STATISTICAL ANALYSIS PLAN
ALX0061-C203

A Phase II Multicenter, Open-Label Extension Study Assessing the Long-Term Efficacy and Safety of Subcutaneous ALX-0061 in Subjects with Moderate to Severe Rheumatoid Arthritis who Have Completed One of the Preceding Phase IIb Studies with ALX-0061

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LIST OF ABBREVIATIONS

ADaM	Analysis data model
ACR	American college of rheumatology
ADA	Anti-drug antibody
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
CI	Confidence interval
CDAI	Clinical disease activity index
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CXCL	Chemokine (C-X-C motif) ligand
DAS28	Disease activity score using 28 joint counts
DBP	Diastolic blood pressure
DSMB	Data safety monitoring board
DT	Drug Tolerance (immunogenicity assay characteristic)
DY	Relative day
ESR	Erythrocyte sedimentation rate
EULAR	European league against rheumatism
FACIT	Functional assessment of chronic illness therapy
GGT	Gamma-glutamyl transferase
HAQ-DI	Health assessment questionnaire – disability index
ICF	Informed consent form
ICH	International Council for Harmonisation
IGRA	Interferon-gamma release assay
IL-6	Interleukin-6
ITO	Intent-to-observe

IWRS	Interactive web response system
LDA	Low disease activity
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase
MTX	Methotrexate
NA	Not Analyzed
NAb	Neutralizing antibody
NR	No Result
NRI	Non-responder imputation
OC	Observed cases
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic
q2w	Every two weeks
q4w	Every four weeks
RA	Rheumatoid arthritis
SAP	Statistical analysis plan
SBP	Systolic blood pressure
s.c.	Subcutaneously
SD	Standard deviation
SDAI	Simplified disease activity index
SDTM	Study data tabulation model
SE	Standard error
SF-36	Short form (36) health form
SGS-LS	SGS-Life Sciences – Clinical Research
SOP	Standard operating procedure
STAT	Statistics
SJC	Swollen joint count
TB	Tuberculosis
TEAE	Treatment-emergent adverse event

TJC	Tender joint count
VAS	Visual analogue scale
WHO	World Health Organisation

1 INTRODUCTION

ALX-0061 (vobarilizumab) has been developed by the sponsor as a new therapeutic protein neutralizing pro-inflammatory activity in the interleukin-6 (IL-6) pathway. ALX-0061 is a therapeutic protein called nanobody which inhibits the interaction between the IL-6 ligand and the receptor subunit, thereby preventing receptor signaling hence pro-inflammatory activity of IL-6. The investigator's brochure contains more detailed background information. This clinical study (ALX0061-C203) is an open-label extension of Phase IIb studies ALX0061-C201 and ALX0061-C202 and is intended to evaluate the long-term efficacy and safety of ALX-0061 administered subcutaneously (s.c.) to subjects with active rheumatoid arthritis (RA), a chronic systemic inflammatory autoimmune disease.

This statistical analysis plan (SAP) describes the final statistical analysis to be performed for the ALX0061-C203 study. This SAP covers the efficacy, safety, pharmacokinetic, and general characteristics parts of the statistical analysis. It specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol. The statistical analysis will process and present the results following the International Council for Harmonisation (ICH) standards, in particular the ICH-E3, ICH-E6, and ICH-E9 guidelines.

2 STUDY OBJECTIVES

The objective of this study is to evaluate the long-term efficacy and safety of ALX-0061 administered s.c. to subjects with active RA.

3 STUDY DESIGN

3.1 Overall Study Design

This is a multicenter, open-label extension (OLE) phase II study of ALX-0061 administered s.c.in subjects with active RA who have completed the ALX-0061 treatment and assessment period of one of the preceding Phase IIb studies with ALX-0061 (C201 or C202) and who achieved at least 20% improvement in swollen joint count (SJC) and/or tender joint count (TJC) (66/68 counts) compared to baseline at the final visit of the preceding study and for the countries where there was approval for the study.

Eligible subjects will receive ALX-0061 150 mg s.c. injections, beginning at Day 1 (Week 0) of the OLE and every 2 weeks (q2w) thereafter up to and including Week 102. Eligible subjects from study ALX0061-C201 will also continue their methotrexate (MTX) treatment. Subjects will return for 12 ambulatory visits planned at Day 1 (Week 0), and Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and 104. Subjects who received study drug up to and including Week 102, should return for the End of Treatment Visit at Week 104 and for the Follow-up Visit 12 weeks after the last study drug administration at Week 102.

In the current OLE study, maintenance of the response will be reassessed at the study visits every 12 weeks from Week 12 until Week 96. Subjects who fail to maintain response and meet efficacy discontinuation criteria (< 20% improvement in both SJC and TJC

compared to baseline of the preceding Phase IIb study) will be discontinued from the study.

The schedule of assessments can be found in Appendix 1: Schedule of assessments.

As this is an OLE study, blinding is not required.

3.2 Sample Size

This is an extension study and is not set by statistical power. Subjects who have completed the Week 24 (study ALX0061-C201) or Week 12 (study ALX0061-C202) assessment visit in one of the preceding Phase IIb studies with ALX-0061, and who are qualified for this study per inclusion/exclusion criteria, will be invited to participate in the extension study. Up to a maximum of approximately 501 subjects are planned to participate in this OLE study.

3.3 Study Endpoints

The protocol does not define primary or secondary study endpoints. The following endpoints will be analyzed:

Efficacy endpoints:

- American College of Rheumatology (ACR) ACR20, ACR50, and ACR70 response rate over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Actual values in ACR-N index improvement over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Actual values and change from baseline values in Disease Activity Score using 28 joint counts (DAS28) using CRP and ESR, simplified disease activity index (SDAI) and clinical disease activity index (CDAI) over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Disease activity: response rate of remission and response rate of low disease activity (LDA) based on DAS28(ESR), SDAI, CDAI, Boolean (only remission) over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Disease activity: response rate of DAS28(CRP) < 2.6 and response rate of low disease activity (LDA) based on DAS28(CRP) over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Disease activity: rate of maintained remission at consecutive time points based on DAS28(ESR), SDAI, CDAI, Boolean and rate of maintained LDA at consecutive time points based on DAS28(ESR) over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Disease activity: rate of maintained DAS28(CRP) < 2.6 at consecutive time points and rate of maintained LDA at consecutive time points based on DAS28(CRP) over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).

- European league against rheumatism (EULAR) DAS28 response rate (good, moderate, or no response) over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Actual values and change from baseline values in HAQ-DI over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- HAQ-DI response rate (i.e., those who have a clinically meaningful improvement from baseline of ≥ 0.25 in HAQ-DI) and HAQ-DI normal physical function response rate (i.e., those who have a score of ≤ 0.5) over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).
- Actual values and change from baseline values in Physical and mental component scores of SF-36 over time (Week 0, Week 24, Week 48, Week 72 and Week 104).
- Actual values and change from baseline values in FACIT-Fatigue over time (Week 0, Week 24, Week 48, Week 72 and Week 104).
- Actual values and change from baseline values in duration of morning stiffness at Week 0 and Week 104.

Pharmacokinetic (PK) endpoints:

- ALX-0061 serum concentration over time (Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96 and Week 104).

Immunogenicity endpoints:

- Overall subject classification based on ADA/mADA assays results.
- Overall subject classification based on NAb assay results.

Safety endpoints:

- Number of events as well as number and percentage of subjects with treatment-emergent Adverse Events (TEAEs), treatment-related AEs, Serious Adverse Events (SAEs), non-serious AEs, treatment-related SAEs, SAEs leading to treatment discontinuation and Adverse Events of Special Interest (AESI), categorized by System Organ Class (SOC) and Preferred Term (PT) and Maximum Severity (where applicable). Note that all adverse events reported in this study are considered treatment-emergent.
- Actual values and change from baseline in clinical laboratory parameters, including blood chemistry, hematology, urinalysis, coagulation and the acute phase proteins (CRP, ESR, and fibrinogen) at Week 0, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and Follow-up (Week 0, Week 24, Week 48, Week 72 and Week 104 only for extended clinical laboratory analyses).
- Shift from baseline in clinical laboratory parameters with normal ranges or CTCAE grades at Week 0, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and Follow-up.
- Actual values and change from baseline values in vital signs measurements at Week 0, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and Follow-up.
- Physical examination abnormal findings at Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and Follow-up.

4 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

4.1 Analysis Populations

The following populations will be considered for analysis:

4.1.1 All screened population

The all screened population includes all subjects who signed an informed consent for participation in the ALX0061-C203 study.

4.1.2 Intent-to-observe (ITO) population

The ITO population includes all subjects who enrolled in study ALX0061-C203 and is thus equal to the all screened population. General characteristics and efficacy will be analyzed on the ITO population.

4.1.3 Safety population

The safety population includes all subjects who received at least 1 administration of study drug, as treated. The safety population will be used for the analysis of exposure and safety data.

4.1.4 PK population

The PK population is a subset of the safety population and consists of all subjects who received at least 1 administration of ALX-0061 and for whom at least one ALX-0061 serum concentration has been determined.

The PK population will be used for the analysis of ALX-0061 serum concentrations.

4.2 Key Definitions and Labels

4.2.1 Definition of baseline and change from baseline

The baseline value will be the baseline value of the parent study.

The absolute change from baseline will be calculated for all post-baseline time points as: Change from baseline at time point t = value at time point t – baseline value

For selected efficacy endpoints, the percentage change from baseline will be calculated for all post-baseline time points as: Percentage change from baseline at time point t = 100 * (value at time point t – baseline value) / baseline value. As percentage change can not be calculated for subjects with a baseline value of 0, these subjects will not be included for the corresponding summary analysis (if planned) and the respective column(s) will be kept blank for the corresponding listing.

For the changes from baseline, only subjects with both a baseline value and a value at the post-baseline time point will be included.

Wherever in the document 'change from baseline' is mentioned, it concerns the absolute change from baseline.

4.2.2 Presentation of treatment groups

The following treatment group labels will be used in the tables, listings and figures, unless specified otherwise:

- ALX-0061 150 mg q2w + MTX (C201 PBO + MTX)
- ALX-0061 150 mg q2w + MTX (C201 75 mg q4w + MTX)
- ALX-0061 150 mg q2w + MTX (C201 150 mg q4w + MTX)
- ALX-0061 150 mg q2w + MTX (C201 150 mg q2w + MTX)
- ALX-0061 150 mg q2w + MTX (C201 225 mg q2w + MTX)
- ALX-0061 150 mg q2w + MTX (C201 all subjects)
- ALX-0061 150 mg q2w (C202 150 mg q4w)
- ALX-0061 150 mg q2w (C202 150 mg q2w)
- ALX-0061 150 mg q2w (C202 225 mg q2w)
- ALX-0061 150 mg q2w (C202 all subjects)
- All subjects

4.2.3 Totals over groups

Grand total, pooling all subjects, will be displayed in all tables.

4.2.4 General presentation of results

All results will be presented per treatment group, unless specified otherwise. All listings will be ordered by treatment group, subject, and time point, unless specified otherwise.

The analysis population will always be indicated in a subtitle in the table, listing or figure.

4.2.5 Visit Windows

The visit windows as defined in Section 12.1 will be applied to all parameters.

4.3 General Methods

4.3.1 Calculation of descriptive statistics

Continuous variables will be summarized using descriptive statistics including the number of non-missing observations (n), the arithmetic mean, the standard deviation (SD) for general characteristics and for PK summaries or standard error (SE) for efficacy, safety and immunogenicity, the median, minimum and maximum.

Descriptive statistics of efficacy will additionally include a 95% confidence interval (CI) of the mean, calculated based on the large sample normal approximation. For changes from

baseline of efficacy parameters, the least squares (LS) mean and 95% CI derived from an ANCOVA model with treatment group as factor and baseline as covariate will be shown.

Descriptive statistics of PK concentrations will additionally include 5% and 95% percentiles, coefficient of variation (CV)% of arithmetic mean, geometric mean and geometric SD.

Descriptive statistics of continuous variables will be presented when n≥2. When n=1, only sample size (n) and mean are shown.

Categorical variables will be summarized using frequency counts and percentages. For efficacy, a Wilson score 95% CI on the percentage in each treatment group will also be shown. When count data are presented, the percentage will be suppressed when the count is zero. Missing values will not be included in the denominator count when computing percentages. For demographics and baseline disease characteristics a 'missing' row will be included to indicate the number of missing values, without percentages.

For the graphs showing mean values of continuous variables, an SE flag will be shown, while for graphs showing percentages, this will be the Wilson score asymptotic SE on the binomial proportions.

Calculated parameters will not be rounded in the derived datasets. The rounding will be done at the reporting level. Mean, median, 95% CI limits will be presented with one decimal more than data collected. Minimum and maximum will be reported with the same precision as data collected and SD and SE with two decimals more than data collected. Percentages will be tabulated with 1 decimal.

4.3.2 Handling of values below (or above) a threshold

Values below (above) the detection limit will be imputed by the value of the detection limit itself, unless indicated otherwise. Listings will always present the original value. Example: if the database contains values like "<0.04", then for the descriptive statistics the value of the detection limit (0.04) shall be used. A value like ">1000" will be imputed by "1000".

Individual pharmacokinetic concentrations below the limit of detection or below the quantification limit (BQL) will be reported as BQL. To compute descriptive statistics (i.e. mean (or median or geomean), SD, CV%, minimum and maximum), all BQL values will be treated as missing. When the total number of BQL values exceeds 1/3 of the total number of values at that time point, descriptive statistics will not be computed. Descriptive statistics not calculated for the above reasons will be reported as not calculated (NC).

For handling of titer values from immunogenicity analysis, see section 9.

4.3.3 Handling of outliers

There will be no outlier detection. All measured values will be included in the analyses.

4.4 Software and Validation Model

SAS version 9.4 or higher will be used for programming.

Currently valid[redacted] standard operating procedures (SOPs) will be followed.

ACR20 response will be validated following Model C, other efficacy endpoints, general and safety parts following validation model B:

Model B: review of the output, source code and program log by an independent person (i.e., somebody different from the developer).

Model C: review of the output, source code and program log by an independent person, plus independent programming of the parameters indicated in this SAP.

5 GENERAL CHARACTERISTICS

All analyses on general characteristics will be run on the ITO population, unless specified otherwise.

5.1 Subject Disposition

Subject disposition will be presented descriptively for the all screened population. This includes the number and percentage of subjects in each of the analysis populations defined in section 4.1. Percentages will be calculated relative to the all screening population. A disposition summary by region and country and a summary by time point will be given for the ITO population. The number and percentage of subjects who completed the study and those who prematurely discontinued from the study will be summarized, along with the primary reasons for discontinuation.

A detailed list of tables and listings can be found in section 13.1 and section 15.1, respectively.

5.2 Protocol Deviations and Eligibility Criteria

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations are considered as major if they concern criteria and disease characteristics that are critical to define the study population and criteria that determine or influence clinical endpoints or criteria that may cause immediate hazard to the subjects (impact on subjects' rights, safety or well-being) or increase the safety risk to subjects.

The list of (potentially) major protocol deviations will be reviewed by the sponsor and finalized prior to database lock. Detailed information can be found in the trial protocol deviation criteria list.

Major protocol deviations will be tabulated according to their category. The following categories are considered:

- Selection criteria not met
- Subject not withdrawn as per protocol
- Prohibited concomitant medication
- Treatment non-compliance
- Safety assessment deviation
- Efficacy assessment deviation
- Other

Additionally, major protocol deviations will be listed including categorization and description.

A detailed list of tables and listings can be found in section 13.1 and section 15.1, respectively.

5.3 Demographic and Other Baseline Characteristics

Demographic data and baseline disease characteristics will be summarized descriptively by treatment group and overall on the ITO population. The following demographic parameters and baseline disease characteristics will be included in the tables and/or listings:

Demographic parameters:

- Sex at birth (male, female)
- Women of childbearing potential (yes, no), only listed
- Age (years): the age at baseline of the parent trial is used.
- Age categories (<65 years, ≥65 years)
- Year of birth: only listed
- Date of signing the ICF: only listed
- Race (white, black or African American, Asian, American Indian or Alaska native, native Hawaiian or other Pacific islander, other, not allowed to ask). Specification for Asian and other race will only be listed.
- Ethnicity (Hispanic or Latino, non-Hispanic or non-Latino, not allowed to ask)
- Geographic region (Latin America, Europe):
    - Latin America: Mexico
    - Europe: Spain, Germany, Poland, Belgium, Bulgaria, Republic of Moldova, Georgia, Hungary, Romania, Macedonia and Serbia
- Height (cm)
- Weight (kg)
- Weight categories (≤100 kg, >100 kg; ≤median, >median)
- Body mass index BMI = (weight in kg) / (height in m)² (kg/m²)

Age, height, weight and their derived parameters will be extracted from the parent study. Previously calculated parameters will not be recalculated.

Baseline disease characteristics:

Please refer to the efficacy section 12.3 for detailed definitions of the parameters. Below baseline parameters will be extracted from the parent study and calculated parameters will not be recalculated.

- Swollen joint count (SJC66): number of swollen joints out of 66 assessed joints
- Tender joint count (TJC68): number of tender joints out of 68 assessed joints
- Swollen joint count (SJC28): number of swollen joints out of 28 assessed joints used for DAS28 calculation
- Tender joint count (TJC28): number of tender joints out of 28 assessed joints used for DAS28 calculation
- Tender joint count categories (<10, 10-20, >20)
- Swollen joint count categories (<7, 7-11, >11)
- CRP (mg/dL)
- CRP categories (<= upper limit of normal range [ULN], >ULN and <=1.2xULN, >1.2xULN and <=3xULN, >3xULN)
- ESR (mm/h)
- Physician's global assessment of the disease (VAS; 0-100 mm)
- Patient's global assessment of the disease (VAS; 0-100 mm)
- Patient's assessment of pain (VAS; 0-100 mm)
- HAQ-DI (0-3)
- SF-36 Physical component summary
- SF-36 Mental component summary
- Time since first RA symptoms (years)
- Time since RA diagnosis (years)
- ACR functional class at screening (of parent trial): class I / class II / class III / class IV
- Extra-articular symptom location: any of the following: skin, eyes, gastrointestinal, heart, lung, renal, nervous system, other
- Extra-articular symptoms: only listed
- Rheumatoid factor (RF) concentration (kIU/L)
- RF category (positive [>ULN], negative [<=ULN])
- Anti-CCP category (positive [>ULN], negative [<=ULN])
- Combined RF and anti-CCP category (double positive, double negative, mixed negative and positive)
- DAS28 Score (ESR)
- DAS28 Score (CRP)
- DAS28(ESR) and DAS28(CRP) categories (<=3.2, >3.2 and <=5.1, >5.1)
- Clinical Disease Activity Index (CDAI)
- Simplified Disease Activity Index (SDAI)
- MTX use (dose)

- Corticosteroid use (prednisone equivalent dose)
- Duration of morning stiffness (minutes)
- FACIT

A detailed list of tables and listings can be found in section 13.1 and section 15.1, respectively.

5.4 Exposure to Study Medication and Treatment Compliance

Extent of exposure will be analyzed descriptively by treatment group and overall based on the safety population. Note that only exposure during the OLE will be analyzed, so this will not reflect the total exposure of a subject to ALX-0061.

The following parameters will be summarized: total treatment duration, total number of study drug doses received, cumulative dose of study drug received, compliance and home administration. The derivation of these parameters can be found in section 12.2.1. A detailed list of tables and listings can be found in section 13.1 and section 15.1, respectively.

5.5 Medical history

Medical history was listed in the parent trials.

5.6 Concomitant Therapies

Any concomitant therapy taken during the study will be recorded in the eCRF, including ongoing concomitant therapies from the parent trial. Concomitant therapies are defined as therapies with a stop date on or after date of first dose of study drug in the C203 study. Therapies stopped before the study are not recorded. Analysis of prior medications is available in the parent trials.

All therapies are coded using the latest WHO-DRUG version. No anatomical therapeutic chemical classification system (ATC) selection is performed.

Concomitant therapies will be tabulated by generic term, for RA and non-RA medications separately, by treatment group and overall using the ITO population. Multiple records of the same generic term for the same subject will be counted only once. The table will therefore present subjects, not occurrences. The tables are sorted by decreasing frequency based on all subjects.

Systemic corticosteroids are selected as steroid RA-therapy with intravenous or intramuscular administration (not intra articular)

A detailed list of tables and listings can be found in section 13.1 and section 15.1, respectively.

6 EFFICACY

6.1 Main Efficacy Analysis

No inferential statistical analyses will be performed. All tables will be presented by treatment group and overall, including treatment groups defined by previous dosing regimen of the parent trial (cfr. section 4.2.2). All analyses will be run on the ITO. The main analysis will be on observed cases (OC).

Continuous efficacy endpoints will be summarized as follows:

- Actual values: descriptive statistics (mean, 95% CI on the mean [normal approximation], SE, median, minimum, and maximum) per endpoint and time point. The baseline value from the parent trial will be included to the summary, if applicable.
- Changes from baseline: baseline adjusted LS means and 95% CI from an ANCOVA model with treatment as factor and baseline as covariate,median, minimum and maximum per endpoint and post-baseline time point.

