SDAI remission at Week 48	Observed count (percentage) of subjects achieving SDAI remission as defined by Observed_SDAI_remission as detailed in Section 6.5 at Week 48 for the Rescue Analysis Set.	Similar analysis as the Primary Analysis Method but using the Disease-Worsening Analysis Set.

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11.5.3 Exploratory Endpoints

For the exploratory endpoints listed below, unless otherwise noted, the Chi-squared test will be used for categorical endpoints, the t-test for continuous endpoints, and Log-rank test for time-to-event endpoints. In comparison of means, the Satterthwaite t-test may be used when variances between the two groups are different. These tests will evaluate etanercept monotherapy vs methotrexate monotherapy and etanercept and methotrexate combination therapy vs methotrexate monotherapy.

Components of SDAI at all measured timepoints

The five components of SDAI will be summarized as observed with descriptive statistics by treatment arm for the PAS.

HAQ-DI at all measured timepoints

HAQ-DI will be summarized with descriptive statistics as observed by treatment arm for the PAS.

SF-36 domains, physical component summary, and mental component summary at all measured timepoints

SF-36 domains will be summarized with descriptive statistics as observed by treatment arm for the PAS.

SDAI score at run-in visits

SDAI score at Run-In Visit 1, Run-In Visit 2, and Run-In Visit 3 will be summarized with descriptive statistics as observed for the FAS. No statistical tests will be performed.

Time to run-in failure

Kaplan-Meier curves will assess time to run-in failure for the FAS. Subjects who do not experience run-in failure are censored at their end of run-in date, where reason is not stated as protocol specified criteria or ineligibility determined due to failing to meet Part 2 Inclusion Criteria (116) or due to fulfilling Part 2 Exclusion Criteria (228) per Section 4.2.1 and 4.2.2, respectively, in the protocol.

Time to Randomization Failure

Kaplan-Meier curves will assess time to randomization failure for the FAS. Subjects who are randomized are censored at their end of run-in date.

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Patient Global Assessment of Joint Pain at all measured timepoints

Patient Global Assessment of Joint Pain will be summarized with descriptive statistics as observed by treatment arm for the PAS.

Observed SDAI remission at all measured timepoints

Observed SDAI remission at each analysis visit will be summarized for the Primary Analysis Set, where observed SDAI remission is defined in Section 6.5.

Observed SDAI remission at visits following rescue

Observed SDAI remission by Rescue_Visit and by DW_Visit will be summarized for the Rescue Analysis Set and the Disease-Worsening Analysis Set, respectively, where Rescue_Visit and DW_Visit are defined in Appendix A.

SDAI LDA, DAS28-ESR LDA at all measured timepoints, SDAI LDA, DAS28-ESR LDA at visits following rescue

The observed proportion of subjects achieving SDAI LDA and DAS28-ESR LDA will be tabulated at each Analysis Visit for the PAS. A similar analysis will be done for the Rescue Analysis Set and the Disease-Worsening Analysis Set by Rescue_Visit and DW_visit, respectively.

DAS28-ESR remission and DAS28-CRP remission at all measured timepoints, DAS28-ESR remission and DAS28-CRP remission at visits following rescue

The observed proportion of subjects achieving DAS28-ESR remission and DAS28-CRP remission will be tabulated at each Analysis Visit for the PAS. A similar analysis will be done for the Recue Analysis Set and the Disease-Worsening Analysis Set by Rescue_Visit and DW_visit, respectively.

Reason for Disease-Worsening (DW)

Reason for Disease-Worsening (DW) will be summarized by Analysis Visit for the Disease-Worsening Analysis Set. If a subject's visit results in fulfillment of more than one of these criteria, only a single reason for disease-worsening will be counted, with priority given in the following order:

Priority 1: SDAI > 11
Priority 2: SDAI > 3.3 and ≤ 11 on two consecutive visits at least two weeks apart

Priority 3: SDAI > 3.3 and ≤ 11 on three or more separate visits
No statistical tests will be performed.

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SDAI score at Disease-Worsening and at visits following rescue; Change in SDAI from Disease-Worsening Date at visits following rescue

SDAI score at Disease-Worsening Date and by DW_Visit will be summarized with descriptive statistics by treatment arm for the Disease-Worsening Analysis Set. A similar analysis will be done for Change in SDAI from Disease-Worsening Date by DW_Visit. Similar analyses will be performed for the Rescue Analysis Set by Rescue Visit. The latest SDAI score on or prior to a subject's rescue date is used as their Rescue Baseline SDAI value.

Disease Activity at Disease-Worsening

The magnitude of disease activity as measured by the SDAI score at Disease-Worsening Date will be summarized per the definition in Section 6.5 for the Disease-Worsening Analysis Set. Chi-squared tests will evaluate etanercept monotherapy vs methotrexate monotherapy and etanercept and methotrexate combination therapy vs methotrexate monotherapy.

Time to SDAI LDA, Time to DAS28-ESR Remission, Time to DAS28-CRP Remission

Time to SDAI LDA, time to DAS28-ESR remission, time to DAS28-CRP remission will be evaluated with Kaplan Meier curves and Log-rank tests for the Rescue Analysis Set and the Disease-Worsening Analysis Set.

Table 2. Exploratory Endpoints Summary Table

Endpoint	Primary Summary and Analysis Method	Exploratory Analysis
Exploratory Endpoints		
Components of SDAI at all measured timepoints	Summary statistics for the components of SDAI at each Analysis Visit for the PAS. T-test comparing etanercept monotherapy vs methotrexate monotherapy T-test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
HAQ-DI at all measured timepoints	Summary statistics for the components of HAQ-DI at each Analysis Visit for the PAS. T-test comparing etanercept monotherapy vs methotrexate monotherapy T-test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	

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Table 2. Exploratory Endpoints Summary Table

Endpoint	Primary Summary and Analysis Method	Exploratory Analysis
Exploratory Endpoints(Continued)		
SF-36 domains, physical component summary, and mental component summary at all measured timepoints	Summary statistics for SF-36 domains at each Analysis Visit for the PAS. T-test comparing etanercept monotherapy vs methotrexate monotherapy T-test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
SDAI score at run-in visits	Summary statistics for SDAI for the FAS. A scatter plot for each subject's SDAI score at Run-in Visits 1, 2, and 3.	
Time to run-in failure	Kaplan-Meier curves assessing Time to run-in failure for the FAS. Subjects who do not experience run-in failure are censored at their End of Run-In date.	
Time to Randomization Failure	Kaplan-Meier curves assessing Time to end of run-in for the FAS. Subjects who are randomized are censored at End of Run-In Date.	
Observed SDAI Remission (<= 3.3) at all timepoints	Similar analysis as SDAI remission at all measured timepoints for the PAS. See definitinition of Observed SDAI Remission in Section 6.5.	
Patient Global Assessment of Joint Pain at all timepoints	Summary statistics for PtGAJP at each Analysis Visit for the PAS. T-test comparing etanercept monotherapy vs methotrexate monotherapy T-test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
SDAI LDA at all timepoints	Similar analysis as SDAI remission at all measured timepoints for the PAS.	
DAS28-ESR remission at all timepoints	Similar analysis as SDAI remission at all measured timepoints for the PAS.	
DAS28-ESR LDA at all timepoints	Similar analysis as SDAI remission at all measured timepoints for the PAS.	
DAS28-CRP remission at all timepoints	Similar analysis as SDAI remission at all measured timepoints for the PAS.	
Reason for Disease-Worsening	Observed count (percentage) of reason for disease-worsening at each Analysis Visit for the Disease-Worsening Analysis Set.	

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Table 2. Exploratory Endpoints Summary Table

Endpoint	Primary Summary and Analysis Method	Exploratory Analysis
Exploratory Endpoints(Continued)		
SDAI score at Disease-Worsening	Summary statistics for the SDAI score at DW Date for the Disease-Worsening Analysis Set. T-test comparing etanercept monotherapy vs methotrexate monotherapy T-test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
Disease Activity at Disease-Worsening	Observed count (percentage) of subjects in each Disease Activity category (Low, Moderate, High) at DW Date for the Disease-Worsening Analysis Set. Chi-squared test comparing etanercept monotherapy vs methotrexate monotherapy Chi-squared test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	
Observed SDAI remission at visits following rescue	Observed count (percentage) of subjects achieving observed SDAI remission by Rescue_Visit for the Rescue Analysis Set. Chi-squared test comparing etanercept monotherapy vs methotrexate monotherapy Chi-squared test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set and DW_Visit.
SDAI LDA at visits following rescue	Similar analysis as for SDAI remission at visits following rescue	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set.
Time to SDAI LDA	Similar analysis as Time to recapture SDAI remission after starting rescue treatment.	Similar analysis as the Primary Analysis Method but using the Disease-Worsening Analysis Set, looking at time to SDAI LDA from DW Date.

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Table 2. Exploratory Endpoints Summary Table

Endpoint	Primary Summary and Analysis Method	Exploratory Analysis
Exploratory Endpoints(Continued)		
SDAI score on Disease-Worsening Date and at visits following rescue	Summary statistics for SDAI by Rescue_Visit for the Rescue Analysis Set. T-test comparing etanercept monotherapy vs methotrexate monotherapy T-test comparing etanercept and methotrexate combination therapy vs methotrexate monotherapy	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set and DW_Visit.
Change in SDAI from Disease-Worsening Date and at visits following rescue	Similar anlaysis as for SDAI score on Disease-Worsening Date and at visits following rescue	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set and DW_Visit.
DAS28-ESR remission at visits following rescue	Similar analysis as for SDAI remission at visits following rescue	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set and DW_visit.
Time to DAS28-ESR remission	Kaplan-Meier curves assessing Time to DAS28-ESR remission from Rescue Date for the Rescue Analysis Set. Subjects with more than one event of DAS28-ESR remission will be analyzed using their first event date. Subjects who do not have DAS28-ESR remission are censored at their last SDAI assessment date. Log-rank test comparing etanercept monotherapy versus methotrexate monotherapy.	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set, from DW Date.
DAS28-ESR LDA(yes/no) at visits following rescue	Similar analysis as for SDAI remission at visits following rescue	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set and DW_Visit.
DAS28-CRP remission (yes/no) at visits following rescue	Similar analysis as for SDAI remission at visits following rescue	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set and DW_Visit.
Time to DAS28-CRP remission	Similar analysis as Time to DAS28-ESR remission	Similar to the Primary Analysis Method but using the Disease-Worsening Analysis Set, from DW Date.

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11.6 Safety Analyses

All safety analyses will be conducted using the Run-in Period Safety Analysis Set and the Post-Run-In Safety Analysis Set. Subjects will be analyzed according to the actual treatment received as defined in Section 6.3.