This will be done for the following parameters: ACR-N, DAS28(CRP), DAS28(ESR), SDAI, CDAI, HAQ-DI, SF-36 physical and mental component scores, FACIT-Fatigue, duration of morning stiffness, patient's assessment of pain (VAS-scale), patient's global assessment of disease activity (VAS-scale), physician's global assessment of disease activity (VAS-scale), CRP, ESR, TJC68, TJC28, SJC68, SJC28, MTX dose, corticosteroids dose. Different types of sytemic corticosteroids will be converted to Prednisolone equivalent doses before calculating the cumulative dose of corticosteroids. The cumulative dose will be given in mg/day (Please refer to Appendix 2 section 16.2 for more details).

Categorical efficacy endpoints will be presented using a frequency tabulation of the parameter at each time point, including a Wilson score 95% CI on the percentage of subjects in the category of interest. The baseline value from the parent trial will be included to the summary, if applicable. This wil be done for the following parameters: ACR20, ACR50, ACR70, EULAR response (including EULAR good response), DAS28(ESR) low disease activity / remission / maintained remission / maintained low disease activity, DAS28(CRP) low disease activity / DAS(CRP) < 2.6 / maintained DAS(CRP) < 2.6 / maintained low disease activity, SDAI low disease activity / remission / maintained remission, CDAI low disease activity / remission / maintained remission, Boolean remission / maintained remission, HAQ-DI clinically meaningful improvement, HAQ-DI normal physical function, MTX dose reduction rate, MTX discontinuation rate.

All 95% CIs will be two-sided.

In addition, line plots of the mean actual values per time point, including SE bars, for continuous endpoints, and line plots of the response rates (in percentage) per time point, including SE bars, for categorical endpoints, will be provided.

Definitions and calculation of efficacy parameters are detailed in section 12.3.

A detailed list of tables, figures and listings can be found in section 13.2, section 14 and section 15.2, respectively.

6.2 Other Efficacy Analyses

The sensitivity of results to missing data will be assessed by conducting a sensitivity analysis using LOCF imputed cases. Missing post-baseline values are imputed by the last non-missing preceding post-baseline value. Baseline itself is not imputed.

The sensitivity analysis will be done for the following efficacy endpoints:

- ACR20/50/70
- DAS28(ESR) actual values and changes from baseline
- DAS28(ESR) remission/low disease activity
- DAS28(CRP) actual values and changes from baseline
- DAS28(CRP) < 2.6/low disease activity

A second sensitivity analysis will be done using NRI imputed cases. Missing post-baseline ACR values are imputed with the value corresponding to that of non-responders.

This sensitivity analysis will be done for the following efficacy endpoints:

- ACR20/50/70
- DAS28(ESR) remission/low disease activity
- DAS28(CRP) < 2.6/low disease activity

In addition, for the same efficacy endpoints, a subgroup analysis will be conducted on the observed cases.

The following subgroups will be considered:

- Age category (<65 yrs at baseline, >= 65 yrs at baseline)
- Geographic region
- If any subcategory has less than 10% of the total number of patients then the subgroup analysis will not be produced.

A detailed list of tables can be found in section 13.2.

7 SAFETY

7.1 Adverse Events

All safety summaries will be based on the safety population and presented by treatment group (see section 4.2.2). As study drug treatment is not interrupted between the parent study and this study, all adverse events reported in this study are considered treatment-emergent. However, unless specified otherwise, only adverse events that started after the first dose of C203 will be considered in the tables.

All adverse events will be coded and classified by System Organ Class (SOC) and Preferred Term (PT) using the medical dictionary for regulatory activity (MedDRA) that is current at the time of database lock.

A TEAE will be categorized as study drug-related if the relationship to study drug is reported to be ‘possibly related’ or ‘related’, or missing. In tabulations this categorization

will be used, but in the listings the original reported relationship will be presented. If the relationship is reported to be 'not applicable', it will not be considered in the tabulations.

A TEAE is reported as related to study procedure or not related to study procedure. Missing study procedure relationship will be considered as related.

A general summary table with AE events starting after first dose of C203 only will be produced to report the number and percentage of subjects with at least one event, the number of events and the incidence per 100 patient years, which will be calculated as: 100 x (Number of subjects with AE)/(Total number of years observed while on C203, summed for all subjects). Percentages will be calculated out of the number of subjects in the relevant treatment group.

The following categories will be included in the summary table:

- TEAE
- serious TEAE
- TEAE leading to death
- severe TEAE as classified by the investigator
- TEAE for which the study drug was interrupted
- TEAE for which the study drug was discontinued
- study drug-related TEAE
- serious study drug-related TEAE
- injection-site reaction.

Note that the TEAE here refers to the AEs starting after first dose of study drug in C203 study.

A similar summary table will be produced for all TEAEs including those of the parent trials (C201 and C202). Any event happening either on parent trial or on the current trial will be considererd for deriving the number and percentage of subjects with at least one event, and the number of events. The incidence per 100 patient years will be calculated as: 100 x (Number of subjects with AE)/(Total number of years observed starting from the first dose in parent trial, summed for all subjects).

Another summary table will be presented selecting adverse events of special interest. Search criteria for these adverse events can be found in section 16.5.

The following categories will be included in the summary table:

- infection
- serious infection (requiring hospitalization or i.v. antimicrobial treatment)
- opportunistic infection, excluding TB
- active TB infection
- latent TB infection
- Herpes zoster infection
- malignancy
- hypersensitivity reaction (including anaphylaxis and angioedema)
- hypersensitivity reaction (including anaphylaxis and angioedema) leading to withdrawal
- GI perforation
- demyelinating disorder
- MACE

This table will represent events which occurs only after the first dose of study drug in C203 study.

One more summary table for AEs of special interest will be produced including events from the parent trials as well. Any event happening either on parent trial or on the current trial will be considererd for deriving the number and percentage of subjects with at least one event, and the number of events. The incidence per 100 patient years will be calculated as: 100 x (Number of AEs)/(Total number of years observed starting from the first dose in parent trial, summed for all subjects).

Tables by SOC and PT will report the number and percentage of subjects with at least one event, occurring only after the first dose of study drug on C203 study. Percentages will be calculated out of the number of subjects in the relevant treatment group.

These tables will be prepared for the following selections of AEs:

- TEAEs
- TEAEs by severity (Mild, Moderate, Severe)
- TEAEs with an incidence of at least 3%
- serious TEAEs
- non-serious TEAEs
- study drug-related TEAEs
- study procedure-related TEAEs
- TEAE for which the study or the study drug were discontinued

The tables by SOC and PT will be sorted in descending order starting from the SOC with the highest incidence in the all subjects group. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in the same manner as the SOCs. At each level of subject summarization, a subject is counted once if the subject reported one or more events. In the summary table by severity, if a subject reported multiple occurences of the same TEAE, only the most severe will be presented. TEAEs with missing severity will be presented in a separate 'Missing' category.

The AE onset day and the AE duration will not be presented in the tabulations, but will be listed. Their derivation is provided in section 12.4.1.

A detailed list of tables and listings can be found in section 13.4 and section 15.4, respectively.

7.2 Laboratory Evaluations

The following laboratory parameters will be summarized and displayed at the scheduled time points:

- **Biochemistry**: total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, AST, ALT, lactate dehydrogenase, creatinine, urea, total protein, albumin, glucose, inorganic phosphate, sodium, potassium, calcium, and chloride. In the extended clinical laboratory analysis, fasting serum lipids will be included as well (i.e. total cholesterol, HDL-cholesterol, LDL-cholesterol, LDL/HDL cholesterol ratio (calculated as LDL/HDL) and triglycerides)
- **Hematology**: leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, partial automated differentiation (lymphocytes, monocytes, eosinophils, basophils, neutrophils and neutrophils segmented), mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- **Acute phase proteins**: fibrinogen, CRP, and ESR.
- **Urinalysis**: erythrocytes/blood, urobilinogen, ketones, glucose, protein, pH, and leukocytes.
- **Coagulation**: activated partial prothrombin time, prothrombin time, and INR (the latter for subjects on warfarin only).

For lab tests with numeric values, tables showing descriptive statistics (mean, median, standard error, minimum, and maximum) per lab test category (hematology, biochemistry, acute phase proteins, urinalysis, coagulation), lab test and unit and time point by treatment group and using the safety population will be prepared for:

- actual values
- absolute changes from baseline (definition in section 4.2.1)

Urinalysis results will be presented in a frequency table per lab test and time point.

The statistical summary will only present results in Standard International (SI) units. Other units will not be presented. In the tables, the number of significant digits of the original values will be used to determine the number of decimals that will be printed.

All values will be compared to their matching normal ranges (low, normal, high). For both values and normal ranges the SI units will be considered to determine abnormalities. Additionally, for key hematology and biochemistry parameters, toxicities will be derived according to the common terminology criteria for adverse events (CTCAE, see appendix 16.2) grading, version 4.03 (ALT, AST, total bilirubin, gamma-glutamyltransferase, leukocytes, neutrophils, thrombocytes, fibrinogen and cholesterol). Details for derivation of classification based on normal ranges of laboratory parameters can be found in section 12.4.2.

Cross-tabulations per lab test category (hematology, biochemistry, acute phase proteins, urinalysis, coagulation), lab test and time point will show the shift at each post-baseline time point versus the baseline.

The following types of cross-tabulations will be prepared:

- for all tests with normal ranges: shift in abnormality (L/N/H)
- for ALT, AST, total bilirubin, GGT, leukocytes, neutrophils, thrombocytes, fibrinogen and lipids test results only: shift in CTCAE toxicity grades (grade 1 to 4)

Longitudinal box plots will be prepared for the following variables: neutrophils, platelets, ALT, AST and LDL/HDL ratio.

A detailed list of tables, figures and listings can be found in section 13.4, section 14 and section 15.4, respectively.

7.3 Physical Examination

Abnormal physical examination findings will be listed (see section 15.4). No summaries will be provided.

7.4 Vital Signs

The following parameters will be analysed: weight, systolic and diastolic blood pressure, pulse rate and body temperature.

Tables showing descriptive statistics (mean, median, standard error, minimum, and maximum) per vital sign test and unit and time point by treatment group and using the safety population will be prepared for:

- actual values
- absolute change from baseline

A detailed list of tables and listings can be found in section 13.4 and section 15.4, respectively.

8 ANALYSIS OF PHARMACOKINETICS

All analyses will be run on the PK population.

Drug concentration will be analyzed descriptively (n, arithmetic mean, SD and SE, median, minimum and maximum, 5% and 95% percentiles, CV% of arithmetic mean, geometric mean and geometric SD) by treatment group and timepoint.

Individual pharmacokinetic concentrations will be reported in µg/mL. Concentrations in ng/mL will be converted. Values BQL will be handled as detailed in section 4.3.2.

Pharmacokinetic concentrations and descriptive statistics will be reported to 3 significant digits for values up to, but not including 1000. Values equal to and above 1000 will be reported as the value without decimal signs. In case the actual sampling time deviates more than allowed per study protocol from the nominal time, these samples will not be included in the calculation of descriptive statistics.

A detailed list of tables and listings can be found in section 13.3 and section 15.4, respectively.

9 ANALYSIS OF IMMUNOGENICITY

9.1 Available parameters

Immunogenicity is assessed via a tiered sample analysis approach (illustrated in Figure 1). In a first step all samples will be analyzed in the conventional anti-drug antibody (ADA) assay and only samples from subjects classified as 'Pre-Ab Pos – Equivocal' will be further analyzed in the mADA assay. This assay is a characterization assay and has been developed to enable detection of TE ADA in presence of (high) pre-existing antibody (pre-Ab) levels. Furthermore, positive ADA samples will be evaluated for their neutralizing potential in the neutralizing antibody (NAb) assay.

As such, the available parameters per sample are:

- ADA log10(titer) (no data imputation)
- mADA log10(titer) (for subset of subjects only, no data imputation)
- NAb normalized response (for subset of samples only, data imputation required for ADA negative samples)

Additional provided information needed for data interpretation is:

- ADA Minimum Significance Ratio (MSR): MSR is an assay parameter reflecting precision of titer assessments and is needed to interpret the treatment emergent (TE) response for subjects presenting with pre-Ab. In such cases, pre- and post-dose titers will be compared. The titer is considered to be significantly increased post-dose, if the highest post-dose titer compared to the highest pre-dose titer is higher than the MSR value. The increase of the log10(titer) post- versus pre-dose should be > log10(MSR).
- mADA MSR: MSR value determined in the mADA assay, similar application as described above, but applied to mADA titers.
- NAb assay cutpoint (CP): cut-off value to determine if a sample is negative or positive. Since the NAb assay is an inhibition assay, samples equal to or below the CP will be considered positive.

Figure 1: Schematic representation of tiered immunogenicity testing

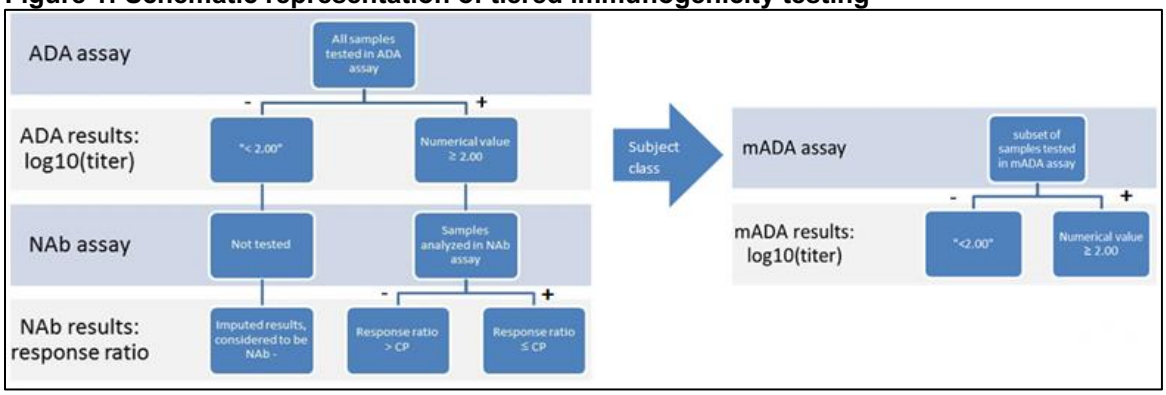

Table 1 provides clarification on when the reported value of a sample needs to be categorized as "negative", "positive" or "missing" in each of the respective assays. Samples scoring negative in the ADA or mADA assay are not titrated and the respective log10(titer) is reported as <log10(Minimal required dilution [MRD]) with MRD=100, i.e. log10(titer) <2.00. The latter will not to be included in descriptive statistics on titers; but they will be included in the individual line plot, set arbitrarily to 1.80. Similarly, NAb negative results should not be included in descriptive statistics on response ratios, but will be included in the individual line plot, set arbitrarily to 1.00.

Table 1: Reported values in each assay and corresponding data interpretation

Reported value				Data interpretation
ADA: log10(titer)	**mADA: log10(titer)**	**NAb data from parent trial: neutralizing response[1]**	**NAb data C203 post-baseline visits[2]: response ratio**	
"< 2.00"	"< 2.00"	"Y"	Numeric value > CP[3]	**NEGATIVE (NEG) (ISORRES)**
Numeric value ≥ 2.00	Numeric value ≥ 2.00	"N"	Numeric value ≤ CP[3]	**POSITIVE (POS) (ISORRES)**
"NA" or "NR"	"NA" or "NR"	"NA" or "NR"	"NA" or "NR"	**MISSING (COVAL)**

[1] Parent trial screening and baseline visit as well as OLE baseline visit (corresponding to w24/w12 for C201/C202 respectively)
[2] NAb results reporting strategy has been adapted for study C203 compared to parent trial: NAb data are reported as response ratios, in contrast to C201/C202 results, which were reported as Y/N in the clinical database
[3] CP will be reported along with actual sample results

The immunogenicity status prior to drug administration will be derived from the parent trial (ALX0061-C201 or ALX0061-202) screening and baseline sample results (see further). The TE/post-dose response will be evaluated based on samples collected within ALX0061-C203 (OLE) at following timepoints according to schedule of assessment: Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and

FU or ET visit. In all immunogenicity TFLs organized per timepoint, both parent screening & baseline as well as Week 0 need to be included.

9.2 Missing results and data imputation

The mADA assay will only be performed on a subset of samples ('Pre-Ab Pos – Equivocal'). In case no mADA results are reported for a given subject, the corresponding fields in the listing will remain empty and no data imputation is to be done.

The NAb assay will only be performed on a subset of samples (ADA positive samples). In case no NAb results are reported (empty field), the following imputations will be made (imputed values will be followed by "*" in listings):

- No NAb record and corresponding ADA result NEGATIVE: these samples will be considered NEGATIVE and should appear as "NEG*" in listings
- No NAb record and corresponding ADA result Not Analyzed (NA): these samples will be considered "NA" and should appear as "NA*" in listings
- No NAb record and corresponding ADA result POSITIVE or No Result (NR): these samples will be considered "NR" and should appear as "NR*" in listings

9.3 Subject classifications (derived parameters)

Subject classification on immunogenicity results (ADA, mADA and NAb) will be based on the assay results (titers or response ratios outlined in 9.1). Subject classifications will be attributed based on all available data for each subject.

One subject will either have three or four subject classifications:

- an ADA subject classification (mandatory)
- a mADA subject classification (optional, only for subjects with ADA classification "Pre-Ab positive – Equivocal")
- an overall subject classification (combining results of ADA and mADA analysis)
- a NAb subject classification (mandatory, derived from reported and/or imputed results)

Subjects will be classified based on their pre-dose status (i.e. screening and baseline) and treatment-emergent (TE) status (post-dose response). The immunogenicity status prior to drug administration will be derived from the parent trial (ALX0061-C201 or ALX0061-C202) screening and baseline sample results. The TE/post-dose response will be evaluated based on samples collected within ALX0061-C203 at following time points: Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and FU or ET visit.

9.3.1 ADA subject classification

All available ADA assay results (positive or negative) per subject will be evaluated and subjects will be classified based on a combined statement on pre-Ab status (pre-Ab neg or pre-Ab pos, to be derived from parent trial) and the TE ADA response (TE neg, TE pos, Equivocal (EQ) or inconclusive) as outlined in Table 2.

For each subject, one ADA subject classification will be determined. This implies that in the listing subject classification will be identical for all ADA visits of the given subject.

Table 2: ADA subject classification

ADA subject class	Evaluation based on all ADA assay results (titer) of the respective subject	
	Pre-Ab status evaluated on screening and baseline sample of parent trial	**TE ADA Response evaluated based on Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and FU or ET visit**
PRE-AB NEG - TE ADA NEG	All pre-dose samples negative	All post-dose samples ADA negative
PRE-AB NEG - TE ADA POS	All pre-dose samples negative	At least one positive ADA sample(s) post-dose
PRE-AB NEG - TE ADA INCONCLUSIVE	All pre-dose samples negative	All post-dose samples(/results) are missing
PRE-AB POS - TE ADA NEG	One or more of the pre-dose samples is positive	All post-dose samples are ADA negative
PRE-AB POS - TE ADA POS	One or more of the pre-dose samples is positive	Significant increase in titer post-dose versus pre-dose*
PRE-AB POS - EQ	One or more of the pre-dose samples is positive	Positive ADA sample(s) post-dose and no significant increase in titer post-dose versus pre-dose*
PRE-AB POS – TE ADA INCONCLUSIVE	One or more of the pre-dose samples is positive	All post-dose samples(/results) are missing
MISSING	No pre-dose samples are available	N/A

* The titer is considered to be significantly increased post-dose, if the highest post-dose titer compared to the highest pre-dose titer is higher than the ADA MSR value: the increase of the log10(titer) post- versus pre-dose should be > log10(MSR).

9.3.2 mADA subject classification

All available mADA assay results (positive or negative) per subject will be evaluated and subjects will be classified based on a combined statement on pre-Ab status (pre-Ab neg or pre-Ab pos, to be derived from parent trial) and the TE ADA response (TE neg, TE pos, EQ or inconclusive) as outlined in Table 3.

For each subject tested in the mADA assay (i.e. “PRE-AB POS – EQ” subjects based on ADA assessment), one mADA subject classification will be determined. This implies that in the listing this will be identical for all ADA visits of the given subject. In case the subject was not tested in the mADA assay, corresponding fields in the listing will remain empty.

Table 3: mADA subject classification

mADA subject class	Evaluation based on all mADA assay results (titer) of the respective subject	
	Pre-Ab status evaluated on screening and baseline of parent trial	**TE ADA Response evaluated based on Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and FU or ET visit**
PRE-AB NEG - TE ADA NEG	All pre-dose samples negative	All post-dose samples ADA negative
PRE-AB NEG - TE ADA POS	All pre-dose samples negative	At least one positive ADA sample(s) post-dose
PRE-AB NEG - TE ADA INCONCLUSIVE	All pre-dose samples negative	All post-dose samples(/results) are missing

PRE-AB POS - TE ADA NEG	One or more of the pre-dose samples is positive	All post-dose samples ADA negative
PRE-AB POS - TE ADA POS	One or more of the pre-dose samples is positive	Significant increase in titer post-dose versus pre-dose*
PRE-AB POS - EQ	One or more of the pre-dose samples is positive	Positive ADA sample(s) post-dose and no significant increase in titer post-dose versus pre-dose*
PRE-AB POS – TE ADA INCONCLUSIVE	One or more of the pre-dose samples is positive	All post-dose samples(/results) are missing
MISSING	No pre-dose samples are available	N/A

* The titer is considered to be significantly increased post-dose, if the highest post-dose titer compared to the highest pre-dose titer is higher than the mADA MSR value: the increase of the log10(titer) post- versus pre-dose should be > log10(MSR).