11.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. All adverse events occurring in the Run-In Period will be summarized for the Run-In Period Safety Analysis Set). All adverse events occurring during the double-blind treatment period and 30-day safety follow-up will be summarized for the Post-Run-In Safety Analysis Set. The subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, and fatal AEs.

11.6.2 Laboratory Test Results

Laboratory parameters with grade 3 toxicity or above may be descriptively summarized by study visit and actual treatment received during the study. Shift tables of the worst on-study laboratory toxicity based on the Common Toxicity Criteria (CTC) grade relative to baseline may be tabulated for analytes of interest (ie, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), hemoglobin, platelets, WBC, absolute neutrophil count, lymphocytes) by treatment group. Modifications to CTC version 4.0 used for this analysis are described in Appendix C. Subject listings of grades 3 and 4 laboratory values will be provided.

11.6.3 Vital Signs

Vital signs may be descriptively summarized in baseline disease summaries, if there are unexpected safety findings.

11.6.4 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to etanercept monotherapy, methotrexate monotherapy, and etanercept + methotrexate combination therapy, including number of doses, number of missed doses, and duration of dosing during the Run-in period. Descriptive statistics will be produced to describe the exposure to IP for each treatment group, including number of doses, number of missed doses, and duration of dosing.

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11.6.5 Exposure to Concomitant Medication

A summary of all concomitant medications reported may be provided by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary. Only concomitant medications with a partial or complete end date are tabulated.

12. Changes From Protocol-specified Analyses

Protocol Section 10.5.2 states “Furthermore, the randomized subjects who did not receive any dose of any of the investigational products will also be considered non-responders in the primary analysis.”

However, although subjects may not receive any dose of IP, they may still have an observed SDAI value at week 48. Any randomized subjects with non-missing SDAI at week 48 will be assessed according to their original randomized treatment arm with their observed values.

Changes to Planned Covariates

We modify the listed continuous covariates by dichotomizing them at clinically meaningful cutoffs to demonstrate their influence on the primary endpoint. The following dichotomizations are used:

Age (years): < 65 years, ≥ 65 years

Disease duration: <= median, > median; <= mean, > mean

Baseline methotrexate dose: <15 mg, ≥15 mg

> This dichotomous variable has been added to the pre-specified analysis because when a subject is taken off a biologic, we suspect that subjects on a higher dose of methotrexate at baseline would have a higher probability of SDAI remission than subjects on a lower dose of methotrexate at baseline. The threshold of <15 mg / ≥15 mg was selected based on the minimum and maximum methotrexate doses in this study, 10mg and 25mg, respectively.

Smoking: Never, former, current

> This categorical variable has been added to the pre-specified analysis due to recognition of association of poorer arthritis disease activity with smoking.

Maintenance of SDAI remission is the primary endpoint of interest; subgroup analyses shall not be performed on secondary endpoints.

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Changes to Analysis Sets

The protocol states that time to recapture SDAI remission and SDAI remission at week 48 will be evaluated for subjects that receive rescue treatment during the double-blind period. This led to the creation of the **Rescue Analysis Set** detailed in Section 7.4.

However, due to the possibility of subjects fulfilling the definition of Disease-Worsening but not receiving rescue therapy, we also added a **Disease-Worsening Analysis Set**, as detailed in Section 7.3.

A **Full Analysis Set** was also added to evaluate all subjects who enrolled.

The Safety Analysis Set defined in the protocol was re-named to **Post-Run-In Safety Analysis Set** for clarity, detailed in Section 7.7. For the separate evaluation of safety events during Run-In, the **Run-In Safety Analysis Set** detailed in Section 7.6 was also created.

Changes to Exploratory Endpoints

Biomarkers and Pharmacogenetic Parameters were listed in the protocol as exploratory endpoints. Samples were collected from this study for potential future analyses.

Exploratory endpoints not originally included in the protocol are detailed in Section 4.1.4. Their addition to the exploratory analysis is due to our interest in seeing a) the Disease Activity at disease-worsening; b) the degree of improvement after rescue, even if a subject does not recapture SDAI remission; c) the proportion of disease-worsening subjects who achieve SDAI remission at Week 48. Further analyses on additional endpoints may be performed later on an ad-hoc basis.

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13. Literature Citations / References

Mantel, N. (1963). Chi-square tests with one degree of freedom: Extensions of the Mantel-Haenszel procedure, *Journal of the American Statistical Association*, 58, 690-700.

Ratitch, B., Lipkovich, I., O'Kelly, M. (2013). *Combining Analysis Results from Multiply Imputed Categorical Data*, PharmaSUG 2013. https://www.pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP03.pdf

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Stokes M. E., Davis C. S., Koch G. G. (2000). *Categorical Data Analysis Using the SAS System*, Cary, NC: SAS Institute Inc. pp 75,128.

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14. Appendices

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Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Visit Windows for Selected Efficacy and Safety Evaluations

Per protocol, visits are to be performed within 7 days of the protocol-specified study day. To allow for variations in scheduling, the following visit windows will be applied to selected efficacy and safety evaluations (ie, vital signs, laboratory evaluations) to assign a most appropriate nominal visit for the analysis (ie, analysis visit). If more than one visit falls within the same defined window, the closest visit to the target day (ie, scheduled visit week x 7 + 1) will be considered for analysis. If two assessment dates are the same distance from the target day, then the latest visit will be considered for analysis. If more than one evaluation exists on the same date and time, the record with the lower accession number will be used.