9.3.3 Overall subject classification

Overall subject classification will be determined based on the combined results of ADA and/or mADA analysis. The classification is identical to the ADA subject classification, except for subjects classified as “pre-Ab pos - EQ” based on ADA assay results which are further evaluated in the mADA assay. For those subjects, a re-classification is done based on combined ADA and mADA assay. This is illustrated in Table 4. For each subject, one overall subject classification is to be assigned. This implies that in the listing the overall subject classification will be identical for all ADA visits of the given subject.

Table 4: ADA, mADA and Overall subject classification

ADA subject classification	mADA subject classification	Overall subject classification
Missing	-	Missing
PRE-AB NEG - TE ADA NEG	-	PRE-AB NEG - TE ADA NEG
PRE-AB NEG - TE ADA POS	-	PRE-AB NEG - TE ADA POS
PRE-AB NEG - TE ADA INCONCLUSIVE	-	PRE-AB NEG - TE ADA INCONCLUSIVE
PRE-AB POS - TE ADA NEG	-	PRE-AB POS - TE ADA NEG
PRE-AB POS - TE ADA POS	-	PRE-AB POS - TE ADA POS
PRE-AB POS - TE ADA INCONCLUSIVE	-	PRE-AB POS - TE ADA INCONCLUSIVE
PRE-AB POS - EQ	Missing	PRE-AB POS - EQ
	PRE-AB NEG - TE ADA NEG	PRE-AB POS - EQ
	PRE-AB NEG - TE ADA POS	PRE-AB POS - TE ADA POS
	PRE-AB NEG - TE ADA INCONCLUSIVE	PRE-AB POS - EQ
	PRE-AB POS - TE ADA POS	PRE-AB POS - TE ADA POS
	PRE-AB POS - TE ADA INCONCLUSIVE	PRE-AB POS - EQ
	PRE-AB POS – TE ADA NEG	PRE-AB POS – EQ
	PRE-AB POS – EQ	PRE-AB POS – EQ

9.3.4 NAb subject class

All available NAb assay results (*) (positive or (imputed) negative) per subject will be evaluated and subjects will be classified based on a combined statement on pre-dose status (pre-dose neg or pre-dose pos, to be derived from parent trial) and the post-dose response (negative, positive or inconclusive) as outlined in Table 5.

(*) Note that for the pre-dose Nab results (screening and baseline) from the parent trials (ALX0061-C201 or ALX0061-C202) 'Y' (Yes) should be imputed to POS and 'N' (No) should be imputed to NEG.

For each subject, one NAb subject classification is to be determined. This implies that in the listing this will be identical for all NAb visits of the given subject. For subjects with no positive ADA samples, the NAb results were imputed as "NEG*", and the NAb subject class will be "PRE-DOSE NEG - NEG ON TREATMENT". The latter also has to appear in the Listing.

Table 5: NAb subject classification

NAb subject class	**Evaluation based on all NAb assay results (titer) of the respective subject**	
	Pre-dose status evaluated on screening and baseline of parent trial	**Response on treatment evaluated based on Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and FU or ET visit**
PRE-DOSE NEG - NEG ON TREATMENT	All pre-dose samples negative (reported or imputed)	All post-dose samples are negative (reported or imputed)
PRE-DOSE NEG - POS ON TREATMENT	All pre-dose samples negative (reported or imputed)	At least one positive sample(s) post-dose
PRE-DOSE POS - NEG ON TREATMENT	One or more of the pre-dose samples is positive	All post-dose samples are negative (reported or imputed)
PRE-DOSE POS - POS ON TREATMENT	One or more of the pre-dose samples is positive	At least one positive sample(s) post-dose
PRE-DOSE NEG - INCONCLUSIVE	All pre-dose samples negative (reported or imputed)	All post-dose samples(/results) are missing
PRE-DOSE POS - INCONCLUSIVE	One or more of the pre-dose samples is positive	All post-dose samples(/results) are missing
MISSING	No pre-dose (and/or post-dose) samples are available	No pre-dose (and/or post-dose) samples are available

9.4 Pre-Ab prevalence and TE ADA Incidence calculations

9.4.1 Incidence of ADA and derived sets

The following subject categories (1-8) and derived sets (9-15) will be used in the ADA incidence tables:

1. PRE-AB NEG - TE ADA NEG
2. PRE-AB NEG - TE ADA POS
3. PRE-AB NEG - TE ADA INCONCLUSIVE
4. PRE-AB POS - TE ADA NEG
5. PRE-AB POS - TE ADA POS
6. PRE-AB POS - EQ
7. PRE-AB POS – TE ADA INCONCLUSIVE

8. MISSING
9. TOTAL PRE-AB NEG (equals 1 + 2 + 3)
10. TOTAL PRE-AB POS (equals 4 + 5 + 6 + 7)
11. TOTAL TE ADA NEG (equals 1 + 4)
12. TOTAL TE ADA POS (equals 2 + 5)
13. TOTAL TE INCONCLUSIVE (3 + 7)
14. TE POS within PRE-AB NEG POPULATION (equals 2/9)
15. TE POS within PRE-AB POS POPULATION (equals 5/10)

Incidences will be shown per treatment group. The number of subjects (s) in each subject category or derived set (excluding 14-15) is divided by the number of subjects (n) within each treatment group, excluding the subjects who are classified as missing. Incidences are shown as s/n (%), with the calculated percentage added in between brackets.

9.4.2 Incidence of mADA subject classes and derived sets

The same subject categories (1-8) and derived sets (9-15) as shown above in 9.4.1 will be presented in the mADA incidence table, but the denominator to calculate incidences differs.

Incidences will be shown per treatment group. The number of subjects (s) in each subject category or derived set (excluding 14-15) is divided by the number of subjects (n) within each treatment group which were characterized in mADA assay (i.e. “PRE-AB POS – EQ” in ADA assay), excluding the subjects who are classified as missing. Incidences are shown as s/n (%), with the calculated percentage added in between brackets.

9.4.3 Incidence of overall subject classification (ADA, mADA results) and derived sets

The following subject categories (1-8) and derived sets (9-13) will be used in the overall incidence tables:

1. PRE-AB NEG - TE ADA NEG
2. PRE-AB NEG - TE ADA POS
3. PRE-AB NEG - TE ADA INCONCLUSIVE
4. PRE-AB POS - TE ADA NEG
5. PRE-AB POS - TE ADA POS
6. PRE-AB POS - EQ
7. PRE-AB POS – TE ADA INCONCLUSIVE
8. MISSING
9. TOTAL PRE-AB NEG (equals 1 + 2 + 3)
10. TOTAL PRE-AB POS (equals 4 + 5 + 6 + 7)
11. TOTAL TE ADA NEG (equals 1 + 4)
12. TOTAL TE ADA POS (equals 2 + 5)
13. TOTAL TE INCONCLUSIVE (3 + 7)
14. TE POS within PRE-AB NEG POPULATION (equals 2/9)
15. TE POS within PRE-AB POS POPULATION (equals 5/10)

Incidences will be shown per treatment group. The number of subjects (s) in each subject category or derived set (excluding 14-15) is divided by the number of subjects (n) within each treatment group, excluding the subjects who are classified as missing. Incidences are shown as s/n (%), with the calculated percentage added in between brackets.

9.4.4 Incidence of NAb subject classes and derived sets

The following subject categories (1-7) and derived sets (8-14) will be used in the mADA incidence tables:

1. PRE-DOSE NEG - NEG ON TREATMENT
2. PRE-DOSE NEG - POS ON TREATMENT
3. PRE-DOSE POS - NEG ON TREATMENT
4. PRE-DOSE POS - POS ON TREATMENT
5. PRE-DOSE NEG - INCONCLUSIVE
6. PRE-DOSE POS - INCONCLUSIVE
7. MISSING

8. TOTAL PRE-DOSE NEG (equals 1 + 2 + 5)
9. TOTAL PRE-DOSE POS (equals 3 + 4 + 6)
10. TOTAL NEG ON TREATMENT (equals 1 + 3)
11. TOTAL POS ON TREATMENT (equals 2 + 4)
12. TOTAL INCONCLUSIVE (5 + 6)

13. POS ON TREATMENT within PRE-DOSE NEG POPULATION (equals 2/8)
14. POS ON TREATMENT within PRE-DOSE POS POPULATION (equals 4/9)

Incidences will be shown per treatment group. The number of subjects (s) in each subject category or derived set (excluding 13-14) is divided by the number of subjects (n) within each treatment group, excluding the subjects who are classified as missing. Incidences are shown as s/n (%), with the calculated percentage added in between brackets.

9.4.5 Safety subgroup analysis

For the following subgroups, the incidence rates will be determined of the different overall subject classifications (1-8) as listed in 9.4.3.

- Injection-site reaction
  - No injection-site reaction
  - At least 1 injection-site reaction
- Hypersensitivity reaction
  - No hypersensitivity reaction
  - At least 1 hypersensitivity reaction

9.4.6 ADA and NAb incidence over time

For ADA and NAb data, incidence of positive samples over time will be calculated. Positivity needs to be deducted based on reported titer values (ADA) or response ratio (NAb), as clarified in Table 1. Incidence calculation should account for subject drop-out: for each visit, the number of positive samples is divided by the available results for the given visit (positive + negative samples (reported and/or imputed), excluding missing values (NA & NR)). The latter should be clarified in a footnote of the concerning tables.

10 INTERIM ANALYSES

No interim analysis are foreseen.

11 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The subgroup analysis for efficacy according to the protocol included demographics (including weight and region), baseline disease characteristics, and baseline and prior medications, but will be limited to age category and geographic region.

A second sensitivity analysis will be done for efficacy based on NRI for the categorical endpoints analysed in the first sensitivity analysis.

The protocol mentions a subgroup analysis for safety which will not be performed.

The protocol states descriptive statistics will be used to summarize changes from baseline, but model-based, baseline-adjusted LS means and 95% CI will be used for efficacy endpoints.

12 CONVENTIONS

12.1 Analysis Phases and Visit Windows

12.1.1 Algorithm of allocating visits to time windows

All assessments (including unscheduled assessments) will be placed into time windows according to their relative day (DY) in the study, according to the following allocation table:

Time point label	Target day	Interval lower bound	Interval upper bound
Week 4	29	1	43
Week 8	57	44	71
Week 12	85	72	126
Week 24	169	141	197
Week 36	253	225	281

Time point label	Target day	Interval lower bound	Interval upper bound
Week 48	337	309	365
Week 60	421	393	449
Week 72	505	477	533
Week 84	589	561	617
Week 96	673	645	700
Week 104	729	701	Week 102 visit date + 28 days
Follow-up		Last treatment date + 29 days	+INF

The definition of the time window for “Follow-up” implies that for Week 4 to Week 104 assessments, if the assessment or sample date is more than 28 days after the last dose of treatment, the assessment will be mapped to the Follow-up visit. If the assessment or sample date is less than or equal to 28 days after the last dose of treatment (including for assessments or samples taken at the early termination visit, if this condition holds), the assessment will be mapped to the corresponding analysis visit, in case it falls within the interval lower and upper bound for this analysis visit.

Baseline is defined in section 4.2.1.

Tables, figures and listings will present the time points as defined above, not the case report form (CRF) visits.

12.1.2 Selection of visits

It is possible that more than one visit gets allocated into the same time window. In that case, only one visit will be selected for analysis tables and figures. The nonselected visit(s) will only be listed. In case an assessment gets allocated to a time window at which the assessment was not scheduled as per protocol, this assessment will not be shown in the tables or figures but will only be listed.

The visit with a DY closest to the target day will be selected. In case of ties on the same day with time not available, the assessment linked with the CRF visit will be selected for analysis.

In case more than one parameter is measured per time point (e.g. for lab), the selection is performed per parameter and per time point, not per “sample” and per time point. Missing values are removed before the selection is made.

12.2 General characteristics

12.2.1 Derivation of exposure parameters

The following exposure parameters will be derived:

- Total treatment duration = date of last study drug administration – date of first study drug administration in C203 + 14 days
- Total number of study drug doses received during C203
- Cumulative dose of study drug received: total dose of study drug in mg administered during C203
- Compliance = 100 * (total number of study drug doses actually received during C203/expected number of study drug doses during C203)

  Where the expected number of study drug doses is calculated as follows:

  - For subjects completing the study: 52
  - For subjects prematurely discontinuing the study: 1 baseline dose + integer of (date of last study drug administration – date of first study drug administration in C203)/14

12.3 Efficacy

The following assessments will be used to derive the efficacy parameters:

- Physician's assessment of tender/painful and swollen joint count: 68 joints are assessed for tenderness (TJC) and 66 joints are assessed for swelling (SJC). Joints that underwent intra-articular (IA) corticosteroid injection during the last 4 weeks will be considered as swollen and tender. Only joints that were ticked 'Yes' will be taken into account. Left and right will be summed to obtain one overall joint count.
- Physician's assessment of tender/painful and swollen joint count, selected: a selection of 28 joints are assessed for tenderness (TJC28) and for swelling (SJC28)
- Average duration of morning stiffness
- Patient's assessment of pain (100 mm) (VAS)
- Patient's global assessment of disease activity (100 mm) (VASPA)
- Physician's global assessment of disease activity (100 mm) (VASPHA)
- C-reactive protein concentration (mg/L) (CRP)
- Erythrocyte sedimentation rate (mm/h) (ESR)

- HAQ-DI (/60): 20-question instrument to assess the degree of difficulty to accomplish tasks in 8 functional areas (dressing and grooming, hygiene, arising, reach, eating, grip, walking, common daily activities) over the previous week. Responses for each question range from 0 (no difficulty) to 3 (unable to do). The score is calculated in 3 steps:
    - Derivation of the 8 category scores, by selecting the highest sub-category score
    - Adjusting for use of aids/devices and/or help from another person: scores of 0 or 1 will then be increased to 2
    - Calculating the mean of the category scores. In case less than 6 category scores are available, the HAQ-DI score will not be computed.
- SF-36 questionnaire: 36 item questionnaire that can be summarized into 8 domains (physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, mental health) and into 2 summary measures (physical component and mental component). Version 2 of the questionnaire was used (see Section 16.6. Appendix 6)
- FACIT-F: quality of life (QOL) questionnaire consisting of 40 questions ranging from 0 to 4, grouped in 5 domains (physical well-being, social/family well-being, emotional well-being, functional well-being and fatigue). Scoring guidelines to derive subscores and total scores can be found in section 16.4.

Based on the above assessments, the following parameters will be derived:

- ACR20 response:
    - YES if ALL of the following criteria are fulfilled:
        - % improvement relative to baseline in tender/painful joint count >= 20%
        - % improvement relative to baseline in swollen joint count >= 20%
        - % improvement relative to baseline >= 20% for at least 3 of the following assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI, CRP
    - NO if not all of the above criteria are fulfilled
    - Handling of missing values:
        - if TJC or SJC are missing, ACR response will be missing
        - if any of patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI or CRP are missing, but at least 3 have a change from baseline >= 20% or at least 3 have a change from baseline < 20%, ACR response can be derived, otherwise it will be missing.
- ACR50 response: definition similar to ACR20 response, but using 50% as cut-off
- ACR70 response: definition similar to ACR20 response, but using 70% as cut-off

- ACR-N index of improvement: minimum of the following 3 criteria:
  - % improvement relative to baseline in tender/painful joint count
  - % improvement relative to baseline in swollen joint count
  - Median % improvement relative to baseline of the following assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI, CRP
- $DAS28(ESR) = \left(0.56 \times \sqrt{TJC28}\right) + \left(0.28 \times \sqrt{SJC28}\right) + (0.70 \times ln[ESR]) + (0.014 \times VASPA)$, with VASPA measured in mm
- $DAS28(CRP) = \left(0.56 \times \sqrt{TJC28}\right) + \left(0.28 \times \sqrt{SJC28}\right) + (0.36 \times ln[CRP + 1]) + (0.014 \times VASPA) + 0.96$, with VASPA measured in mm and CRP in mg/L
- EULAR response is defined as follows based on the actual value of DAS28 (DAS28) in both ESR and CRP and the change from baseline in DAS28 (ΔDAS28) in both ESR and CRP:
  - Good response: $\Delta DAS28 > 1.2\ AND\ DAS28 \leq 3.2$
  - Moderate response $(\Delta DAS28 > 1.2\ AND\ DAS28 > 3.2)\ OR\ (0.6 < \Delta DAS28 \leq 1.2\ AND\ DAS28 \leq 5.1)$
  - No response $(\Delta DAS28 \leq 0.6)\ OR\ (0.6 < \Delta DAS28 \leq 1.2\ AND\ DAS28 > 5.1)$
  - Pooled category Moderate+Good will be shown as well.
- Disease activity is defined as follows based on the actual value of DAS28(ESR):
  - Remission: $DAS28(ESR) < 2.6$
  - Low disease activity: $2.6 \leq DAS28(ESR) \leq 3.2$
  - Moderate disease activity: $3.2 < DAS28(ESR) \leq 5.1$
  - High disease activity: $DAS28(ESR) > 5.1$
  - Pooled category Remission + Low disease activity will be shown as well
- Disease activity is defined as follows based on the actual value of DAS28(CRP):
  - $DAS28(CRP) < 2.6$
  - Low disease activity: $2.6 \leq DAS28(CRP) \leq 3.2$
  - Moderate disease activity: $3.2 < DAS28(CRP) \leq 5.1$
  - High disease activity: $DAS28(CRP) > 5.1$
  - Pooled category $DAS28(CRP) < 2.6$ + Low disease activity will be shown as well
- Boolean remission is defined as follows:
  - Yes: $TJC28 \leq 1\ AND\ SJC28 \leq 1\ AND\ VASPA \leq 1\ \text{cm}\ AND\ CRP \leq 1\ \text{mg/dL}$
  - No: else
- Clinically meaningful improvement in HAQ-DI (clinically meaningful improvement from baseline – absolute change) is defined as follows:
  - Yes: $\Delta HAQDI \geq 0.25$
  - No: $\Delta HAQDI < 0.25$

- Normal physical function based on HAQ-DI is defined as follows:
  - Yes: $HAQDI \leq 0.5$
  - No: $HAQDI > 0.5$
- CDAI score = TJC28 + SJC28 + VASPA (cm) + VASPHA (cm)
- CDAI classification:
  - Remission: $CDAI \leq 2.8$
  - Low disease activity: $2.8 < CDAI \leq 10$
  - Moderate disease activity: $10 < CDAI \leq 22$
  - High disease activity: $22 < CDAI$
  - Pooled category Remission+Low disease activity will be shown as well
- SDAI score = TJC28 + SJC28 + VASPA (cm) + VASPHA (cm) + CRP (mg/dL)
- SDAI classification:
  - Remission: $SDAI \leq 3.3$
  - Low disease activity: $3.3 < SDAI \leq 11$
  - Moderate disease activity: $11 < SDAI \leq 26$
  - High disease activity: $26 < SDAI$
  - Pooled category Remission+Low disease activity will be shown as well
- Maintained remission at Week x: remission at Week x and all consecutive time points.

MTX and corticosteroid dose related endpoints will be derived as follows:

- MTX dose decrease from baseline at W0,W48 and W104:
  - Yes: daily dose at Week 0/ Week 48 / Week 104 visit < baseline dose
  - No: else
- Discontinuation of MTX dose at W0,W48 and W104:
  - Yes: daily dose at Week 0/ Week 48 / Week 104 visit = 0
  - No: else
- Change from baseline of MTX dose at Week 0/ Week 48 / Week 104
- Change from baseline of corticosteroid dose at Week 0/ Week 48 / Week 104

12.4 Safety

12.4.1 Adverse events

AE onset day and AE duration are defined as follows:

AE onset day

- AE start date – date of first study drug intake in C203 + 1 day (when the AE start date is completely known)
- missing (when the AE start date is incomplete or unknown).

AE duration

- AE stop date – AE start date + 1 day (when both dates are completely known)
- trial termination date – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the trial): in this case the duration will be presented as “>x days” in the listing rather than “x days”
- missing (when the AE start date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date).

12.4.2 Laboratory

Values will be scored as abnormally low (L), normal (N) or abnormally high (H). A value is classified as abnormally low when the value < lower limit of the normal range. A value is classified as abnormally high when the value > upper limit of the normal range. Tests without normal ranges will not be scored.

An original value like “<X” where X equals the lower limit of the normal range will be classified as abnormally low (L). An original value like “>X” where X equals the upper limit of the normal range will be classified as abnormally high (H).