Run-In Period Visits

Visit Week	Target Day	Window Definition	Interval (days)
Run-in 1	Run-in Day 1	Last evaluation prior to or on Run-In Study Day 1 and after Enrollment Date	43+
Run-in 2	Run-in Day 86	Run-in Day 44 to 125	82
Run-in 3	Run-in Day 162	Run-in Day > = 126	43

Double-Blind Treatment Period Analysis Visits

Visit Week	Target Day	Window Definition	Interval (days)
Baseline	Study Day 1	Last evaluation prior to or on Study Day 1 and after Run-in Visit 3*	N/A
Week 12	Study Day 85	Study Day 2 to 126	125
Week 24	Study Day 169	Study Day 127 to 210	84
Week 36	Study Day 253	Study Day 211 to 294	84
Week 48	Study Day 337	> =Study Day 295	N/A

* Hematology and chemistry profiles were not assessed on Day 1; their Run-in Visit 3 values will be used when reporting baseline.

Visit window for SF-36 and HAQ-DI

Visit Week	Target Day	Window Definition	Interval (days)
Baseline (Day1)	1	Last evaluation prior to or on study day 1 in DB	N/A
Week 24	169	Study Day 2 to 253	252
Week 48	337	> =Study Day 254	n/a

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Time After Disease-Worsening

Let $Visit_0$ = the Analysis Visit at which a subject fulfills disease-worsening criteria, where Analysis Visit is for SDAI score and is defined in the Double-Blind Treatment Period Analysis Visits Table above. $Visit_0$ will be summarized in tables as "Disease-Worsening Baseline".

Let $Visit_1$ represent the Analysis Visit on or after $Visit_0$.

Then DW_visit will be defined as follows:

- DW_visit = 12,
  If $Visit_1 - Visit_0$ = 0 or 12
- DW_visit = $Visit_1 - Visit_0$,
  Otherwise.

If a subject has multiple observations for the same DW_Visit, the latest observation will be used in the analysis.

Time After Rescue

"Rescue Baseline" is defined as the latest assessment on or before a subject's rescue date.

Let $Visit_0$ = the Analysis Visit at which a subject initiates rescue, where Analysis Visit is for SDAI score and is defined in the Double-Blind Treatment Period Analysis Visits Table above.

Let $Visit_1$ represent the Analysis Visit on or after $Visit_0$.

Then Rescue_visit will be defined as follows:

If subject has received rescue (Study Day Subject Received Rescue <= Study Day):

- Rescue_visit = 12,
  If $Visit_1 - Visit_0$ = 0 or 12
- Rescue_visit = $Visit_1 - Visit_0$,
  Otherwise.

If a subject has not yet received rescue at a specific visit, Rescue_visit missing.

If a subject has multiple observations for the same Rescue_Visit, the latest observation will be used in the analysis.

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Efficacy Endpoint Scoring Algorithms

Abbreviations:

TEN28	28-joint Tender Joint Count
SW28	28-Joint Tender Joint Count
PtGA	Patient Global Assessment
PhGA	Physician Global Assessment
ESR	Erythrocyte Sedimentation Rate

Simplified Disease Activity Index (SDAI)

The SDAI is a composite measure that sums the total number of tender and swollen 28-joint counts, the PtGA on a 0-10 scale, the PhGA on a 0-10 scale, and the CRP in mg/dL. PtGA and PhGA are collected in a 0-100 scale, so they will need to be divided by 10.

The SDAI is scored as follows:

TEN28 + SW28 + PtGA/10 + PhGA/10 + CRP (mg/dL)

Clinical Disease Activity Index (CDAI)

The CDAI is a further simplification of the SDAI that excludes the acute phase reactant. It sums the total number of tender and swollen 28-joint counts, the PtGA on a 0-10 scale and the PhGA on a 0-10 scale. PtGA and PhGA are collected in a 0-100 scale, so they will need to be divided by 10.

The CDAI is calculated using the following formula:

TEN28 + SW28 + PtGA/10 + PhGA/10

DAS28-CRP

A subject's DAS28-CRP score is calculated as follows:

DAS28-CRP = $0.56*\sqrt{TEN28} + 0.28*\sqrt{SJC28} + 0.36*\ln(CRP+1) + 0.014*PtGA + 0.96$,

where CRP is measured in mg/L.

DAS28-ESR

A subject's DAS28-ESR score is calculated as follows:

DAS28-ESR = $0.56*\sqrt{\ } TEN28 + 0.28*\sqrt{SJC28} + 0.70*\ln(ESR) + 0.014*PtGA$,

where ESR is measured in mm/hr.

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Swollen Joint Count

The swollen joint count is an assessment of the swelling of joints using 0-1 point scale (0=none, 1=present). Joints that are marked as permanently inevaluable due to being replaced or fused are not counted as swollen for that specific visit. Joints that are marked with an intra-articular corticosteroid injection are considered swollen for that specific visit. The total swollen joint count is calculated by summing the number of joints with present swelling.