Urinalysis tests for which a normal range is available, will also be categorized as L, N, or H. If there is doubt on whether the result is within normal range or not, the worst-case will be taken. E.g., when the test result equals “4 to 6” and the normal range is 0-5, then the test result will be classified as abnormally high (H) if it is a post-baseline visit, and will be classified as normal (N) if it is a baseline visit. In such cases, the original urinalysis test result will not be used for the tables, but will only be listed. Urinalysis tests for which no normal range is available, will be tabulated separately as categorical data.

All nonmissing post-baseline values (including unscheduled measurements and follow-up measurements) will be used to derive the following worst-case abnormalities for each parameter:

- H = abnormally high: at least one postdose measurement is above the normal range, and there are no values below the normal range.
- L = abnormally low: at least one postdose measurement is below the normal range, and there are no values above the normal range.
- H+L = abnormally high and low: at least one postdose measurement is above the normal range, and at least one other postdose measurement is below the normal range.
- N = normal: all postdose measurements are within normal limits.

13 INDEX OF TABLES

13.1 General

Table 14.1.1.1: Subject disposition: Tabulation by analysis population

Tabulation of the number of subjects in each of the analysis populations defined in section 4.1.

Population: all screened population.

Table 14.1.1.2: Subject disposition: Tabulation by region and country

Tabulation of the number of subjects per region and country.

Population: ITO population.

Table 14.1.1.3: Subject disposition: Tabulation by time point

Tabulation of the number of subjects per time point.

Population: ITO population.

Table 14.1.1.4: Trial termination: Tabulation

Tabulation of study completion / study discontinuations and the primary reason for discontinuation.

Population: ITO population.

Table 14.1.1.5: Major protocol deviations: Tabulation

Tabulation of the major protocol deviations per category including Selection criteria not met / Subject not withdrawn as per protocol / Prohibited concomitant medication / Treatment non-compliance / Safety assessment deviation / Efficacy assessment deviation / Other.

Population: ITO population.

Table 14.1.2.1: Demographic data: Tabulation and descriptive statistics

Descriptive statistics for continuous parameters and frequency tabulation for categorical parameters.

Population: ITO population.

Table 14.1.2.2: Baseline disease characteristics: Tabulation and descriptive statistics

Descriptive statistics for continuous parameters and frequency tabulation for categorical parameters.

Population: ITO population.

Table 14.1.2.3: Tabulation of RA related concomitant therapies by generic term

Tabulation of the generic terms of RA related concomitant therapies.

Population: safety population.

Table 14.1.2.4: Tabulation of non-RA related concomitant therapies by generic term

Tabulation of the generic terms of non-RA related concomitant therapies.

Population: safety population.

Table 14.1.2.5: Exposure to study medication: Descriptive statistics

Descriptive statistics of exposure parameters except home administration, including compliance.

Population: safety population.

Table 14.1.2.6: Exposure to study medication: Home administration

Tabulation of any study drug administration received at home (yes/no) and of all study drug administrations received at home, except those received during a scheduled study visit (yes/no).

Population: safety population.

13.2 Efficacy

Table 14.2.1.1.1: ACR response - ACR20 response

Frequency tabulation of the ACR20 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR20 response.

Population: ITO.

Table 14.2.1.1.2: ACR response - ACR50 response

Frequency tabulation of the ACR50 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR50 response.

Population: ITO.

Table 14.2.1.1.3: ACR response - ACR70 response

Frequency tabulation of the ACR70 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR70 response.

Population: ITO.

Table 14.2.1.1.4: ACR response - ACR-N index of improvement

Descriptive statistics of the ACR-N index actual values at each time point.

Population: ITO.

Table 14.2.1.2.1: DAS28 Score – Actual values and change from baseline

Descriptive statistics of the DAS28(CRP) and the DAS28(ESR) score actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline DAS28 score as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.2.2: DAS28 Score – EULAR (using CRP and using ESR) response

Frequency tabulation of the EULAR response, based on the DAS28(CRP) and the DAS28(ESR) score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving EULAR response.

Population: ITO.

Table 14.2.1.2.3: DAS28 Score – Disease activity (ESR)

Frequency tabulation of the disease activity, based on the DAS28(ESR) score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving LDA/remission, remission and maintained remission.

Population: ITO.

Table 14.2.1.2.4: DAS28 Score – Disease activity (CRP)

Frequency tabulation of the disease activity, based on the DAS28(CRP) score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving DAS28(CRP) ≤ 3.2, DAS28(CRP) < 2.6 and maintained DAS28(CRP) < 2.6.

Population: ITO.

Table 14.2.1.3.1: Boolean disease remission definition

Frequency tabulation of the disease remission, based on the Boolean definition at each time point, including a Wilson score 95% CI on the percentage of subjects achieving remission and maintained remission.

Population: ITO.

Table 14.2.1.4.1: CDAI Score – Actual values and change from baseline

Descriptive statistics of the CDAI score actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline CDAI score as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.4.2: CDAI Score – Disease activity

Frequency tabulation of the disease activity, based on the CDAI score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving LDA/remission, remission and maintained remission.

Population: ITO.

Table 14.2.1.5.1: SDAI Score – Actual values and change from baseline

Descriptive statistics of the SDAI score actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline SDAI score as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.5.2: SDAI Score – Disease activity

Frequency tabulation of the disease activity, based on the SDAI score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving LDA/remission, remission and maintained remission.

Population: ITO.

Table 14.2.1.6.1: HAQ-DI Score – Actual values and change from baseline

Descriptive statistics of the HAQ-DI score actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline HAQ-DI score as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.6.2: HAQ-DI Score – Clinically meaningful improvement

Frequency tabulation of the clinically meaningful improvement, based on the HAQ-DI score ($\Delta HAQDI \geq 0.25$) at each time point, including a Wilson score 95% CI on the percentage of subjects with HAQ-DI response.

Population: ITO.

Table 14.2.1.6.3: HAQ-DI Score – Normal physical function

Frequency tabulation of normal physical function, based on the HAQ-DI score ($HAQDI \leq 0.5$) at each time point, including a Wilson score 95% CI on the percentage of subjects achieving normal physical function.

Population: ITO.

Table 14.2.1.7.1: SF-36 – Physical and mental component scores - Actual values and change from baseline

Descriptive statistics of the physical and mental component scores actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline score as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.8.1: FACIT-F – Actual values and change from baseline

Descriptive statistics of the FACIT-F total score and scores of subscales actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline FACIT-F score as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.9.1: Duration of morning stiffness – Actual values and change from baseline

Descriptive statistics of the duration of morning stiffness actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline duration as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.10.1: VAS scales – Actual values and change from baseline

Descriptive statistics of the patient's assessment of pain VAS, patient's global assessment of disease activity VAS and the physician's global assessment of disease activity VAS actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline VAS as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.11.1: CRP and ESR – Actual values and change from baseline

Descriptive statistics of CRP and ESR concentrations actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline CRP/ESR as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.12.1: TJC and SJC – Actual values and change from baseline

Descriptive statistics of tender joint counts and swollen joint counts actual values and change from baseline at each time point. Additionally, the change from baseline at each

time point will be modelled using an ANCOVA model with treatment group and baseline TJC/SJC count as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.13.1: RA therapy reduction – MTX dose reduction

Frequency tabulation of MTX dose reduction at 1 and 2 years, including a Wilson score 95% CI on the percentage of subjects achieving MTX dose reduction.

Population: ITO.

Table 14.2.1.13.2: RA therapy reduction – MTX discontinuation

Frequency tabulation of MTX discontinuation at 1 and 2 years, including a Wilson score 95% CI on the percentage of subjects discontinuing MTX.

Population: ITO.

Table 14.2.1.13.3: RA therapy reduction – Actual values and change from baseline in MTX dose

Descriptive statistics of the actual values and change from baseline in MTX dose at 1 and 2 years. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline MTX dose as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.1.13.4: RA therapy reduction – Actual values and change from baseline in corticosteroids dose

Descriptive statistics of the actual values and change from baseline in prednisolone equivalent corticosteroids dose at 1 and 2 years. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline prednisolone equivalent corticosteroids dose as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.2.1.1: ACR response - ACR20 response – Last observation carried forward (LOCF)

Frequency tabulation of the ACR20 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR20 response.

Population: ITO.

Table 14.2.2.1.2: ACR response - ACR50 response – Last observation carried forward (LOCF)

Frequency tabulation of the ACR50 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR50 response.

Population: ITO.

Table 14.2.2.1.3: ACR response - ACR70 response – Last observation carried forward (LOCF)

Frequency tabulation of the ACR70 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR70 response.

Population: ITO.

Table 14.2.2.2.1: DAS28 Score – Actual values and change from baseline – Last observation carried forward (LOCF)

Descriptive statistics of the DAS28(CRP) and the DAS28(ESR) score actual values and change from baseline at each time point. Additionally, the change from baseline at each time point will be modelled using an ANCOVA model with treatment group and baseline DAS28 score as covariates and the LS means with 95% CI will be reported.

Population: ITO.

Table 14.2.2.2.2: DAS28 Score – Disease activity (ESR) – Last observation carried forward (LOCF)

Frequency tabulation of the disease activity, based on the DAS28(ESR) score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving LDA/remission, remission and maintained remission.

Population: ITO.

Table 14.2.2.2.3: DAS28 Score – Disease activity (CRP) – Last observation carried forward (LOCF)

Frequency tabulation of the disease activity, based on the DAS28(CRP) score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving DAS28(CRP) ≤ 3.2, DAS28(CRP) < 2.6 and maintained DAS28(CRP) < 2.6.

Population: ITO.

Table 14.2.3.1.1: ACR response - ACR20 response – Non-responder imputation (NRI)

Frequency tabulation of the ACR20 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR20 response.

Population: ITO.

Table 14.2.3.1.2: ACR response - ACR50 response – Non-responder imputation (NRI)

Frequency tabulation of the ACR50 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR50 response.

Population: ITO.

Table 14.2.3.1.3: ACR response - ACR70 response – Non-responder imputation (NRI)

Frequency tabulation of the ACR70 response at each time point, including a Wilson score 95% CI on the percentage of subjects achieving ACR70 response.

Population: ITO.

Table 14.2.3.2.1: DAS28 Score – Disease activity (ESR) – Non-responder imputation (NRI)

Frequency tabulation of the disease activity, based on the DAS28(ESR) score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving LDA/remission, remission and maintained remission.

Population: ITO.

Table 14.2.3.2.2: DAS28 Score – Disease activity (CRP) – Non-responder imputation (NRI)

Frequency tabulation of the disease activity, based on the DAS28(CRP) score at each time point, including a Wilson score 95% CI on the percentage of subjects achieving DAS28(CRP) ≤ 3.2, DAS28(CRP) < 2.6 and maintained DAS28(CRP) < 2.6.

Population: ITO.

Table 14.2.4.1.1: ACR response - ACR20 response by age category

Frequency tabulation of the ACR20 response by age category, including a Wilson score 95% CI on the percentage of subjects achieving ACR20 response for each treatment group.

Population: ITO.

Table 14.2.4.1.2: ACR response - ACR50 response by age category

Frequency tabulation of the ACR50 response by age category, including a Wilson score 95% CI on the percentage of subjects achieving ACR50 response for each treatment group.

Population: ITO.

Table 14.2.4.1.3: ACR response - ACR70 response by age category

Frequency tabulation of the ACR70 response by age category, including a Wilson score 95% CI on the percentage of subjects achieving ACR70 response for each treatment group.

Population: ITO.

Table 14.2.4.2.1: DAS28 Score – Actual values and change from baseline by age category

Descriptive statistics of the DAS28(CRP) and the DAS28(ESR) score actual values and change from baseline at each time point by age category.

Population: ITO.

Table 14.2.4.2.2: DAS28 Score – Disease activity (ESR) by age category

Frequency tabulation of the disease activity, based on the DAS28(ESR) score by age category at each time point, including a Wilson score 95% CI on the percentage of subjects achieving LDA/remission, remission and maintained remission.

Population: ITO.

Table 14.2.4.2.3: DAS28 Score – Disease activity (CRP) by age category

Frequency tabulation of the disease activity, based on the DAS28(CRP) score by age category at each time point, including a Wilson score 95% CI on the percentage of subjects achieving DAS28(CRP) ≤ 3.2, DAS28(CRP) < 2.6 and maintained DAS28(CRP) < 2.6.

Population: ITO.

Table 14.2.5.1.1: ACR response - ACR20 response by region

Frequency tabulation of the ACR20 response by region, including a Wilson score 95% CI on the percentage of subjects achieving ACR20 response for each treatment group.

Population: ITO.

Table 14.2.5.1.2: ACR response - ACR50 response by region

Frequency tabulation of the ACR50 response by region, including a Wilson score 95% CI on the percentage of subjects achieving ACR50 response for each treatment group.

Population: ITO.

Table 14.2.5.1.3: ACR response - ACR70 response by region

Frequency tabulation of the ACR70 response by region, including a Wilson score 95% CI on the percentage of subjects achieving ACR70 response for each treatment group.

Population: ITO.

Table 14.2.5.2.1: DAS28 Score – Actual values and change from baseline by region

Descriptive statistics of the DAS28(CRP) and the DAS28(ESR) score actual values and change from baseline at each time point by region.

Population: ITO.

Table 14.2.5.2.2: DAS28 Score – Disease activity (ESR) by region

Frequency tabulation of the disease activity, based on the DAS28(ESR) score by region at each time point, including a Wilson score 95% CI on the percentage of subjects achieving LDA/remission, remission and maintained remission.

Population: ITO.

Table 14.2.5.2.3: DAS28 Score – Disease activity (CRP) by region

Frequency tabulation of the disease activity, based on the DAS28(CRP) score by region at each time point, including a Wilson score 95% CI on the percentage of subjects achieving DAS28(CRP) ≤ 3.2, DAS28(CRP) < 2.6 and maintained DAS28(CRP) < 2.6.

Population: ITO.

13.3 Pharmacokinetics

Table 14.2.6.1: PK: Descriptive statistics of drug concentrations

Descriptive statistics of drug concentrations by scheduled sampling time and treatment group.

Population: PK population.

13.4 Safety

Table 14.3.1.1: Treatment-emergent adverse events: Summary table

Summary table of TEAEs presenting the number of events, the number and percentage of subjects and the incidence per 100 patient years.

Population: safety population.

Table 14.3.1.2: Treatment-emergent adverse events: Summary table including TEAEs from the parent trials

Summary table of TEAEs including TEAEs from the parent trials presenting the number of events, the number and percentage of subjects and the incidence per 100 patient years.

Population: safety population.

Table 14.3.1.3: Treatment-emergent adverse events: Incidence of adverse events of special interest

Summary table of TEAEs of special interest presenting the number and percentage of subjects, the number of events and the incidence per 100 patient years.

Population: safety population.

Table 14.3.1.4: Treatment-emergent adverse events: Incidence of adverse events of special interest including TEAEs from the parent trials

Summary table of TEAEs of special interest including TEAEs from the parent trials presenting the number and percentage of subjects, the number of events and the incidence per 100 patient years.

Population: safety population.

Table 14.3.1.5: Treatment-emergent adverse events: Tabulation of all adverse events

Tabulation of TEAE preferred terms per system organ class and preferred term.

Population: safety population.

Table 14.3.1.6: Treatment-emergent adverse events: Tabulation of all adverse events by severity

Tabulation of TEAE preferred terms per system organ class and preferred term by severity.

Population: safety population.

Table 14.3.1.7: Treatment-emergent adverse events: Tabulation of adverse events with an incidence of at least 3%

Tabulation of TEAE preferred terms per system organ class. The incidence cut-off of 3% is to be calculated by treatment group.

Population: safety population.

Table 14.3.1.8: Treatment-emergent adverse events: Tabulation of serious adverse events

Tabulation of serious TEAE preferred terms per system organ class and preferred term.

Population: safety population.

Table 14.3.1.9: Treatment-emergent adverse events: Tabulation of non-serious adverse events

Tabulation of non-serious TEAE preferred terms per system organ class and preferred term.

Population: safety population.

Table 14.3.1.10: Treatment-emergent adverse events: Tabulation of study drug-related adverse events

Tabulation of TEAE preferred terms per system organ class and preferred term,selecting only the TEAEs that were study drug-related (as defined in section 7.1).

Population: safety population.

Table 14.3.1.11: Treatment-emergent adverse events: Tabulation of adverse events related to study procedures

Tabulation of TEAE preferred terms per system organ class and preferred term, selecting only the TEAEs that were related to study procedures.

Population: safety population.

Table 14.3.1.12: Treatment-emergent adverse events: Tabulation of the adverse events for which the trial or the study medication were discontinued

Tabulation of TEAE preferred terms per system organ class. Selecting only the TEAEs for which the study treatment was permanently discontinued, or for which the study was discontinued.

Population: safety population.

Table 14.3.2.1: Laboratory data: Descriptive statistics of the actual values and change from baseline per time point

Descriptive statistics per lab test category (hematology, biochemistry, acute phase proteins, urinalysis, coagulation), lab test and unit and time point.

Population: safety population.

Table 14.3.2.2: Laboratory data: Frequency table of urinalysis results per time point

Frequency-tabulation per lab test and time point. The table will present the categorical results of urinalysis tests without normal range at each time point.

Population: safety population.

Table 14.3.2.3: Laboratory data: Cross-tabulation of the abnormalities per time point

Cross-tabulation per lab test category (hematology, biochemistry, acute phase proteins, urinalysis, coagulation), lab test and time point.

Population: safety population.

Table 14.3.2.4: Laboratory data: Cross-tabulation of the CTCAE toxicity per time point for key hematology and biochemistry parameters

Cross-tabulation per lab test category, lab test and time point.

Population: safety population.

Table 14.3.2.5: Laboratory data: Cross-tabulation of the worst-case abnormalities

Cross-tabulation per lab test category (hematology, biochemistry, acute phase proteins, urinalysis, coagulation) and lab test.

Population: safety population.

Table 14.3.2.6: Laboratory data: Cross-tabulation of the worst-case CTCAE toxicity for key hematology and biochemistry parameters

Cross-tabulation per lab category and lab test.

Population: safety population.

Table 14.3.3.1: Vital signs: Descriptive statistics of the actual values and change from baseline per time point

Descriptive statistics per test and unit and time point.

Population: safety population.

13.5 Immunogenicity

Table 14.3.4.1: Immunogenicity: Prevalence and incidence table of pre-Ab and treatment-emergent ADA based on ADA assay results

Table sorted by treatment group. The table will present the incidence of different ADA subject categories and derived sets (see 9.4.1)

Population: safety population.

Table 14.3.4.2: Immunogenicity: Prevalence and incidence table of pre-Ab and treatment-emergent ADA based on mADA assay results

Table sorted by treatment group. The table will present the incidence of different mADA subject categories and derived sets (see 9.4.2).

Population: safety population.

Table 14.3.4.3: Immunogenicity: Prevalence and incidence table of pre-Ab and treatment-emergent ADA based on ADA and mADA assay results (overall subject classification)

Table sorted by treatment group. The table will present the incidence of different overall subject categories and derived sets (see 9.4.3)

Population: safety population.

Table 14.3.4.4: Immunogenicity: Prevalence and incidence table of pre-dose and treatment-emergent ADA based on NAb results

Table sorted by treatment group. The table will present the NAb subject classification and derived sets (see 9.4.4).

Population: safety population.

Table 14.3.4.5: Immunogenicity: Prevalence and incidence table of pre-Ab and treatment-emergent ADA based on ADA and mADA assay results (overall subject classification) by injection-site reaction

Table sorted by injection-site reaction category (see 9.4.5) and treatment group. The table will present the incidence of different overall subject classifications (no derived sets).

Population: safety population.

Table 14.3.4.6: Immunogenicity: Prevalence and incidence table of pre-Ab and treatment-emergent ADA based on ADA and mADA assay results (overall subject classification) by hypersensitivity reaction

Table sorted by hypersensitivity reaction category (see 9.4.5) and treatment group. The table will present the incidence of different overall subject classifications (no derived sets).

Population: safety population.

Table 14.3.4.7: Immunogenicity: ADA incidence over time by pre-Ab population

Incidence of positive ADA samples at each time point by pre-Ab population and treatment group (see 9.4.6). NA & NR samples will be excluded from the incidence calculation.

Population: Safety population.

Table 14.3.4.8: Immunogenicity: NAb incidence over time

Incidence of positive NAb samples (reported or imputed) at each time point by treatment group. NA & NR samples will be excluded from the incidence calculation.

Population: Safety population

Table 14.3.4.9: Immunogenicity: ADA/mADA log10(Titer) over time by pre-Ab population

Descriptive statistics at each time point of titer values by pre-Ab population and treatment group. Within the pre-Ab negative population, only ADA log10(titers) will be available to calculate descriptive statistics. For the pre-Ab positive population, table will be subdivided in ADA and mADA log10(titer) results.

Population: Safety population.

Table 14.3.4.10: Immunogenicity: NAb response ratio over time of NAb positive samples

Descriptive statistics at each time point of NAb response ratio by treatment group.

Population: Safety population.

14 INDEX OF FIGURES

Figure 14.2.1.1.1: ACR response - ACR20 response

Line plot of the percentage of subjects with ACR20 response at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.1.2: ACR response - ACR50 response

Line plot of the percentage of subjects with ACR50 response at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.1.3: ACR response - ACR70 response

Line plot of the percentage of subjects with ACR70 response at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.1.4: ACR response - ACR-N index of improvement

Line plot of the mean ACR-N index at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.2.1: DAS28 Score – Actual values

Line plot of the mean DAS28(CRP) and the DAS28(ESR) score at each time point, including SE bars, with one line per treatment group. Separate graphs will be created for the DAS28(CRP) and the DAS28(ESR) score.

Population: ITO.

Figure 14.2.1.2.2: DAS28 Score – EULAR (using CRP and using ESR) response

Line plot of the percentage of subjects with EULAR good response at each time point, including SE bars, with one line per treatment group. Separate graphs will be created for EULAR response based on the DAS28(CRP) and on the DAS28(ESR).

Population: ITO.

Figure 14.2.1.2.3: DAS28 Score – Disease activity

Line plot of the percentage of subjects with disease remission at each time point, including SE bars, with one line per treatment group. Separate graphs will be created for remission based on the DAS28(ESR) and for the DAS28(CRP)<2.6 category. The graphs will be repeated for percentage of subjects with LDA/disease remission.

Population: ITO.

Figure 14.2.1.3.1: Boolean disease remission definition

Line plot of the percentage of subjects with disease remission based on the Boolean definition at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.4.1: CDAI Score – Actual values

Line plot of the mean CDAI score at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.4.2: CDAI Score – Disease activity

Line plot of the percentage of subjects with disease remission based on the CDAI score at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.5.1: SDAI Score – Actual values

Line plot of the mean SDAI score at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.5.2: SDAI Score – Disease activity

Line plot of the percentage of subjects with disease remission based on the SDAI score at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.6.1: HAQ-DI Score – Actual values

Line plot of the mean HAQ-DI score at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.6.2: HAQ-DI Score – Clinically meaningful improvement

Line plot of the percentage of subjects with HAQ-DI response at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.6.3: HAQ-DI Score – Normal physical function

Line plot of the percentage of subjects with normal physical function, based on the HAQ-DI score at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.7.1: SF-36 – Physical and mental component scores – Actual values

Line plot of the mean physical and mental component score at each time point, including SE bars, with one line per treatment group. Separate graphs will be created for the physical and mental component score.

Population: ITO.

Figure 14.2.1.8.1: FACIT-F – Actual values

Line plot of the mean FACIT-F total score and scores of subscales at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.9.1: Duration of morning stiffness – Actual values

Line plot of the mean duration of morning stiffness at each time point, including SE bars, with one line per treatment group.

Population: ITO.

Figure 14.2.1.10.1: VAS scales – Actual values

Line plot of the mean patient's assessment of pain VAS, patient's global assessment of disease activity VAS and the physician's global assessment of disease activity VAS, including SE bars, with one line per treatment group. Separate graphs will be created for the patient's assessment of pain VAS, patient's global assessment of disease activity VAS and the physician's global assessment of disease activity VAS.

Population: ITO.

Figure 14.2.1.11.1: CRP and ESR – Actual values

Line plot of the mean CRP and ESR concentrations, including SE bars, with one line per treatment group. Separate graphs will be created for CRP and ESR concentrations.

Population: ITO.

Figure 14.2.1.12.1: TJC and SJC – Actual values

Line plot of the mean TJC and SJC, including SE bars, with one line per treatment group. Separate graphs will be created for TJC and SJC.

Population: ITO.

Figure 14.2.1.13.1: PK: Mean drug concentrations

Line plot of the mean drug concentrations, including SE bars, with one line per treatment group. Plots will be created with both linear and semi-logarithmic PK profiles. Both graphs will be displayed on the same page.

Population: PK population.

Figure 14.2.1.13.2: PK: Mean drug concentrations (geometric mean)

Line plot of the geometric mean drug concentrations, including geometric SD bars, with one line per treatment group. Plots will be created with both linear and semi-logarithmic PK profiles. Both graphs will be displayed on the same page.

Population: PK population.

Figure 14.2.1.13.3: Immunogenicity: Individual line plot of ADA log10(titer), mADA log10(titer), NAb response, PK concentration, DAS 28 Score and ACR50 over time

For all subjects, line plot of ADA titer, mADA titer, NAb response ratio, PK, DAS28(CRP), and ACR50 vs. time (incl. parent screening & baseline visit). Different responses can be plotted against separate Y-axes above each other, but scale of time-axis should be identical for each plotted response. Note that for parent screening and baseline visit and OLE baseline visit, NAb response will be indicated by a flag (pos="Y" or neg="N") above the corresponding ADA titer. For PK and DAS28(CRP), a treatment group average over time plot will be added with each of the individual plot.

Population: safety population.

Figure 14.3.1.1: Laboratory – box plots of parameters of interest

Longitudinal box plots per treatment group of neutrophils, platelets, ALT, AST and cholesterol ratio. Separate graphs will be created for each parameter.

Population: ITO.

15 INDEX OF LISTINGS

15.1 General

Listing 16.2.1.1: Subject disposition

Listing of subject numbers, parent trial, dose in parent trial, population indicators, investigator and country.

Population: ITO population.

Listing 16.2.1.2: Trial visits

Listing of all visits, including the visit date and study day.

Population: ITO population.

Listing 16.2.1.3: Subject disposition: First and last contact in the trial

List with the following 3 dates:

- Date of the first signature on (C203) trial ICF
- Last visit date (all visits; including unscheduled visits)
- Last date of contact in the study with any subject.

Population: all screened population.

Listing 16.2.1.4: Trial termination

Listing of completion/discontinuation, the reason for discontinuation and the number of days since first study treatment administration at trial termination. In case the discontinuation was due to AE, the AE will be presented in this listing. If there is another explanation on the discontinuation reason collected in the CRF, this will also be presented in this listing.

Population: ITO population.

Listing 16.2.1.5: Trial termination for adverse event

Same as previous listing for subjects with primary reason for study discontinuation adverse event.

Population: ITO population.

Listing 16.2.1.6: Major protocol deviations

Listing of all major protocol deviations.

Population: ITO population.

Listing 16.2.1.7: No-treatment subjects

Listing of all subjects that were not treated, including the screening failures. The trial termination reason and/or the reason for being a no-treatment subject will be listed, whichever is available.

Population: all screened population, minus the safety population.

Listing 16.2.2.1: Demographic data

Listing of all demographic parameters. Country will be presented on this listing as well.

Population: ITO population.

Listing 16.2.2.2: Baseline disease characteristics

Listing of all baseline disease characteristics parameters which are not listed in the efficacy section.

Population: ITO population.

Listing 16.2.2.3: Concomitant therapies

Listing of all data on concomitant therapies, including coding information.

Population: ITO population.

Listing 16.2.2.4: Exposure to study medication: Actual data

Listing of all data collected in the CRF related to the use of study medication.

Population: safety population.

Listing 16.2.2.5: Exposure to study medication: Derived data

Listing of all derived data related to the use of study medication.

Population: safety population.

Listing 16.2.2.6: Comments

Listing of remarks and comments written in the CRF.

Population: ITO population.

15.2 Efficacy

Listing 16.2.3.1: ACR response

Listing per subject and visit of ACR20, ACR50 and ACR70 response and ACR-N index

Population: ITO.

Listing 16.2.3.2: TJC and SJC

Listing per subject and visit of TJC and SJC actual values, changes and percentage changes from baseline

Population: ITO.

Listing 16.2.3.3: DAS28

Listing per subject and visit of TJC28, SJC28, CRP, ESR, DAS28(ESR), DAS28(CRP), EULAR response, DAS28(ESR) disease activity, DAS28(CRP) disease activity, VASPA and Boolean remission.

Population: ITO.

Listing 16.2.3.4: CDAI and SDAI

Listing per subject and visit of CDAI actual values, changes from baseline, disease activity and of SDAI actual values, changes from baseline, disease activity.

Population: ITO.

Listing 16.2.3.5: HAQ-DI

Listing per subject and visit of HAQ-DI actual values, changes from baseline, percentage changes from baseline, response (clinically meaningful improvement) and normal physical function.

Population: ITO.

Listing 16.2.3.6: SF-36

Listing per subject and visit of the actual values and changes from baseline for the physical and mental component scores and for the 8 subscales (original scores).

Population: ITO.

Listing 16.2.3.7: FACIT-F and duration of morning stiffness

Listing per subject and visit of the actual values and changes from baseline for FACIT-F total score and subscales and of the actual values and changes from baseline for duration of morning stiffness.

Population: ITO.

Listing 16.2.3.8: VAS scales

Listing per subject and visit of the actual values, percentage changes from baseline and changes from baseline for VAS, VASPA and VASPHA.

Population: ITO.

Listing 16.2.3.9: CRP and ESR

Listing per subject and visit of the actual values, percentage changes from baseline and changes from baseline for CRP and ESR concentrations.

Population: ITO.

15.3 Pharmacokinetics

Listing 16.2.4.1: PK: Study drug concentrations

Listing of all individual study drug concentrations.

Population: PK population.

Listing 16.2.4.2: PK: Sampling times

Listing of nominal sampling times, actual sampling times and sampling time deviations. In case the actual sampling time deviates more than allowed per study protocol from the nominal time, the time point will be flagged.

Population: PK population.

15.4 Safety

Listing 16.2.7.1: Adverse events

Listing of all adverse events (started or ongoing in the C203 study) of the following:

- AE verbatim
- AE preferred term (flagging serious TEAEs with an asterisk *)
- AE start and end
- AE onset day
- AE duration
- AE severity
- AE drug relatedness: relation to study drug, to MTX (C201 subjects only), to folic acid and to study procedure
- AE outcome
- AE action taken related to study drug
- Concomitant therapy started (yes/no)

Population: safety population.

Listing 16.2.7.2: Serious adverse events

Same as the previous listing, but only selecting SAEs. Additionally, the reason(s) for SAE will be listed as well.

Population: safety population.

Listing 16.2.7.3: Treatment-related adverse events

Same as the previous listing, but only selecting treatment-related TEAEs.

Population: safety population.

Listing 16.2.7.4: Adverse events leading to discontinuation of the study or the study medication

Same as the previous listing, but only selecting TEAEs that lead to a stop of trial medication, or of the trial itself.

Population: safety population.

Listing 16.2.7.5: Adverse events leading to death

Same as the previous listing, but only selecting TEAEs that lead to death.

Listing 16.2.7.6: Severe/Serious hypersensitivity adverse events

Listing of severe/serious hypersensitivity adverse events, including ADA/mADA log10(titer) and biomarker test results (tryptase, total complement (CH50) and circulating immune complexes).

Population: safety population.

Listing 16.2.7.7: Physical examinations: Abnormalities

Listing of all abnormal findings, including the clinically significance status.

Population: safety population.

Listing 16.2.7.8: Pregnancy tests

Listing of all pregnancy test results, for women of childbearing potential only.

Population: ITO population.

Listing 16.2.8.1: Laboratory data: Full listing

Listing of raw laboratory data and changes, including a fasted (Y/N) flag, an abnormality L/H flag, the test's normal range and a clinical relevance flag.

Population: safety population.

Listing 16.2.8.2: Laboratory data: Abnormalities

Listing similar to 16.2.8.1, but only consisting of data scored as out-of-normal-range or clinically significant, plus also the baseline reference time point.

Population: safety population.

Listing 16.2.8.3: Laboratory data: Abnormalities for key hematology and biochemistry parameters

Listing of ALT, AST, total bilirubin, gamma-glutamyltransferase, leukocytes, neutrophils, thrombocytes, fibrinogen and lipids scored as at least CTCAE toxicity grade 1, plus also the baseline reference time point.

Population: safety population.

Listing 16.2.8.4: Laboratory data: Comments

Listing of all comments. This listing will be linked to the full listing and the abnormalities listings via numbered entries like "[C13]".

Population: safety population.

Listing 16.2.9.1: Vital signs: Full listing

Listing of all parameters: raw values, changes from baseline, and flagging clinically significant results.

Population: safety population.

Listing 16.2.9.2: Vital signs: Abnormalities

Listing of all data scored as clinically significant, plus also the baseline reference time point.

Population: safety population.

15.5 Immunogenicity

Listing 16.2.10.1: Immunogenicity: Full listing

Listing of all immunogenicity parameters (ADA log10(titer), ADA subject classification, mADA log10(titer), mADA subject classification, overall subject classification, NAb result (“yes”/”no” for data obtained from parent trial; ratio for OLE post-baseline visits) and nAb subject classification at each time point (parent trial screening and/or baseline sample results, the "C203 baseline" results and Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 104 and FU or ET visit) .

Population: safety population.

16 APPENDICES

16.1 Appendix 1: Schedule of assessments

Study Period	**Screening/Baseline, Treatment and Assessment period (weeks)**												**Early Termination [C] (weeks)**	**Follow-up (weeks)**
Study Visit [D]	**Screening/ Baseline [B] 0**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**104**	**2 (after last study drug administration)**	**12 (after last study drug dosing)**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12		13
Ambulatory visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Written informed consent	X													
Review of entry criteria	X													
Smoking history	X													
Study drug injection card dispensation	X													
Study drug administration (via interactive web response system [IWRS]) [E]	X	Injections to continue every 2 weeks up to and including week 102												
Physical examination	X [B]			X	X	X	X	X	X	X	X	X	X	X
Vital signs [F]	X [B]	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis (TB) evaluation (questioning) [G]	X [B]			X	X	X	X	X	X	X	X	X	X	X
Routine clinical laboratory analyses [H]	X [B]	X	X	X		X		X		X	X			X
Extended clinical laboratory analyses (including fasting serum lipids) [I]	X [B]				X		X		X			X	X	
Pregnancy test (urine) for females of childbearing potential only	X [B]			X	X	X	X	X	X	X	X	X	X	
Morning stiffness duration	X [B]											X	X	
Joint assessment (66/68-joint count)	X [B]			X	X	X	X	X	X	X	X	X	X	
IWRS notification of tender & swollen joint counts	X [B]			X	X	X	X	X	X	X	X			

Patient pain visual analogue scale (VAS)	X [B]			X	X	X	X	X	X	X	X	X	X	
Health Assessment Questionnaire – Disability Index (HAQ-DI)	X [B]			X	X	X	X	X	X	X	X	X	X	
Short Form (36) Health Survey (SF-36)	X [B]				X		X		X			X	X	
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)	X [B]				X		X		X			X	X	
Physician and Patient global assessment of disease activity	X [B]			X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X [B]	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse events (AEs) [J]	X [B]	→	→	→	→	→	→	→	→	→	→	→	→	→
Pharmacokinetic (PK) samples [K]	X [B]			X	X	X	X	X	X	X	X	X	X	
Immunogenicity samples	X [B]			X	X	X	X	X	X	X	X	X	X	X

A. All assessments are to be completed prior to the study drug administration, except for subjects who discontinue study drug injections. The order of assessments if more than 1 assessment is planned at the same time should be performed according to the following principles: vital signs should be assessed prior to blood sampling; patient reported outcomes should occur prior to the physician's joint evaluation, independent joint assessment should occur prior to physician's global assessment, and study drug should be dosed after all other assessments have been performed.

B. The Baseline Visit will coincide with the 24-week End of Treatment Visit of the preceding Study ALX0061-C201, or with the 12-week End of Treatment Visit of Study ALX0061-C202. The results from the End of Treatment Visit assessments for these studies do not have to be repeated at baseline for this study, and include physical examination, vital signs, TB evaluation (questioning), routine/extended clinical laboratory analyses (at Week 22 in Study ALX0061-C201 or at Week 10 in Study ALX0061-C202), pregnancy test (urine), morning stiffness duration, joint assessment (66/68-joint count), patient pain VAS, HAQ-DI, SF-36, FACIT-F, physician and patient global assessment, concomitant medication, AEs, PK blood samples, and immunogenicity.

C. The Early Termination Visit is to be performed 2 weeks after the last study drug dosing for subjects who discontinue from the trial for other reasons than described in the efficacy discontinuation criteria (see section 3.2.3.2), unless they discontinue during a study visit, in which case that becomes their Early Termination Visit. For subjects who will meet the efficacy discontinuation criteria at Week 12, 24, 36, 48, 60, 72, 84 or 96, the visit at which subjects will meet these discontinuation criteria is defined as the Early Termination Visit.

D. All post baseline visits may occur at the indicated week ± 3 days throughout the trial.

E. At the study visits at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96, study drug is to be administered s.c. at the study site. At all other time points, subjects are allowed to self-administer away from the clinic. Subjects unable to have injections administered away from the study site will be required to return to the site every 2 weeks for administration of study drug by an authorized health professional.

F. Vital signs (assessment after 5 minutes in supine position) will include weight, blood pressure, pulse, and temperature. A height measurement is not required (data available from the preceding study). In case blood sampling is to be performed at the same visit, the vital signs assessment is to be performed prior to the blood sampling.

G. If TB is suspected at any time during the study, chest x-ray and interferon-gamma release assay (IGRA) should be performed.

H. Samples for routine clinical laboratory analyses will be collected predose, and include blood chemistry, hematology, acute phase proteins (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], fibrinogen) and urinalysis (urinalysis at Weeks 48 and 104). For subjects on warfarin, international normalized ratio (INR) will be performed at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96, or at the Early Termination Visit.

I. At the indicated visits, samples for extended clinical laboratory analyses, including fasting serum lipids on top of the routine clinical laboratory analyses, will be performed predose. Extended clinical laboratory samples will be taken predose after the subject has been fasting for at least 10 h.

J. AEs will be recorded from the time the informed consent form is signed through the Follow-up Visit. The Investigator must follow-up on all SAEs and AEs until the events have subsided, returned to baseline, or the subject's condition has stabilized in cases of permanent impairment. In case of acute or delayed severe/serious hypersensitivity reactions, an additional serum sample should be collected as soon as possible after the start of the event (blood volume: 5 mL).

K. PK and immunogenicity samples will be taken predose.

16.2 Appendix 2: Prednisolone equivalent dose chart

	Approx. equivalent dose (mg/day)*	Conversion factor
Cortisone	25	0.20
Hydrocortisone	20	0.25
Methylprednisolone	4	1.25
Prednisolone	5	1.00
Prednisone	5	1.00
Triamcinolone	4	1.25
Betamethasone	0.70	7.15
Dexamethasone	0.75	6.67
Deflazacort	6	0.83

* Based on Prednisolone dose of 5 mg/day.

References:

Dixon JS (1991), Meikle AW and Tyler FH (1977), Webb R, Singer M. and Nayal S et al. (2005)

16.3 Appendix 3: CTCAE grades (version 4.03 14JUN2010)

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen.					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g. , >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.					
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin I in a biological specimen.					
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin T in a biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen.					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen.					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.					

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.					
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen.					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds.					
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.					
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.					
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.					
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

16.4 Appendix 4: FACIT-F Scoring Guidelines (version 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the

number of items answered. This produces the subscale score.

4. Add subscale scores to derive total scores (TOI, FACT-G & FACIT-F).

5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1 =_____	4	-	_____	
WELL-BEING	GP2 =_____	4	-	_____	
(PWB)	GP3 =_____	4	-	_____	
Score range: 0-28	GP4 =_____	4	-	_____	
	GP5 =_____	4	-	_____	
	GP6 =_____	4	-	_____	
	GP7 =_____	4	-	_____	

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____

	GS7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered:

_____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 6: _____

Divide by number of items answered:

_____=**EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered:

_____=**FWB subscale score**

Subscale	**Item Code**	**Reverse item?**	**Item response**	**Item Score**

FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
(FS)	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores:_____

Multiply by 13: _____

Divide by number of items answered: _____**=F**

Subscale score

To derive a FACIT-F Trial Outcome Index (TOI):
Score range: 0-108

_____ + _____ + _____
=_____=**FACIT-F TOI**
(**PWB** score) (**FWB** score) (**FS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACIT-F total score:

Score range: 0-

_____ + _____ + _____ + _____ + _____

=_____=**FACIT-F Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**FS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

16.5 Appendix 5: Search criteria for adverse events of special interest

Search criteria for AESIs are either MedDRA PT clusters or SMQs. The SMQs and the individual PTs for the PT clusters are provided below. The MedDRA version used for the data coding is v21.0.