Swollen Joint Count (66)	
Temporomandibular joints (n=2)	Metacarpophalangeal joints (MCP) (n=10)
Sternoclavicular joints (n=2)	Fingers distal interphalangeal joints (DIP) (n=8)
Acromioclavicular joints (n=2)	Knees (n=2)
Shoulders (n=2)	Ankles (n=2)
Elbows (n=2)	Tarsi (n=2)
Wrists (n=2)	Metatarsal phalangeal joints (MTP) (n=10)
Fingers proximal interphalangeal joints (PIP) (n=10)	Toes proximal interphalangeal joints (PIP) (n=10)

Swollen Joint Count (28) Plus Feet and Ankles	
Shoulders (n=2)	Metacarpophalangeal joints (MCP) (n=10)
Elbows (n=2)	Proximal interphalangeal joints (Fingers PIP) (n=10)
Wrists (n=2)	Knees (n=2)
Ankles (n=2)	Tarsi (n=2)
Metatarsal phalangeal joints (MTP) (n=10)	Toes proximal interphalangeal joints (PIP) (n=10)

Swollen Joint Count (28)	
Shoulders (n=2)	Metacarpophalangeal joints (MCP) (n=10)
Elbows (n=2)	Proximal interphalangeal joints (Fingers PIP) (n=10)
Wrists (n=2)	Knees (n=2)

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Tender Joint Count

The tender joint count is an assessment of the pain and/or tenderness of joints using 0-1 point scale (0=none, 1=present). Joints that are marked as permanently inevaluable due to being replaced or fused are not counted as tender for that specific visit. Joints that are marked with an intra-articular corticosteroid injection are considered tender for that specific visit. The total tender joint count is calculated by summing the number of joints with present tenderness.

Tender Joint Count (68)	
Temporomandibular joints (n=2)	Metacarpophalangeal joints (MCP) (n=10)
Sternoclavicular joints (n=2)	Metatarsal phalangeal joints (MTP) (n=10)
Acromioclavicular joints (n=2)	Toes proximal interphalangeal joints (PIP) (n=10)
Shoulders (n=2)	Knees (n=2)
Elbows (n=2)	Ankles (n=2)
Wrists (n=2)	Tarsi (n=2)
Fingers proximal interphalangeal joints (PIP) (n=10)	Hip (n=2)
Fingers distal interphalangeal joints (DIP) (n=8)	

Tender Joint Count (28) Plus Feet and Ankles	
Shoulders (n=2)	Metacarpophalangeal joints (MCP) (n=10)
Elbows (n=2)	Proximal interphalangeal joints (Fingers PIP) (n=10)
Wrists (n=2)	Knees (n=2)
Ankles (n=2)	Tarsi (n=2)
Metatarsal phalangeal joints (MTP) (n=10)	Toes proximal interphalangeal joints (PIP) (n=10)

Tender Joint Count (28)	
Shoulders (n=2)	Metacarpophalangeal joints (MCP) (n=10)
Elbows (n=2)	Proximal interphalangeal joints (Fingers PIP) (n=10)
Wrists (n=2)	Knees (n=2)

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Boolean remission status (28-joint counts)

A remission measure defined as having 28-joint tender joint count ≤ 1, 28-joint swollen joint count ≤ 1, CRP (in mg/dL) ≤ 1, and patient global assessment ≤ 1.

Boolean remission status (28-joint count + feet and ankles)

A remission measure defined as having 28-joint + feet and ankles tender joint count ≤ 1, 28-joint + feet and ankles swollen joint count ≤ 1, CRP (in mg/dL) ≤ 1, and patient global assessment ≤ 1.

The joints used in 28-joint count + feet and ankles for both swollen and tender assessments are:

ankles (2), tarsi (2), metatarsal phalangeal joints (10), toes proximal interphalangeal joints (10) and tender: metatarsal phalangeal joints (MTP) (10), toes proximal interphalangeal joints (10), ankles (2), tarsi (2).

Boolean remission (66/68 joint counts)

A remission measure defined as having 68-joint tender joint count ≤ 1, 66-joint swollen joint count ≤ 1, CRP (in mg/dL) ≤ 1, and patient global assessment ≤ 1.

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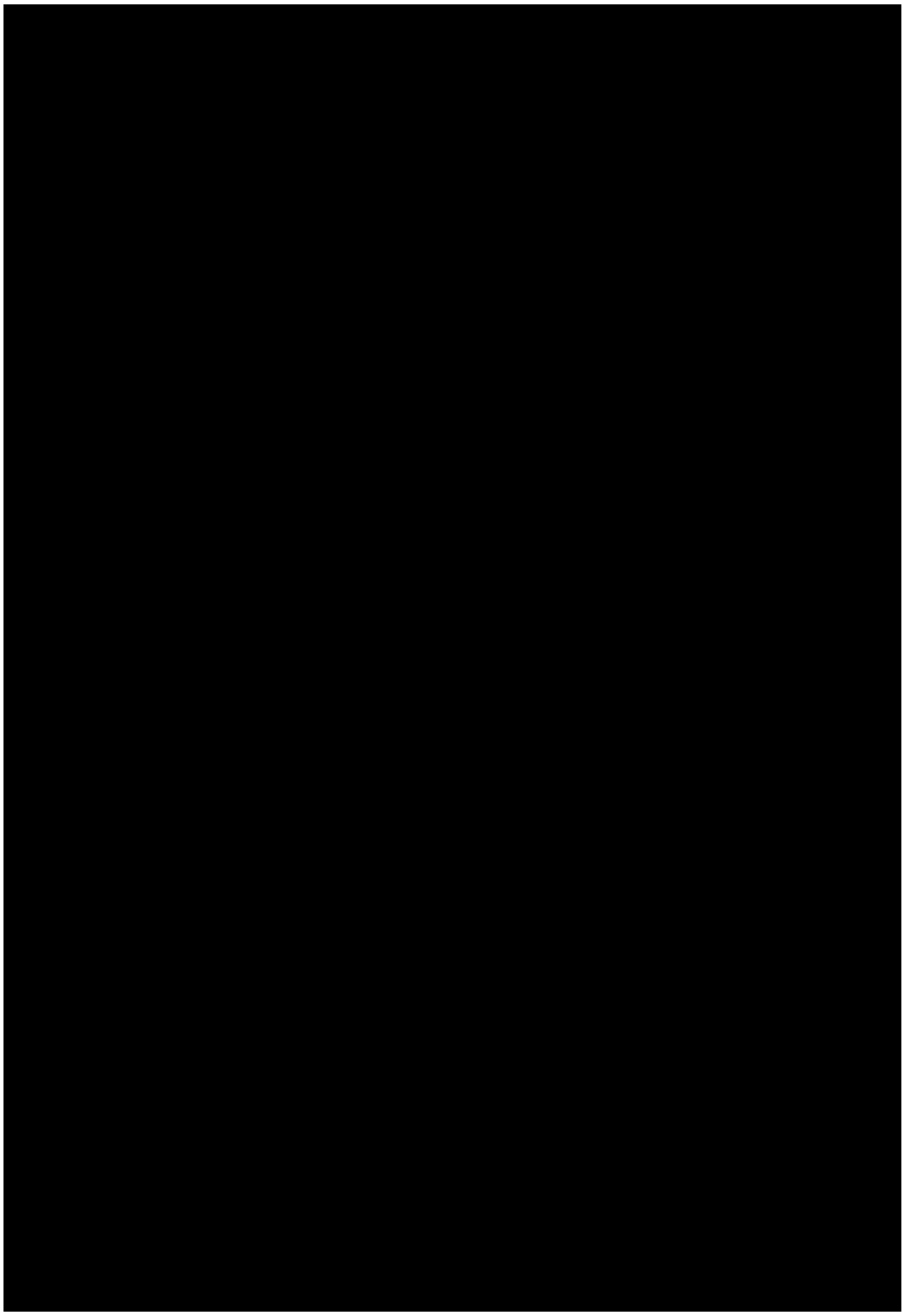
Appendix B. Code Fragments