Infections

Abdominal abscess
Abdominal hernia gangrenous
Abdominal infection
Abdominal lymphadenopathy
Abdominal sepsis
Abdominal wall abscess
Abdominal wall infection
Abortion infected
Abscess
Abscess bacterial
Abscess fungal
Abscess intestinal
Abscess jaw
Abscess limb
Abscess neck
Abscess of external auditory meatus
Abscess of eyelid
Abscess of salivary gland
Abscess oral
Abscess rupture
Abscess soft tissue
Abscess sweat gland
Acanthamoeba infection
Acanthamoeba keratitis
Acariasis
Acarodermatitis
Acid fast bacilli infection
Acinetobacter bacteraemia
Acinetobacter infection
Acinetobacter test positive
Acne pustular
Acquired immunodeficiency syndrome
Acrodermatitis chronica atrophicans
Actinomyces test positive
Actinomycosis
Actinomycotic abdominal infection
Actinomycotic pulmonary infection
Actinomycotic skin infection
Acute endocarditis
Acute focal bacterial nephritis
Acute haemorrhagic conjunctivitis
Acute hepatitis B
Acute hepatitis C
Acute HIV infection
Acute pulmonary histoplasmosis
Acute sinusitis
Adenoiditis
Adenopathy syphilitic
Adenoviral conjunctivitis
Adenoviral haemorrhagic cystitis
Adenoviral hepatitis
Adenoviral upper respiratory infection
Adenovirus encephalomyeloradiculitis
Adenovirus infection
Adenovirus test
Adenovirus test positive
Adiponectin increased
Administration site abscess
Administration site cellulitis
Administration site infection
Adrenal gland abscess
Adrenal gland tuberculosis
Adrenalitis
Aeromonas infection
Aeromonas test positive
African trypanosomiasis
AIDS cholangiopathy

AIDS related complex
AIDS related complication
AIDS retinopathy
Air-borne transmission
Alcaligenes infection
Allescheriosis
Alopecia syphilitic
Alpha haemolytic streptococcal infection
Alphaviral infection
Alphavirus test
Alphavirus test positive
Alternaria infection
Alveolar osteitis
American trypanosomiasis
Amniotic cavity infection
Amniotic infection syndrome of Blane
Amoeba test
Amoeba test positive
Amoebiasis
Amoebic brain abscess
Amoebic colitis
Amoebic dysentery
Amoebic lung abscess
Amoebic skin ulcer
Anal abscess
Anal candidiasis
Anal chlamydia infection
Anal fistula infection
Anal fungal infection
Anal infection
Anal tinea
Angina gangrenous
Angiostrongylus infection
Anicteric leptospirosis
Anisakiasis
Anogenital warts
Anorectal cellulitis
Anorectal human papilloma virus infection
Anorectal infection
Anorectal infection bacterial
Anthrax
Anthrax sepsis
Antifungal treatment
Antimicrobial susceptibility test
Antimicrobial susceptibility test intermediate
Antimicrobial susceptibility test resistant
Antimicrobial susceptibility test sensitive
Aortic aneurysm syphilitic
Aortitis salmonella
Aortitis syphilitic
Aphthovirus test positive
Apical granuloma
Appendiceal abscess
Appendicitis
Appendicitis perforated
Application site abscess
Application site cellulitis
Application site folliculitis
Application site infection
Application site pustules
Arachnoiditis
Arboviral infection
Arbovirus test positive
Arenaviral haemorrhagic fever
Arenavirus test positive
Argentine haemorrhagic fever
Arteriosclerotic gangrene
Arteriovenous fistula site infection
Arteriovenous graft site abscess
Arteriovenous graft site infection
Arteritis infective
Arthritis bacterial
Arthritis fungal
Arthritis gonococcal
Arthritis helminthic
Arthritis infective
Arthritis reactive
Arthritis rubella
Arthritis salmonella
Arthritis viral
Arthropod infestation
Arthropod-borne disease
Ascariasis
Aspergilloma
Aspergillosis oral

Aspergillus infection
Aspergillus test
Aspergillus test positive
Astrovirus test positive
Asymptomatic bacteriuria
Asymptomatic HIV infection
Asymptomatic viral hepatitis
Atypical mycobacterial infection
Atypical mycobacterial lower respiratory tract infection
Atypical mycobacterial lymphadenitis
Atypical mycobacterial pneumonia
Atypical mycobacterium pericarditis
Atypical mycobacterium test positive
Atypical pneumonia
Avian influenza
Babesiosis
Bacillary angiomatosis
Bacillus bacteraemia
Bacillus infection
Bacillus test positive
Bacteraemia
Bacterascites
Bacterial abscess central nervous system
Bacterial allergy
Bacterial dacryocystitis
Bacterial diarrhoea
Bacterial disease carrier
Bacterial food poisoning
Bacterial infection
Bacterial iritis
Bacterial labyrinthitis
Bacterial pericarditis
Bacterial prostatitis
Bacterial pyelonephritis
Bacterial rhinitis
Bacterial sepsis
Bacterial test
Bacterial test positive
Bacterial toxaemia
Bacterial tracheitis
Bacterial translocation
Bacterial vaginosis
Bacterial vulvovaginitis
Bacteriuria
Bacteriuria in pregnancy
Bacteroides bacteraemia
Bacteroides infection
Bacteroides test positive
Balamuthia infection
Balanitis candida
Balanoposthitis
Balanoposthitis infective
Balantidiasis
Bartholin's abscess
Bartonella test positive
Bartonellosis
Bed bug infestation
Beta haemolytic streptococcal infection
Bifidobacterium infection
Bifidobacterium test positive
Bile culture
Bile culture positive
Biliary abscess
Biliary sepsis
Biliary tract infection
Biliary tract infection bacterial
Biliary tract infection cryptosporidial
Biliary tract infection fungal
Biliary tract infection helminthic
Biliary tract infection viral
BK virus infection
Black piedra
Bladder candidiasis
Bladder diverticulitis
Blastocystis infection
Blastomycosis
Blebitis
Blepharitis
Blister infected
Blood bactericidal activity
Blood beta-D-glucan abnormal
Blood beta-D-glucan decreased
Blood beta-D-glucan increased
Blood culture
Blood culture positive

Blood HIV RNA
Blood HIV RNA below assay limit
Blood HIV RNA decreased
Blood HIV RNA increased
Body tinea
Bolivian haemorrhagic fever
Bone abscess
Bone tuberculosis
Borderline leprosy
Bordetella infection
Bordetella test
Bordetella test positive
Borrelia infection
Borrelia test
Borrelia test positive
Botryomycosis
Botulism
Boutonneuse fever
Bovine pustular stomatitis virus infection
Bovine tuberculosis
Brain abscess
Brain empyema
Breast abscess
Breast cellulitis
Breast discharge infected
Bronchiectasis
Bronchiolitis
Bronchitis
Bronchitis bacterial
Bronchitis fungal
Bronchitis haemophilus
Bronchitis moraxella
Bronchitis pneumococcal
Bronchitis viral
Bronchoalveolar lavage abnormal
Bronchopulmonary aspergillosis
Bronchopulmonary aspergillosis allergic
Bronchoscopy abnormal
Brucella sepsis
Brucella test
Brucella test positive
Brucellosis
Bubonic plague
Bulbar poliomyelitis
Bullous impetigo
Burkholderia cepacia complex infection
Burkholderia cepacia complex sepsis
Burkholderia gladioli infection
Burkholderia infection
Burkholderia mallei infection
Burkholderia pseudomallei infection
Burkholderia test positive
Burn infection
Bursitis infective
Bursitis infective staphylococcal
Calicivirus test positive
Campylobacter gastroenteritis
Campylobacter infection
Campylobacter sepsis
Campylobacter test positive
Candida cervicitis
Candida endophthalmitis
Candida infection
Candida nappy rash
Candida osteomyelitis
Candida pneumonia
Candida retinitis
Candida sepsis
Candida test
Candida test positive
Candiduria
Capillariasis
Capillaritis
Capnocytophaga infection
Capnocytophaga test positive
Carbuncle
Cardiac granuloma
Cardiac infection
Cardiac valve abscess
Cardiac valve vegetation
Cardiovascular syphilis
Carditis
Cat scratch disease
Catheter culture
Catheter culture positive
Catheter site abscess

Catheter site cellulitis
Catheter site infection
Catheter site pustule
Catheter site warmth
Cavernous sinus thrombosis
Cellulitis
Cellulitis enterococcal
Cellulitis gangrenous
Cellulitis laryngeal
Cellulitis of male external genital organ
Cellulitis orbital
Cellulitis pasteurella
Cellulitis pharyngeal
Cellulitis staphylococcal
Cellulitis streptococcal
Central nervous system abscess
Central nervous system enteroviral infection
Central nervous system fungal infection
Central nervous system infection
Central nervous system inflammation
Central nervous system viral infection
Cerebral aneurysm ruptured syphilitic
Cerebral aspergillosis
Cerebral fungal infection
Cerebral malaria
Cerebral septic infarct
Cerebral toxoplasmosis
Cervicitis
Cervicitis gonococcal
Cervicitis human papilloma virus
Cervicitis mycoplasmal
Cervicitis streptococcal
Cervicitis trichomonal
Cervix warts
Cestode infection
Chancroid
Chest wall abscess
Chikungunya virus infection
Chlamydia test
Chlamydia test positive
Chlamydial cervicitis
Chlamydial infection
Chlamydial pelvic inflammatory disease
Cholangitis infective
Cholecystitis infective
Cholera
Cholesteatoma
Cholesterol granuloma
Choriomeningitis lymphocytic
Chorioretinitis
Choroid tubercles
Choroiditis
Chromoblastomycosis
Chronic gastritis
Chronic hepatitis
Chronic hepatitis B
Chronic hepatitis C
Chronic pulmonary histoplasmosis
Chronic recurrent multifocal osteomyelitis
Chronic sinusitis
Chronic tonsillitis
Citrobacter infection
Citrobacter sepsis
Citrobacter test positive
Clitoris abscess
Clonorchiasis
Clostridial infection
Clostridial sepsis
Clostridium bacteraemia
Clostridium colitis
Clostridium difficile colitis
Clostridium difficile infection
Clostridium test
Clostridium test positive
CNS ventriculitis
Coccidioides encephalitis
Coccidioidomycosis
Colitis herpes
Colon gangrene
Colonic abscess
Colorado tick fever
Colorado tick fever virus test positive
Colostomy infection
Community acquired infection
Condyloma latum
Congenital condyloma

Congenital cytomegalovirus infection
Congenital hepatitis B infection
Congenital herpes simplex infection
Congenital HIV infection
Congenital infection
Congenital malaria
Congenital pneumonia
Congenital rubella infection
Congenital syphilis
Congenital syphilitic encephalitis
Congenital syphilitic meningitis
Congenital syphilitic osteochondritis
Congenital toxoplasmosis
Congenital tuberculosis
Congenital varicella infection
Congo-Crimean haemorrhagic fever
Conjunctivitis
Conjunctivitis bacterial
Conjunctivitis chlamydial
Conjunctivitis gonococcal neonatal
Conjunctivitis tuberculous
Conjunctivitis viral
Corneal abscess
Corneal endotheliitis
Corneal infection
Corona virus infection
Coronavirus test positive
Corynebacterium infection
Corynebacterium sepsis
Corynebacterium test
Corynebacterium test positive
Cow pox
Coxiella infection
Coxiella test positive
Coxsackie carditis
Coxsackie endocarditis
Coxsackie myocarditis
Coxsackie pericarditis
Coxsackie viral disease of the newborn
Coxsackie viral infection
Coxsackie virus test
Coxsackie virus test positive
Cranial nerve infection
Creutzfeldt-Jakob disease
Cronobacter bacteraemia
Cronobacter infection
Cronobacter necrotising enterocolitis
Cronobacter test positive
Cross infection
Croup infectious
Cryptococcal cutaneous infection
Cryptococcal fungaemia
Cryptococcosis
Cryptococcus test
Cryptococcus test positive
Cryptosporidiosis infection
CSF culture
CSF culture positive
CSF immunoglobulin G index
CSF leukocyte/erythrocyte ratio
CSF leukocyte/erythrocyte ratio increased
CSF measles antibody positive
CSF virus identified
CSF virus no organisms observed
Culture
Culture cervix
Culture cervix positive
Culture positive
Culture stool
Culture stool positive
Culture throat
Culture throat positive
Culture tissue specimen
Culture tissue specimen positive
Culture urine
Culture urine positive
Culture wound
Culture wound positive
Cutaneous anthrax

Cutaneous coccidioidomycosis
Cutaneous larva migrans
Cutaneous leishmaniasis
Cutaneous sporotrichosis
Cutaneous tuberculosis
Cyclitis
Cyclosporidium infection
Cystitis
Cystitis bacterial
Cystitis erosive
Cystitis escherichia
Cystitis glandularis
Cystitis gonococcal
Cystitis haemorrhagic
Cystitis helminthic
Cystitis interstitial
Cystitis klebsiella
Cystitis noninfective
Cystitis pseudomonal
Cystitis radiation
Cystitis ulcerative
Cystitis viral
Cytomegalovirus chorioretinitis
Cytomegalovirus colitis
Cytomegalovirus duodenitis
Cytomegalovirus enteritis
Cytomegalovirus enterocolitis
Cytomegalovirus gastritis
Cytomegalovirus gastroenteritis
Cytomegalovirus gastrointestinal infection
Cytomegalovirus hepatitis
Cytomegalovirus infection
Cytomegalovirus mononucleosis
Cytomegalovirus mucocutaneous ulcer
Cytomegalovirus myelomeningoradiculitis
Cytomegalovirus myocarditis
Cytomegalovirus oesophagitis
Cytomegalovirus pancreatitis
Cytomegalovirus pericarditis
Cytomegalovirus syndrome
Cytomegalovirus test
Cytomegalovirus test positive
Cytomegalovirus urinary tract infection
Cytomegalovirus viraemia
Dacryoadenitis acquired
Dacryocanaliculitis
Dacryocystitis
Deltaretrovirus test positive
Demodicidosis
Dengue fever
Dental caries
Dental fistula
Dental gangrene
Dermatitis infected
Dermatomyositis
Dermatophytosis
Dermo-hypodermitis
Device related infection
Device related sepsis
Diabetic foot infection
Diabetic gangrene
Diaphragmatic hernia gangrenous
Diarrhoea infectious
Diarrhoea infectious neonatal
Diphtheria
Diphtheria carrier
Diphyllobothriasis
Direct infection transmission
Disseminated cryptococcosis
Disseminated cytomegaloviral infection
Disseminated tuberculosis
Diverticulitis
Douglas' abscess
Dracunculiasis
Dural abscess
Dysentery
Ear infection
Ear infection bacterial
Ear infection fungal

Ear infection staphylococcal
Ear infection viral
Ear lobe infection
Ear tuberculosis
Ebola disease
Ebola Reston virus infection
Ebola virus test positive
Echinococciasis
Echo virus infection
Echovirus test
Echovirus test positive
Ecthyma
Eczema herpeticum
Eczema impetiginous
Eczema infected
Eczema vaccinatum
Ehrlichia test
Ehrlichia test positive
Elephantiasis nostras verrucosa
Embolic pneumonia
Empedobacter brevis infection
Empedobacter test positive
Emphysematous cholecystitis
Emphysematous cystitis
Emphysematous pyelonephritis
Empyema
Encephalitis
Encephalitis allergic
Encephalitis australia
Encephalitis brain stem
Encephalitis california
Encephalitis cytomegalovirus
Encephalitis eastern equine
Encephalitis enteroviral
Encephalitis fungal
Encephalitis haemorrhagic
Encephalitis influenzal
Encephalitis Japanese B
Encephalitis lethargica
Encephalitis meningococcal
Encephalitis mumps
Encephalitis post immunisation
Encephalitis post varicella
Encephalitis protozoal
Encephalitis rickettsial
Encephalitis toxic
Encephalitis venezuelan equine
Encephalitis viral
Encephalitis western equine
Encephalomyelitis
Encephalomyelitis rubella
End stage AIDS
Endemic syphilis
Endocarditis
Endocarditis bacterial
Endocarditis candida
Endocarditis enterococcal
Endocarditis gonococcal
Endocarditis haemophilus
Endocarditis helminthic
Endocarditis histoplasma
Endocarditis meningococcal
Endocarditis pseudomonal
Endocarditis Q fever
Endocarditis rheumatic
Endocarditis staphylococcal
Endocarditis syphilitic
Endocarditis viral
Endometritis
Endometritis bacterial
Endometritis decidual
Endometritis gonococcal
Endophthalmitis
Endotoxaemia
Endotoxic shock
Enteritis infectious
Enteritis necroticans
Enterobacter bacteraemia
Enterobacter infection
Enterobacter pneumonia
Enterobacter sepsis
Enterobacter test positive
Enterobacter tracheobronchitis

Enterobiasis
Enterococcal bacteraemia
Enterococcal infection
Enterococcal sepsis
Enterococcus test positive
Enterocolitis AIDS
Enterocolitis bacterial
Enterocolitis fungal
Enterocolitis helminthic
Enterocolitis infectious
Enterocolitis viral
Enterovirus infection
Enterovirus test
Enterovirus test positive
Eosinophilia myalgia syndrome
Eosinophilic cystitis
Ependymitis
Epidemic pleurodynia
Epidemic polyarthritis
Epidemic typhus
Epidermodysplasia verruciformis
Epididymitis
Epididymitis blastomyces
Epididymitis mumps
Epididymitis tuberculous
Epididymitis ureaplasmal
Epididymo-orchitis gonococcal
Epiglottitis
Epiglottitis haemophilus
Epiglottitis obstructive
Epstein-Barr viraemia
Epstein-Barr virus antibody
Epstein-Barr virus antibody positive
Epstein-Barr virus antigen positive
Epstein-Barr virus associated lymphoma
Epstein-Barr virus associated lymphoproliferative disorder
Epstein-Barr virus infection
Epstein-Barr virus test
Epstein-Barr virus test positive
Erosive balanitis
Eruptive pseudoangiomatosis
Erysipelas
Erysipeloid
Erysipelothrix infection
Erysipelothrix test positive
Erythema induratum
Erythema infectiosum
Erythema migrans
Erythrasma
Escherichia bacteraemia
Escherichia infection
Escherichia pyelonephritis
Escherichia sepsis
Escherichia test positive
Escherichia urinary tract infection
Escherichia vaginitis
Eubacterium infection
Exanthema subitum
Exserohilum infection
External ear cellulitis
Extradural abscess
Extrapulmonary tuberculosis
Eye abscess
Eye infection
Eye infection bacterial
Eye infection chlamydial
Eye infection fungal
Eye infection gonococcal
Eye infection helminthic
Eye infection intraocular
Eye infection staphylococcal
Eye infection syphilitic
Eye infection toxoplasmal
Eye infection viral
Eyelid boil
Eyelid folliculitis
Eyelid infection
Faecal-oral transmission of infection
Fallopian tube abscess
Fascial infection
Fascioliasis
Fasciolopsiasis
Febrile infection

Female genital tract tuberculosis
Femoral hernia gangrenous
Filariasis
Filariasis lymphatic
Filovirus infection
Filovirus test positive
Flavivirus infection
Flavivirus test positive
Flavobacterium infection
Flavobacterium test positive
Flea infestation
Folliculitis
Foot and mouth disease
Francisella test positive
Fungaemia
Fungal abscess central nervous system
Fungal cystitis
Fungal endocarditis
Fungal infection
Fungal labyrinthitis
Fungal oesophagitis
Fungal paronychia
Fungal peritonitis
Fungal retinitis
Fungal rhinitis
Fungal sepsis
Fungal skin infection
Fungal test
Fungal test positive
Fungal tracheitis
Fungating wound
Funisitis
Furuncle
Fusarium infection
Fusobacterium infection
Fusobacterium test positive
Gallbladder abscess
Gallbladder empyema
Gangrene
Gangrene neonatal
Gangrenous balanitis
Gardnerella infection
Gardnerella test positive
Gas gangrene
Gastric infection
Gastric ulcer helicobacter
Gastritis bacterial
Gastritis fungal
Gastritis helminthic
Gastritis herpes
Gastritis viral
Gastroenteritis
Gastroenteritis adenovirus
Gastroenteritis aerobacter
Gastroenteritis aeromonas
Gastroenteritis astroviral
Gastroenteritis bacillus
Gastroenteritis bacterial
Gastroenteritis caliciviral
Gastroenteritis clostridial
Gastroenteritis cryptococcal
Gastroenteritis cryptosporidial
Gastroenteritis enteroviral
Gastroenteritis Escherichia coli
Gastroenteritis norovirus
Gastroenteritis paracolon bacillus
Gastroenteritis proteus
Gastroenteritis pseudomonas
Gastroenteritis rotavirus
Gastroenteritis salmonella
Gastroenteritis sapovirus
Gastroenteritis shigella
Gastroenteritis staphylococcal
Gastroenteritis vibrio
Gastroenteritis viral
Gastroenteritis yersinia
Gastrointestinal anthrax
Gastrointestinal bacterial infection
Gastrointestinal bacterial overgrowth
Gastrointestinal candidiasis
Gastrointestinal fungal infection
Gastrointestinal gangrene
Gastrointestinal infection

Gastrointestinal mucosal necrosis
Gastrointestinal necrosis
Gastrointestinal protozoal infection
Gastrointestinal viral infection
Generalised vaccinia
Genital abscess
Genital candidiasis
Genital herpes
Genital herpes simplex
Genital herpes zoster
Genital infection
Genital infection bacterial
Genital infection female
Genital infection fungal
Genital infection helminthic
Genital infection male
Genital infection viral
Genital tract inflammation
Genitourinary chlamydia infection
Genitourinary tract gonococcal infection
Genitourinary tract infection
Genotype drug resistance test
Genotype drug resistance test abnormal
Genotype drug resistance test positive
Geotrichum infection
Gerstmann Straussler Scheinker syndrome
Gianotti-Crosti syndrome
Giardia test
Giardia test positive
Giardiasis
Gingival abscess
Gingivitis
Gliosis
Gnathostomiasis
Gonococcal pelvic inflammatory disease
Gonorrhoea
Gradenigo's syndrome
Graft infection
Gram stain
Gram stain positive
Granuloma inguinale
Granulomatous dermatitis
Granulomatous liver disease
Granulomatous pneumonitis
Groin abscess
Groin infection
Group B streptococcus neonatal sepsis
Guillain-Barre syndrome
Gynaecological chlamydia infection
H1N1 influenza
Haematoma infection
Haemophilus bacteraemia
Haemophilus infection
Haemophilus sepsis
Haemophilus test positive
Haemorrhagic fever
Haemorrhagic fever with renal syndrome
Haemorrhoid infection
Hand-foot-and-mouth disease
Hantaviral infection
Hantavirus pulmonary infection
Hantavirus test positive
HBV-DNA polymerase increased
Helicobacter gastritis
Helicobacter infection
Helicobacter sepsis
Helicobacter test
Helicobacter test positive
Helminthic infection
Henipavirus test positive
Hepatic amoebiasis
Hepatic candidiasis
Hepatic cyst infection
Hepatic echinococciasis
Hepatic infection
Hepatic infection bacterial
Hepatic infection fungal
Hepatic infection helminthic
Hepatic infiltration eosinophilic
Hepatic necrosis
Hepatitis

Hepatitis A
Hepatitis A antibody
Hepatitis A antibody abnormal
Hepatitis A antibody positive
Hepatitis A antigen positive
Hepatitis A virus test
Hepatitis A virus test positive
Hepatitis acute
Hepatitis B
Hepatitis B antibody
Hepatitis B antibody abnormal
Hepatitis B antibody positive
Hepatitis B antigen
Hepatitis B antigen positive
Hepatitis B core antibody
Hepatitis B core antibody positive
Hepatitis B core antigen
Hepatitis B core antigen positive
Hepatitis B DNA assay
Hepatitis B DNA assay positive
Hepatitis B DNA decreased
Hepatitis B DNA increased
Hepatitis B e antibody
Hepatitis B e antibody positive
Hepatitis B e antigen
Hepatitis B e antigen positive
Hepatitis B surface antibody
Hepatitis B surface antibody positive
Hepatitis B surface antigen
Hepatitis B surface antigen positive
Hepatitis B virus test
Hepatitis B virus test positive
Hepatitis C
Hepatitis C antibody
Hepatitis C antibody positive
Hepatitis C RNA
Hepatitis C RNA decreased
Hepatitis C RNA fluctuation
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C virus test
Hepatitis C virus test positive
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis D
Hepatitis D antibody
Hepatitis D antibody positive
Hepatitis D antigen
Hepatitis D antigen positive
Hepatitis D RNA
Hepatitis D RNA positive
Hepatitis D virus test
Hepatitis D virus test positive
Hepatitis E
Hepatitis E antibody
Hepatitis E antibody abnormal
Hepatitis E antibody positive
Hepatitis E antigen
Hepatitis E antigen positive
Hepatitis E virus test positive
Hepatitis F
Hepatitis fulminant
Hepatitis G
Hepatitis H
Hepatitis infectious mononucleosis
Hepatitis mumps
Hepatitis neonatal
Hepatitis non-A non-B
Hepatitis non-A non-B non-C
Hepatitis post transfusion
Hepatitis syphilitic
Hepatitis toxoplasmal
Hepatitis viral
Hepatitis viral
Hepatitis viral test

Hepatitis viral test positive
Hepatitis virus-associated nephropathy
Hepatobiliary infection
Hepatosplenic candidiasis
Hernia gangrenous
Herpangina
Herpes dermatitis
Herpes oesophagitis
Herpes ophthalmic
Herpes pharyngitis
Herpes sepsis
Herpes simplex
Herpes simplex colitis
Herpes simplex encephalitis
Herpes simplex gastritis
Herpes simplex hepatitis
Herpes simplex meningitis
Herpes simplex meningoencephalitis
Herpes simplex meningomyelitis
Herpes simplex necrotising retinopathy
Herpes simplex oesophagitis
Herpes simplex otitis externa
Herpes simplex pharyngitis
Herpes simplex pneumonia
Herpes simplex sepsis
Herpes simplex test
Herpes simplex test positive
Herpes simplex virus conjunctivitis neonatal
Herpes simplex visceral
Herpes virus infection
Herpes zoster
Herpes zoster cutaneous disseminated
Herpes zoster disseminated
Herpes zoster infection neurological
Herpes zoster meningitis
Herpes zoster meningoencephalitis
Herpes zoster meningomyelitis
Herpes zoster necrotising retinopathy
Herpes zoster oticus
Herpes zoster pharyngitis
Heterophyiasis
Hirudiniasis
Histiocytic necrotising lymphadenitis
Histoplasmosis
Histoplasmosis cutaneous
Histoplasmosis disseminated
HIV antibody
HIV antibody positive
HIV antigen
HIV antigen positive
HIV associated nephropathy
HIV cardiomyopathy
HIV carrier
HIV enteropathy
HIV infection
HIV infection CDC category A
HIV infection CDC category B
HIV infection CDC category C
HIV infection CDC Group I
HIV infection CDC Group II
HIV infection CDC Group III
HIV infection CDC group IV
HIV infection CDC Group IV subgroup A
HIV infection CDC Group IV subgroup B
HIV infection CDC Group IV subgroup C1
HIV infection CDC Group IV subgroup C2
HIV infection CDC Group IV subgroup D
HIV infection CDC Group IV subgroup E
HIV infection WHO clinical stage I
HIV infection WHO clinical stage II
HIV infection WHO clinical stage III

HIV infection WHO clinical stage IV
HIV peripheral neuropathy
HIV test
HIV test positive
HIV tropism test
HIV wasting syndrome
HIV-associated neurocognitive disorder
Hookworm infection
Hordeolum
HTLV test positive
HTLV-1 carrier
HTLV-1 test positive
HTLV-2 test positive
Human anaplasmosis
Human ehrlichiosis
Human herpes virus 6 serology
Human herpes virus 6 serology positive
Human herpes virus 8 test positive
Human herpesvirus 6 infection
Human herpesvirus 7 infection
Human herpesvirus 8 infection
Human immunodeficiency virus transmission
Human papilloma virus test
Human papilloma virus test positive
Human polyomavirus infection
Human rhinovirus test positive
Human T-cell lymphocytic virus type II infection
Human T-cell lymphotropic virus infection
Human T-cell lymphotropic virus type I infection
Hydrocele male infected
Hymenolepiasis
Hypopyon
Iatrogenic infection
Ileal gangrene
Immune reconstitution inflammatory syndrome associated tuberculosis
Impetigo
Implant site abscess
Implant site cellulitis
Implant site infection
Implant site pustules
Incision site abscess
Incision site cellulitis
Incisional hernia gangrenous
Inclusion body myositis
Inclusion conjunctivitis
Inclusion conjunctivitis neonatal
Indeterminate leprosy
Indirect infection transmission
Induced abortion infection
Infantile septic granulomatosis
Infected bite
Infected bunion
Infected cyst
Infected dermal cyst
Infected fistula
Infected lymphocele
Infected naevus
Infected neoplasm
Infected seroma
Infected skin ulcer
Infected varicose vein
Infection
Infection in an immunocompromised host
Infection masked
Infection parasitic
Infection protozoal
Infection reactivation
Infection susceptibility increased
Infection transmission via personal contact
Infection via vaccinee
Infectious colitis
Infectious crystalline keratopathy
Infectious disease carrier
Infectious iridocyclitis
Infectious mononucleosis

Infectious pleural effusion
Infectious thyroiditis
Infective aneurysm
Infective aortitis
Infective chondritis
Infective corneal ulcer
Infective episcleritis
Infective exacerbation of bronchiectasis
Infective exacerbation of chronic obstructive airways disease
Infective gastroduodenitis
Infective glossitis
Infective iritis
Infective mesenteric panniculitis
Infective myositis
Infective periostitis
Infective pulmonary exacerbation of cystic fibrosis
Infective spondylitis
Infective tenosynovitis
Infective thrombosis
Infective uveitis
Infestation
Influenza
Influenza A virus test
Influenza A virus test positive
Influenza B virus test
Influenza B virus test positive
Influenza C virus test positive
Influenza virus test
Influenza virus test positive
Infusion site abscess
Infusion site cellulitis
Infusion site infection
Infusion site pustule
Inguinal hernia gangrenous
Injection site abscess
Injection site cellulitis
Injection site infection
Injection site joint infection
Injection site pustule
Instillation site abscess
Instillation site infection
Instillation site pustules
Intervertebral discitis
Intestinal fistula infection
Intestinal gangrene
Intestinal tuberculosis
Intrauterine infection
Iridocyclitis
Iritis
Isosporiasis
Japanese spotted fever
JC polyomavirus test
JC polyomavirus test positive
JC virus granule cell neuronopathy
JC virus infection
Jejunal gangrene
Joint abscess
Joint tuberculosis
Kaposi's sarcoma AIDS related
Kaposi's varicelliform eruption
Kawasaki's disease
Keratitis
Keratitis bacterial
Keratitis fungal
Keratitis interstitial
Keratitis viral
Keratoconjunctivitis measles
Keratosis gonococcal
Kerion
Kidney infection
Klebsiella bacteraemia
Klebsiella infection
Klebsiella sepsis
Klebsiella test positive
Kuru
Kyasanur Forest disease
Labyrinthitis
Lacrimal sac cellulitis
Lactobacillus infection
Lactobacillus test positive
Laryngitis
Laryngitis bacterial
Laryngitis fungal
Laryngitis viral
Laryngotracheitis obstructive
Lassa fever

Latent syphilis
Latent tuberculosis
Legionella infection
Legionella test
Legionella test positive
Leishmaniasis
Lemierre syndrome
Lentivirus test positive
Lepromatous leprosy
Leprosy
Leptospira test positive
Leptospirosis
Leptotrichia infection
Leuconostoc infection
Lice infestation
Ligneous conjunctivitis
Lineal gingival erythema
Lip infection
Listeria encephalitis
Listeria sepsis
Listeria test positive
Listeriosis
Liver abscess
Localised infection
Lochial infection
Louping ill
Lower respiratory tract infection
Lower respiratory tract infection bacterial
Lower respiratory tract infection fungal
Lower respiratory tract infection viral
Ludwig angina
Lung abscess
Lung infection
Lung infection pseudomonal
Lupus encephalitis
Lupus vulgaris
Lyme disease
Lymph gland infection
Lymph node abscess
Lymph node tuberculosis
Lymphadenitis bacterial
Lymphadenitis fungal
Lymphadenitis helminthic
Lymphadenitis viral
Lymphangitis
Lymphogranuloma venereum
Lyssavirus test positive
Malaria
Malaria antibody test
Malaria antibody test positive
Malarial myocarditis
Male genital tract tuberculosis
Malignant syphilis
Marburg disease
Marburg virus test positive
Mastitis
Mastitis bacterial
Mastitis fungal
Mastitis postpartum
Mastoid abscess
Mastoid empyema
Mastoiditis
Measles
Measles antibody
Measles antibody positive
Measles post vaccine
Mediastinal abscess
Mediastinitis
Meibomian gland discharge
Meibomianitis
Meningitis
Meningitis aseptic
Meningitis aspergillus
Meningitis bacterial
Meningitis borrelia
Meningitis candida
Meningitis chemical
Meningitis coccidioides
Meningitis coxsackie viral
Meningitis cronobacter
Meningitis cryptococcal
Meningitis echo viral
Meningitis enterococcal
Meningitis enteroviral
Meningitis eosinophilic
Meningitis exserohilum
Meningitis fungal
Meningitis gonococcal
Meningitis haemophilus
Meningitis herpes
Meningitis histoplasma
Meningitis leptospiral

Meningitis listeria
Meningitis meningococcal
Meningitis mumps
Meningitis neonatal
Meningitis pneumococcal
Meningitis salmonella
Meningitis staphylococcal
Meningitis streptococcal
Meningitis toxoplasmal
Meningitis trypanosomal
Meningitis tuberculous
Meningitis viral
Meningococcal bacteraemia
Meningococcal carditis
Meningococcal infection
Meningococcal sepsis
Meningoencephalitis amoebic
Meningoencephalitis bacterial
Meningoencephalitis helminthic
Meningoencephalitis herpes simplex neonatal
Meningoencephalitis herpetic
Meningoencephalitis viral
Meningomyelitis herpes
Mesenteric abscess
Mesenteritis
Metagonimiasis
Metapneumovirus infection
Methylobacterium infection
Microbiology test
Microbiology test abnormal
Micrococcal sepsis
Micrococcus infection
Micrococcus test positive
Microsporidia infection
Microsporum infection
Middle ear operation
Middle East respiratory syndrome
Miliary pneumonia
Milker's nodules
Minimum inhibitory concentration
Molluscipoxvirus test positive
Molluscum contagiosum
Monkeypox
Mononucleosis heterophile test
Mononucleosis heterophile test positive
Mononucleosis syndrome
Moraxella infection
Moraxella test positive
Morbillivirus test positive
Morganella infection
Morganella test positive
Mucocutaneous candidiasis
Mucocutaneous leishmaniasis
Mucormycosis
Mucosal infection
Mumps
Mumps antibody test
Mumps antibody test positive
Mumps deafness
Murine typhus
Murray Valley encephalitis
Muscle abscess
Muscular sarcoidosis
Mycetoma mycotic
Mycobacterial disease carrier
Mycobacterial infection
Mycobacterial peritonitis
Mycobacterium abscessus infection
Mycobacterium avium complex immune restoration disease
Mycobacterium avium complex infection
Mycobacterium chelonae infection
Mycobacterium fortuitum infection
Mycobacterium kansasii infection
Mycobacterium leprae test positive
Mycobacterium marinum infection
Mycobacterium test

Mycobacterium test positive

Mycobacterium tuberculosis complex test

Mycobacterium tuberculosis complex test positive

Mycobacterium ulcerans infection

Mycoplasma genitalium infection

Mycoplasma infection

Mycoplasma test

Mycoplasma test positive

Mycoplasmal postabortal fever

Mycoplasmal postpartum fever

Mycotic corneal ulcer

Mycotic endophthalmitis

Mycotoxicosis

Myelitis

Myelitis transverse

Myiasis

Myocardiac abscess

Myocarditis

Myocarditis bacterial

Myocarditis helminthic

Myocarditis infectious

Myocarditis meningococcal

Myocarditis mycotic

Myocarditis post infection

Myocarditis septic

Myocarditis syphilitic

Myocarditis toxoplasmal

Myometritis

Myositis

Myositis ossificans

Myositis-like syndrome

Myringitis

Naegleria infection

Nail bed infection

Nail bed infection bacterial

Nail bed infection viral

Nail candida

Nail infection

Nairovirus test positive

Nasal abscess

Nasal candidiasis

Nasal discharge discolouration

Nasal herpes

Nasal vestibulitis

Nasopharyngitis

Natural killer cell count

Natural killer cell count decreased

Natural killer cell count increased

Natural killer T cell count

Natural killer T cell count decreased

Natural killer T cell count increased

Necrobacillosis

Necrotising fasciitis

Necrotising fasciitis fungal

Necrotising fasciitis staphylococcal

Necrotising fasciitis streptococcal

Necrotising herpetic retinopathy

Necrotising myositis

Necrotising retinitis

Necrotising ulcerative gingivostomatitis

Necrotising ulcerative periodontitis

Neisseria infection

Neisseria test positive

Nematodiasis

Neonatal candida infection

Neonatal infection

Neonatal infective mastitis

Neonatal mucocutaneous herpes simplex

Neonatal pneumonia

Neuroborreliosis

Neurocryptococcosis

Neurocysticercosis

Neurological infection

Neurosarcoidosis

Neurosyphilis

Neutropenic infection

Neutropenic sepsis

Newcastle disease

Newcastle disease virus test positive

Nipah virus infection
Nipple infection
Nipple inflammation
Nocardia sepsis
Nocardia test positive
Nocardiosis
Norovirus test positive
North Asian tick typhus
Nosocomial infection
Obstetric infection
Oculoglandular syndrome
Oesophageal candidiasis
Oesophageal infection
Oesophageal tuberculosis
Oesophagitis bacterial
Omphalitis
Omsk haemorrhagic fever
Onchocerciasis
Oncovirus test positive
Onychomycosis
Oophoritis
Ophthalmia neonatorum
Ophthalmic herpes simplex
Ophthalmic herpes zoster
Opisthorchiasis
Opportunistic infection
Optic neuritis
Optic neuritis meningococcal
Oral bacterial infection
Oral candidiasis
Oral fungal infection
Oral hairy leukoplakia
Oral helminthic infection
Oral herpes
Oral infection
Oral pustule
Oral viral infection
Orbital infection
Orbivirus infection
Orbivirus test positive
Orchitis
Orchitis mumps
Orf
Organic dust toxic syndrome
Oro-pharyngeal aspergillosis
Oropharyngeal candidiasis
Oropharyngeal gonococcal infection
Oropharyngitis fungal
Orthobunyavirus test positive
Orthopox virus infection
Orthopoxvirus test positive
Osler's nodes
Osteomyelitis
Osteomyelitis acute
Osteomyelitis bacterial
Osteomyelitis blastomyces
Osteomyelitis chronic
Osteomyelitis fungal
Osteomyelitis salmonella
Osteomyelitis viral
Otitis externa
Otitis externa bacterial
Otitis externa candida
Otitis externa fungal
Otitis externa viral
Otitis media
Otitis media acute
Otitis media bacterial
Otitis media chronic
Otitis media fungal
Otitis media haemophilus
Otitis media moraxella
Otitis media post measles
Otitis media viral
Otorrhoea
Otosalpingitis
Ovarian abscess
Ovarian bacterial infection
Overgrowth bacterial
Pachymeningitis
Pancreas infection
Pancreatic abscess
Pancreatitis bacterial
Pancreatitis fungal
Pancreatitis helminthic
Pancreatitis mumps
Pancreatitis viral
Panencephalitis
Panophthalmitis

Pantoea agglomerans infection
Pantoea agglomerans test positive
Papilloma viral infection
Paracoccidioides infection
Paragonimiasis
Parainfluenzae viral laryngotracheobronchitis
Parainfluenzae virus infection
Parametric abscess
Parametritis
Paraoesophageal abscess
Parapox virus infection
Parapoxvirus test positive
Parasite allergy
Parasite blood test
Parasite blood test positive
Parasite cervical specimen test positive
Parasite DNA test
Parasite DNA test positive
Parasite stool test
Parasite stool test positive
Parasite tissue specimen test positive
Parasite urine test positive
Parasitic encephalitis
Parasitic gastroenteritis
Parasitic oesophagitis
Parasitic test
Parasitic test positive
Paraspinal abscess
Parathyroid gland abscess
Paratyphoid fever
Paravaccinia
Paravaccinia virus test positive
Parechovirus infection
Paronychia
Parophthalmia
Parotid abscess
Parotitis
Parvovirus B19 test
Parvovirus B19 test positive
Parvovirus infection
Pasteurella infection
Pasteurella test positive
Pathogen resistance
Peliosis hepatis
Pelvic abscess
Pelvic infection
Pelvic inflammatory disease
Pelvic inflammatory disease mycoplasmal
Pelvic sepsis
Penicillium infection
Penile abscess
Penile infection
Penile wart
Peptic ulcer helicobacter
Peptostreptococcus infection
Peptostreptococcus test positive
Perianal streptococcal infection
Pericarditis amoebic
Pericarditis fungal
Pericarditis gonococcal
Pericarditis helminthic
Pericarditis histoplasma
Pericarditis infective
Pericarditis meningococcal
Pericarditis mycoplasmal
Pericarditis rheumatic
Pericarditis syphilitic
Pericarditis tuberculous
Perichondritis
Pericoronitis
Perihepatic abscess
Perihepatitis
Perihepatitis gonococcal
Perinatal HBV infection
Perinatal HIV infection
Perineal abscess
Perineal infection
Perinephric abscess
Periodontal destruction
Periodontal inflammation
Periodontitis
Periorbital abscess
Periorbital cellulitis
Periorbital infection
Peripheral nerve infection