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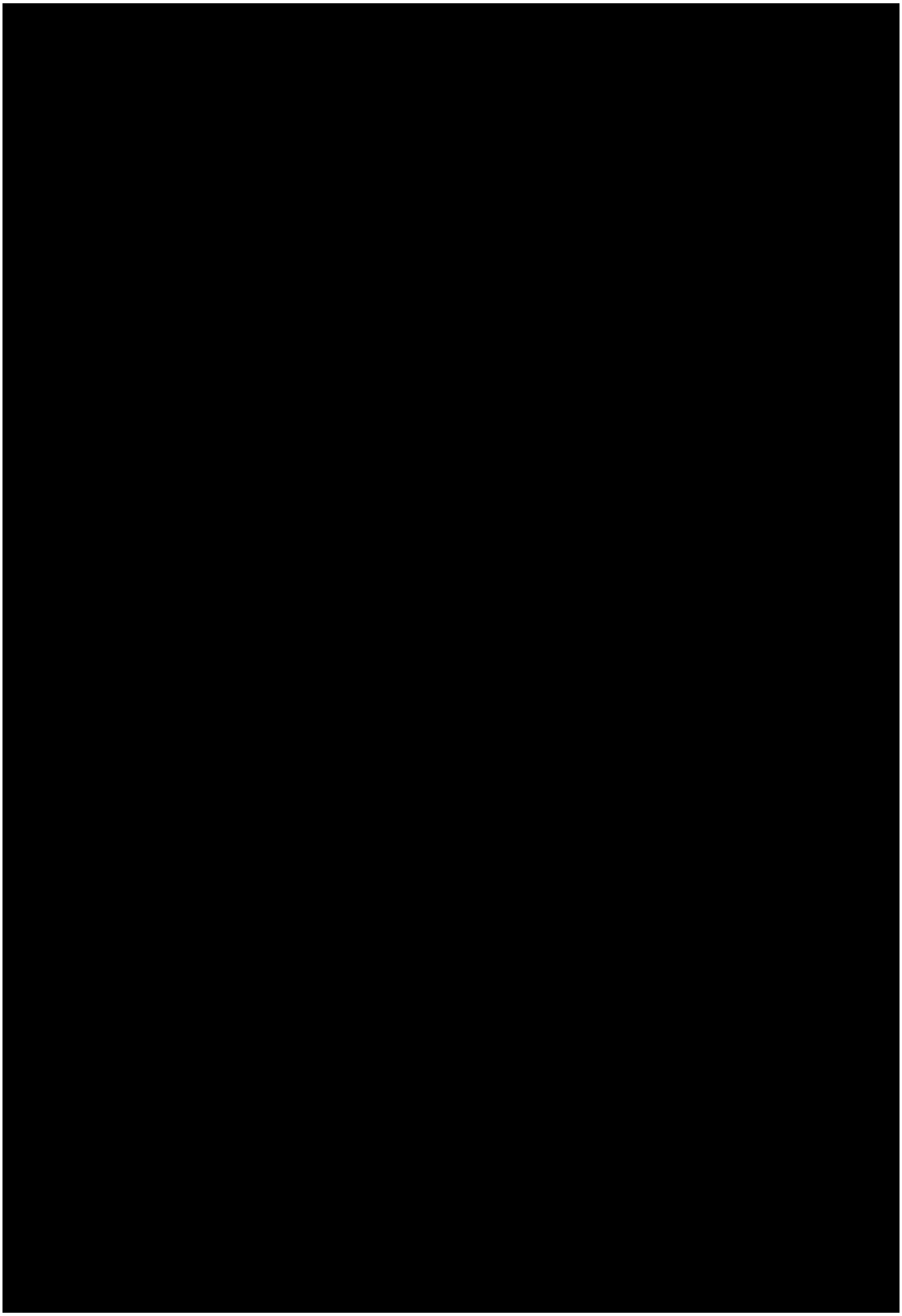
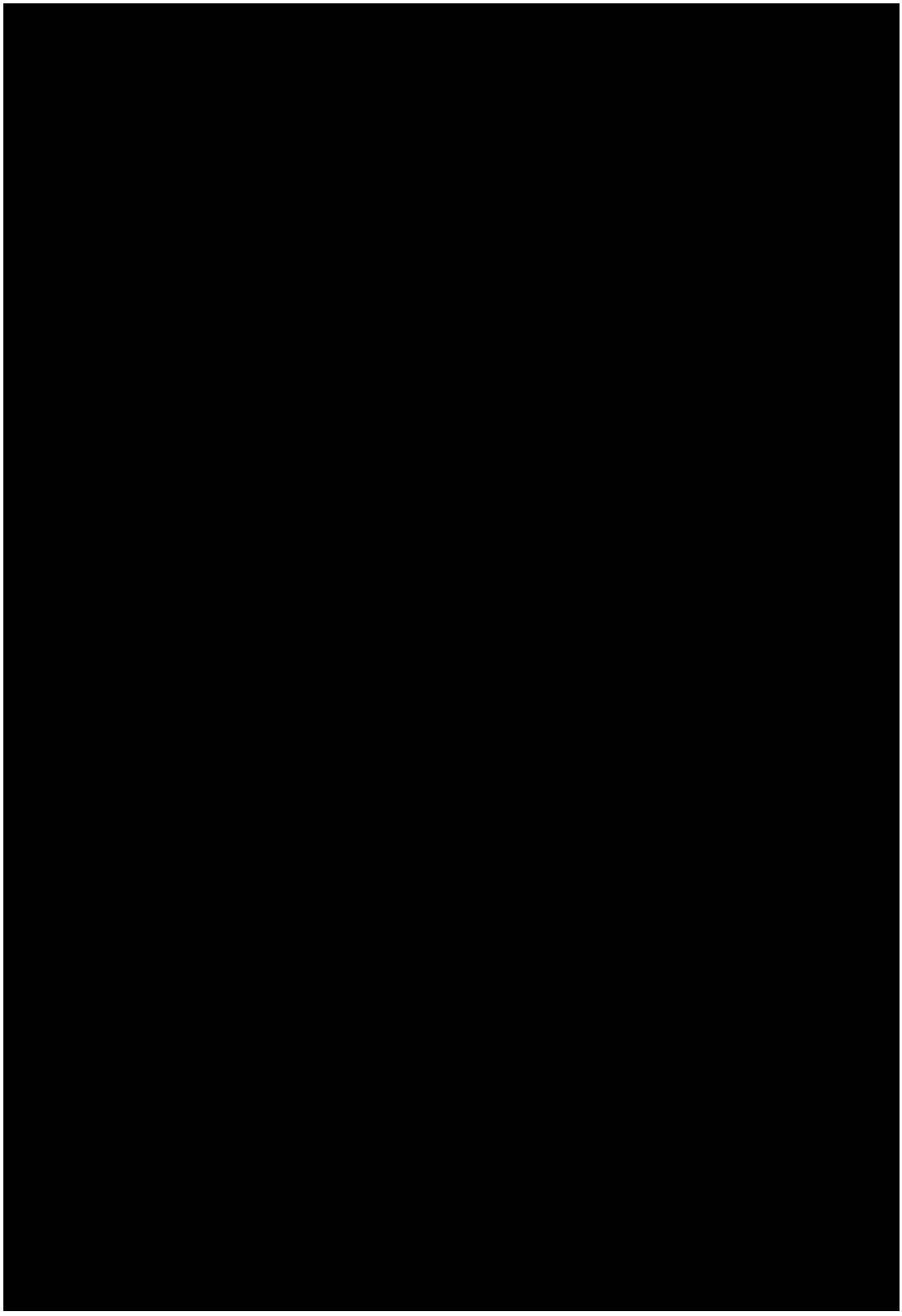


AMGEN®



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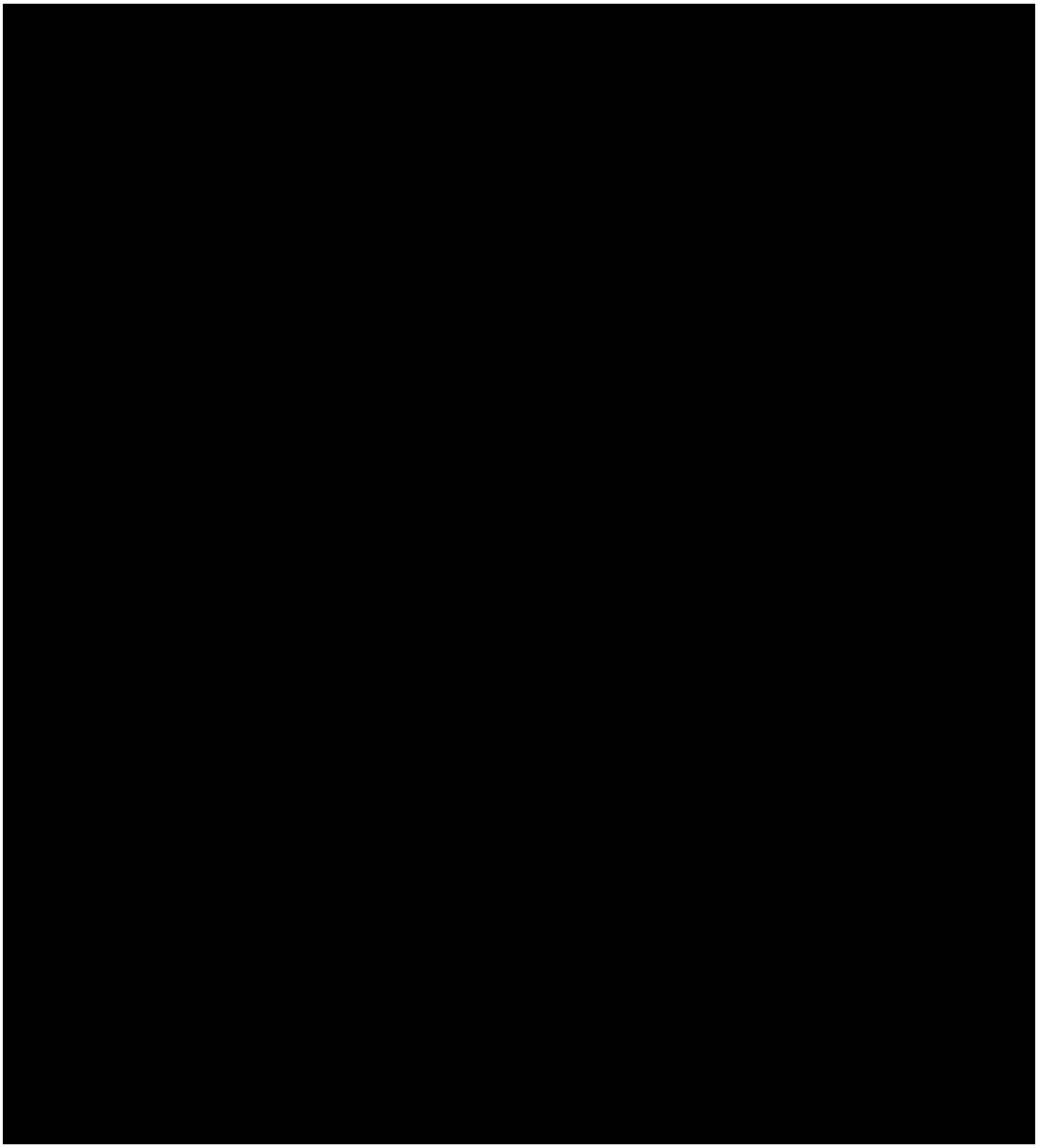

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Appendix C. Reference Values/Toxicity Grades

Adverse event severity is graded based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

Laboratory toxicity is graded based on the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0 with the following additions:

	Grade				
	0	**1**	**2**	**3**	**4**
BUN	WNL	>1.5 – 2.0 x ULN	>2.0 – 3.0 x ULN	>3.0 – 4.0 x ULN	>4.0 x ULN
HGB	WNL	>ULN	>(ULN+1) – (ULN+2)	>(ULN+2)	-
Urine Protein	NEG, NEGATIVE, TRACE, NORMAL, NOT DETECTED	+, +1, 1+	++, +2, 2+, +++, +3, 3+	++++, +4, 4+	-
Platelet Count	WNL	> ULN – 1.0×10^{12}/L	> 1.0×10^{12}/L	-	-
Leukocyte Count	WNL	> ULN – 2.0×10^{10}/L	> 2.0×10^{10}/L – 4.0×10^{10}/L	> 4.0×10^{10}/L	-

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Appendix D. Patient-reported Outcome Forms/Instruments

Scoring Algorithm of Health Assessment Questionnaire Disability Index (HAQ-DI)

All language versions will use the following scoring system.

- HAQ-DI scores range from 0 (no difficulty) to 3 (much difficulty) for each of the 20 questions in the 8 categories.
- Calculate the maximum score for each of the 8 categories. At least one question in each category needs to be answered to compute the maximum score.
- If an aid or device is used or help from another person is needed, adjust the score for the associated category by increasing a zero or a 1 to a 2. If a patient's highest score for that category is a 2, it remains a 2, and if a three, it remains a three.

Sub-domain	Aids or devices
Dressing & Grooming	Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
Arising	Special or built up chair
Eating	Built up or special utensils
Walking	Cane, Walker, Crutches, Wheelchair
Hygiene	Raised toilet seat, Bathtub seat, Bathtub bar, Long-handled appliances in bathroom
Reach	Long-handled appliances for reach
Grip	Jar opener (for jars previously opened)
Activities	N/A

If no more than 2 categories have missing scores, then the disability score is the mean of the non-missing category scores (the summed category scores divide by the number of categories answered). Otherwise, the disability score is set to missing.

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Appendix E. Concomitant Medications

The following concomitant medications will be tabulated:

- hydroxychloroquine,
- sulfasalazine,
- minocycline,
- prednisone (5mg daily or less),
- and NSAIDs

The Prednisone dosage of 5 mg daily or less is of interest because entry criteria allows for this dosage.

Only concomitant medications with a partial or complete end date are tabulated.

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