Periporitis staphylogenes
Perirectal abscess
Peritoneal abscess
Peritoneal candidiasis
Peritoneal chlamydia infection
Peritoneal tuberculosis
Peritonitis
Peritonitis bacterial
Peritonitis gonococcal
Peritonitis helminthic
Peritonitis pneumococcal
Peritonitis syphilitic
Peritonitis viral
Peritonsillar abscess
Peritonsillitis
Periumbilical abscess
Persistent generalised lymphadenopathy
Pertussis
Petrositis
Phaehyphomycosis
Pharyngeal abscess
Pharyngeal chlamydia infection
Pharyngitis
Pharyngitis bacterial
Pharyngitis mycoplasmal
Pharyngitis streptococcal
Pharyngoconjunctival fever of children
Pharyngolaryngeal abscess
Pharyngotonsillitis
Phlebitis infective
Phlebotomus fever
Phlebovirus test positive
Pilonidal cyst
Pilonidal cyst congenital
Pingueculitis
Pinta
Pitted keratolysis
Plague
Plague sepsis
Plasma cell mastitis
Plasmodium falciparum infection
Plasmodium malariae infection
Plasmodium ovale infection
Plasmodium vivax infection
Pleural fluid analysis
Pleural infection
Pleural infection bacterial
Pleurisy viral
Pneumococcal bacteraemia
Pneumococcal infection
Pneumococcal sepsis
Pneumocystis jirovecii infection
Pneumocystis jirovecii pneumonia
Pneumocystis test positive
Pneumonia
Pneumonia adenoviral
Pneumonia anthrax
Pneumonia bacterial
Pneumonia blastomyces
Pneumonia bordetella
Pneumonia chlamydial
Pneumonia cryptococcal
Pneumonia cytomegaloviral
Pneumonia escherichia
Pneumonia fungal
Pneumonia haemophilus
Pneumonia helminthic
Pneumonia herpes viral
Pneumonia influenzal
Pneumonia klebsiella
Pneumonia legionella
Pneumonia measles
Pneumonia moraxella
Pneumonia mycoplasmal
Pneumonia necrotising
Pneumonia parainfluenzae viral
Pneumonia pneumococcal
Pneumonia pseudomonal
Pneumonia respiratory syncytial viral
Pneumonia salmonella
Pneumonia staphylococcal
Pneumonia streptococcal
Pneumonia toxoplasmal
Pneumonia tularaemia

Pneumonia viral
Pneumonic plague
Pneumovirus test positive
Pogosta disease
Polioencephalitis
Poliomyelitis
Poliovirus test
Poliovirus test positive
Polymerase chain reaction
Polymyositis
Polyneuropathy mumps
Polyomavirus test positive
Polyomavirus-associated nephropathy
Pontiac fever
Porphyromonas infection
Porphyromonas test positive
Portal pyaemia
Portal tract inflammation
Post abortion infection
Post herpetic neuralgia
Post polio syndrome
Post procedural cellulitis
Post procedural infection
Post procedural pneumonia
Post procedural sepsis
Post streptococcal glomerulonephritis
Post vaccination autoinoculation
Post viral fatigue syndrome
Postoperative abscess
Postoperative wound infection
Postoperative wound infection
Postpartum sepsis
Potassium hydroxide preparation
Potassium hydroxide preparation positive
Presumed ocular histoplasmosis syndrome
Primary syphilis
Primary transmission
Prion agent test positive
Proctitis bacterial
Proctitis chlamydial
Proctitis fungal
Proctitis gonococcal
Proctitis herpes
Proctitis infectious
Proctitis monilial
Proctitis mycoplasmal
Progressive massive fibrosis
Progressive multifocal leukoencephalopathy
Progressive vaccinia
Propionibacterium infection
Propionibacterium test positive
Prostate infection
Prostatic abscess
Prostatitis
Prostatitis Escherichia coli
Prostatitis gonococcal
Prostatitis trichomonal
Prostatitis tuberculous
Prostatovesiculitis
Proteus infection
Proteus test positive
Protozoal corneal ulcer
Pseudallescheria infection
Pseudallescheria sepsis
Pseudofolliculitis barbae
Pseudomembranous colitis
Pseudomonal bacteraemia
Pseudomonal sepsis
Pseudomonas aeruginosa meningitis
Pseudomonas bronchitis
Pseudomonas infection
Pseudomonas test positive
Psittacosis
Psoas abscess
Psorospermiasis
Puerperal infection
Puerperal pyrexia
Pulmonary echinococciasis
Pulmonary mycosis
Pulmonary sepsis
Pulmonary syphilis

Pulmonary trichosporonosis
Pulmonary tuberculoma
Pulmonary tuberculosis
Pulpitis dental
Punctate keratitis
Puncture site abscess
Puncture site discharge
Puncture site infection
Puncture site oedema
Purulence
Purulent discharge
Purulent pericarditis
Purulent synovitis
Pyelocystitis
Pyelonephritis
Pyelonephritis acute
Pyelonephritis chronic
Pyelonephritis fungal
Pyelonephritis mycoplasmal
Pyelonephritis viral
Pyloric abscess
Pyoderma
Pyoderma streptococcal
Pyometra
Pyomyositis
Pyonephrosis
Pyopneumothorax
Pyospermia
Pythium insidiosum infection
Pyuria
Q fever
Queensland tick typhus
Rabies
Raoultella ornithinolytica infection
Raoultella test positive
Rash pustular
Recrudescent typhus
Rectal abscess
Rectovaginal septum abscess
Reiter's syndrome
Relapsing fever
Renal abscess
Renal cyst infection
Renal syphilis
Renal tuberculosis
Respiratory moniliasis
Respiratory papilloma
Respiratory syncytial virus bronchiolitis
Respiratory syncytial virus bronchitis
Respiratory syncytial virus infection
Respiratory syncytial virus test
Respiratory syncytial virus test positive
Respiratory tract infection
Respiratory tract infection bacterial
Respiratory tract infection fungal
Respiratory tract infection viral
Respirovirus test positive
Retinitis
Retinitis histoplasma
Retinitis viral
Retroperitoneal abscess
Retroperitoneal infection
Retroviral infection
Retroviral rebound syndrome
Reye's syndrome
Rheumatic fever
Rheumatic heart disease
Rhinitis
Rhinolaryngitis
Rhinoscleroma
Rhinosporidiosis
Rhinotracheitis
Rhinovirus infection
Rhodococcus infection
Rhodococcus test positive
Rickettsialpox
Rickettsioses not tick borne
Rickettsiosis
Rift Valley fever
Rocky mountain spotted fever
Root canal infection
Roseola
Roseolovirus test positive
Rotavirus infection
Rotavirus test
Rotavirus test positive
Rubella

Rubella antibody positive
Rubella antibody test
Rubella immunity confirmed
Rubella in pregnancy
Rubella infection neurological
Rubivirus test positive
Rubulavirus test positive
Salmonella bacteraemia
Salmonella sepsis
Salmonella test positive
Salmonellosis
Salpingitis
Salpingitis gonococcal
Salpingitis tuberculous
Salpingo-oophoritis
Sapovirus test positive
Sarcocystis infection
Scarlet fever
Scedosporium infection
Schistosoma test
Schistosoma test positive
Schistosomiasis
Schistosomiasis bladder
Schistosomiasis cutaneous
Schistosomiasis liver
Scrotal abscess
Scrotal gangrene
Scrotal infection
Scrub typhus
Sebaceous gland infection
Secondary syphilis
Secondary transmission
Seminal vesicular infection
Seminal vesiculitis
Seminal vesiculitis gonococcal
Sepsis
Sepsis neonatal
Sepsis pasteurella
Sepsis syndrome
Septic arthritis haemophilus
Septic arthritis neisserial
Septic arthritis staphylococcal
Septic arthritis streptobacillus
Septic arthritis streptococcal
Septic embolus
Septic encephalopathy
Septic necrosis
Septic phlebitis
Septic rash
Septic shock
Septic vasculitis
Seroconversion test
Seroconversion test positive
Serology abnormal
Serology positive
Serology test
Serratia bacteraemia
Serratia infection
Serratia sepsis
Serratia test positive
Severe acute respiratory syndrome
Severe invasive streptococcal infection
Sexual transmission of infection
Sexually transmitted disease
Sexually transmitted disease carrier
Shigella infection
Shigella sepsis
Shigella test positive
Shunt infection
Sialoadenitis
Silicotuberculosis
Sinobronchitis
Sinusitis
Sinusitis aspergillus
Sinusitis bacterial
Sinusitis fungal
Skin bacterial infection
Skin candida
Skin graft infection
Skin infection
Skin infection helminthic
Slit-lamp tests abnormal
Slow virus infection
Small intestine gangrene
Smallpox
Snowshoe hare virus infection
Soft tissue infection

Spermatic cord funiculitis
Spermatic cord inflammation
Sphingomonas paucimobilis infection
Spinal cord abscess
Spinal cord infection
Spirillary fever
Spirillum test positive
Spirochaetal infection
Spleen tuberculosis
Splenic abscess
Splenic candidiasis
Splenic infection
Splenic infection bacterial
Splenic infection fungal
Splenic infection helminthic
Splenic infection viral
Sporotrichosis
Spotted fever rickettsia test positive
Sputum culture
Sputum culture positive
Sputum purulent
St. Louis encephalitis
Staphylococcal abscess
Staphylococcal bacteraemia
Staphylococcal impetigo
Staphylococcal infection
Staphylococcal mediastinitis
Staphylococcal osteomyelitis
Staphylococcal parotitis
Staphylococcal pharyngitis
Staphylococcal scalded skin syndrome
Staphylococcal sepsis
Staphylococcal skin infection
Staphylococcal toxaemia
Staphylococcus test
Staphylococcus test positive
Stenotrophomonas infection
Stenotrophomonas sepsis
Stenotrophomonas test positive
Sternitis
Stitch abscess
Stoma site abscess
Stoma site candida
Stoma site cellulitis
Stoma site infection
Stomach granuloma
Stomatococcal infection
Stomatococcus test positive
Strawberry tongue
Streptobacillary fever
Streptobacillus infection
Streptobacillus test positive
Streptococcal abscess
Streptococcal bacteraemia
Streptococcal endocarditis
Streptococcal impetigo
Streptococcal infection
Streptococcal sepsis
Streptococcal urinary tract infection
Streptococcus test
Streptococcus test positive
Strongyloidiasis
Subacute endocarditis
Subacute sclerosing panencephalitis
Subarachnoid abscess
Subcutaneous abscess
Subdiaphragmatic abscess
Subglottic laryngitis
Subperiosteal abscess
Superinfection
Superinfection bacterial
Superinfection fungal
Superinfection mycobacterial
Superinfection viral
Suspected transmission of an infectious agent via product
Sweat gland infection
Sweating fever
Sycosis barbae
Syphilis
Syphilis anal
Syphilis genital
Syphilis musculoskeletal

Syphilitic endocarditis of heart valve
Systemic candida
Systemic mycosis
Taeniasis
Tertiary syphilis
Testicular abscess
Tetanus
Tetanus neonatorum
Thornwaldt disease
Thrombophlebitis septic
Thymus abscess
Thyroglossal cyst infection
Thyroid echinococciasis
Thyroid gland abscess
Thyroid tuberculosis
Thyroiditis subacute
Tick-borne fever
Tick-borne viral encephalitis
Tinea barbae
Tinea blanca
Tinea capitis
Tinea cruris
Tinea faciei
Tinea imbricata
Tinea infection
Tinea manuum
Tinea nigra
Tinea pedis
Tinea versicolour
Tongue abscess
Tonsillitis
Tonsillitis bacterial
Tonsillitis fungal
Tonsillitis streptococcal
Tooth abscess
Tooth infection
Torulopsis infection
Toxic shock syndrome
Toxic shock syndrome staphylococcal
Toxic shock syndrome streptococcal
Toxocariasis
Toxoplasma serology
Toxoplasma serology positive
Toxoplasmosis
Tracheitis
Tracheitis obstructive
Tracheobronchitis
Tracheobronchitis mycoplasmal
Tracheobronchitis viral
Tracheostomy infection
Trachoma
Transmission of an infectious agent via product
Transplant abscess
Trematode infection
Trench fever
Treponema test
Treponema test false positive
Treponema test positive
Trichiniasis
Trichomoniasis
Trichomoniasis intestinal
Trichophytic granuloma
Trichophytosis
Trichosporon infection
Trichostrongyliasis
Trichuriasis
Trigonitis
Tropical eosinophilia
Tropical infectious disease
Tropical spastic paresis
Tropical ulcer
Trypanosoma serology positive
Trypanosomiasis
Tuberculin test
Tuberculin test positive
Tuberculoid leprosy
Tuberculoma of central nervous system
Tuberculosis
Tuberculosis bladder
Tuberculosis gastrointestinal
Tuberculosis liver
Tuberculosis of central nervous system
Tuberculosis of eye
Tuberculosis of genitourinary system
Tuberculosis of intrathoracic lymph nodes
Tuberculosis of peripheral lymph nodes
Tuberculosis ureter

Tuberculous abscess central nervous system
Tuberculous endometritis
Tuberculous laryngitis
Tuberculous pleurisy
Tuberculous tenosynovitis
Tubo-ovarian abscess
Tularaemia
Type 1 lepra reaction
Type 2 lepra reaction
Typhoid carrier
Typhoid fever
Typhus
Typhus rickettsia test
Typhus rickettsia test positive
Ulcerative keratitis
Umbilical hernia gangrenous
Umbilical sepsis
Upper aerodigestive tract infection
Upper respiratory fungal infection
Upper respiratory tract infection
Upper respiratory tract infection bacterial
Upper respiratory tract infection helminthic
Urachal abscess
Ureaplasma infection
Ureaplasma test positive
Ureter abscess
Ureteritis
Urethral abscess
Urethral carbuncle
Urethral stricture post infection
Urethritis
Urethritis chlamydial
Urethritis gonococcal
Urethritis mycoplasmal
Urethritis trichomonal
Urethritis ureaplasmal
Urinary bladder abscess
Urinary tract abscess
Urinary tract infection
Urinary tract infection bacterial
Urinary tract infection enterococcal
Urinary tract infection fungal
Urinary tract infection neonatal
Urinary tract infection pseudomonal
Urinary tract infection staphylococcal
Urinary tract infection viral
Urinary tract inflammation
Urogenital infection bacterial
Urogenital infection fungal
Urogenital trichomoniasis
Urosepsis
Uterine abscess
Uterine infection
Uveitis
Vaccination site abscess
Vaccination site cellulitis
Vaccination site discharge
Vaccination site infection
Vaccination site pallor
Vaccination site pustule
Vaccine associated paralytic poliomyelitis
Vaccine breakthrough infection
Vaccine virus shedding
Vaccinia test positive
Vaccinia virus infection
Vaginal abscess
Vaginal cellulitis
Vaginal infection
Vaginitis chlamydial
Vaginitis gardnerella
Vaginitis viral
Variant Creutzfeldt-Jakob disease
Varicella
Varicella post vaccine
Varicella virus test
Varicella virus test positive
Varicella zoster gastritis
Varicella zoster oesophagitis
Varicella zoster pneumonia

Vector-borne transmission of infection
Veillonella infection
Veillonella test positive
Vertical infection transmission
Vessel puncture site infection
Vestibular neuronitis
Vestibulitis
Vibrio test positive
Viraemia
Viral cardiomyopathy
Viral corneal ulcer
Viral diarrhoea
Viral epiglottitis
Viral haemorrhagic cystitis
Viral hepatitis carrier
Viral infection
Viral labyrinthitis
Viral load
Viral load decreased
Viral load increased
Viral mastitis
Viral mutation identified
Viral myelitis
Viral myocarditis
Viral myositis
Viral oesophagitis
Viral parotitis
Viral pericarditis
Viral pharyngitis
Viral rash
Viral rhinitis
Viral sepsis
Viral sinusitis
Viral skin infection
Viral test
Viral test positive
Viral titre
Viral titre decreased
Viral titre increased
Viral tonsillitis
Viral tracheitis
Viral upper respiratory tract infection
Viral uveitis
Viral vasculitis
Virologic failure
Visceral larva migrans
Visceral leishmaniasis
Vitreous abscess
Vitritis
Vorticella infection
Vulval abscess
Vulval cellulitis
Vulvitis
Vulvovaginal candidiasis
Vulvovaginal human papilloma virus infection
Vulvovaginal mycotic infection
Vulvovaginal warts
Vulvovaginitis
Vulvovaginitis chlamydial
Vulvovaginitis gonococcal
Vulvovaginitis helminthic
Vulvovaginitis streptococcal
Vulvovaginitis trichomonal
Waterhouse-Friderichsen syndrome
Weil's disease
West Nile viral infection
Whipple's disease
Withdrawal hepatitis
Wound abscess
Wound contamination
Wound infection
Wound infection bacterial
Wound infection fungal
Wound infection helminthic
Wound infection pseudomonas
Wound infection staphylococcal
Wound infection viral
Wound sepsis
Yaws
Yaws of bone
Yaws of skin
Yellow fever
Yellow fever vaccine-associated neurotropic disease
Yellow fever vaccine-associated viscerotropic disease
Yersinia bacteraemia
Yersinia infection
Yersinia sepsis

Yersinia test
Yersinia test positive
Young's syndrome
Zoonosis
Zoonotic bacterial infection

Serious infections

Any events like this will be listed under cluster = Infections, and can be identified based on AESER = Y

Opportunistic infections (excluding TB)

Aeromonas infection
Aeromonas test positive
Allescheriosis
Alternaria infection
Aspergilloma
Aspergillosis oral
Aspergillus infection
Aspergillus test
Aspergillus test positive
Atypical mycobacterial lower respiratory tract infection
Atypical mycobacterial pneumonia
Atypical mycobacterium pericarditis
Bacillary angiomatosis
BK virus infection
Bronchopulmonary aspergillosis
Burkholderia cepacia complex infection
Burkholderia cepacia complex sepsis
Burkholderia gladioli infection
Burkholderia infection
Burkholderia test positive
Candida endophthalmitis
Candida osteomyelitis
Candida pneumonia
Candida retinitis
Candida sepsis
Capnocytophaga infection
Capnocytophaga test positive
Cerebral aspergillosis
Cerebral fungal infection
Cerebral toxoplasmosis
Chronic pulmonary histoplasmosis
Coccidioides encephalitis
Coccidioidomycosis
Colitis herpes
Cryptococcal cutaneous infection
Cryptococcal fungaemia
Cryptococcosis
Cryptococcus test
Cryptococcus test positive
Cutaneous coccidioidomycosis
Cytomegalovirus chorioretinitis
Cytomegalovirus colitis
Cytomegalovirus duodenitis
Cytomegalovirus enteritis
Cytomegalovirus enterocolitis
Cytomegalovirus gastritis
Cytomegalovirus gastroenteritis
Cytomegalovirus gastrointestinal infection
Cytomegalovirus gastrointestinal ulcer
Cytomegalovirus hepatitis
Cytomegalovirus infection
Cytomegalovirus mucocutaneous ulcer
Cytomegalovirus myelomeningoradiculitis
Cytomegalovirus myocarditis
Cytomegalovirus oesophagitis
Cytomegalovirus pancreatitis

Cytomegalovirus pericarditis
Cytomegalovirus syndrome
Cytomegalovirus test
Cytomegalovirus test positive
Cytomegalovirus urinary tract infection
Cytomegalovirus viraemia
Disseminated cryptococcosis
Disseminated cytomegaloviral infection
Encephalitis cytomegalovirus
Encephalitis fungal
Endocarditis histoplasma
Enterocolitis fungal
Exserohilum infection
Exserohilum test
Exserohilum test positive
Eye infection toxoplasmal
Fungaemia
Fungal abscess central nervous system
Fungal oesophagitis
Fungal retinitis
Fungal sepsis
Fungal tracheitis
Fusarium infection
Gastritis fungal
Gastritis herpes
Gastroenteritis cryptococcal
Genital herpes zoster
Hepatic candidiasis
Hepatic infection fungal
Hepatitis toxoplasmal
Hepatosplenic candidiasis
Herpes oesophagitis
Herpes sepsis
Herpes simplex colitis
Herpes simplex encephalitis
Herpes simplex gastritis
Herpes simplex hepatitis
Herpes simplex meningitis
Herpes simplex meningoencephalitis
Herpes simplex meningomyelitis
Herpes simplex necrotising retinopathy
Herpes simplex oesophagitis
Herpes simplex pneumonia
Herpes simplex sepsis
Herpes simplex visceral
Herpes zoster cutaneous disseminated
Herpes zoster disseminated
Herpes zoster infection neurological
Herpes zoster meningitis
Herpes zoster meningoencephalitis
Herpes zoster meningomyelitis
Herpes zoster necrotising retinopathy
Herpes zoster oticus
Herpes zoster pharyngitis
Histoplasmosis cutaneous
Histoplasmosis disseminated
Infection in an immunocompromised host
JC polyomavirus test
JC polyomavirus test positive
JC virus granule cell neuronopathy
JC virus infection
Kaposi's sarcoma AIDS related
Kaposi's varicelliform eruption
Listeria encephalitis
Listeria sepsis
Listeria test positive
Lymphadenitis fungal
Meningitis aspergillus
Meningitis candida
Meningitis coccidioides
Meningitis cryptococcal
Meningitis exserohilum
Meningitis fungal
Meningitis herpes

Meningitis histoplasma
Meningitis listeria
Meningitis toxoplasmal
Meningomyelitis herpes
Methylobacterium infection
Miliary pneumonia
Mucocutaneous candidiasis
Mucormycosis
Mycobacterium avium complex immune restoration disease
Mycobacterium avium complex infection
Mycobacterium chelonae infection
Mycobacterium fortuitum infection
Mycobacterium kansasii infection
Myocarditis toxoplasmal
Necrotising herpetic retinopathy
Neurocryptococcosis
Neutropenic infection
Neutropenic sepsis
Nocardia sepsis
Nocardia test positive
Nocardiosis
Oesophageal candidiasis
Ophthalmic herpes zoster
Opportunistic infection
Oral candidiasis
Oral fungal infection
Oral hairy leukoplakia
Oro-pharyngeal aspergillosis
Oropharyngeal candidiasis
Oropharyngitis fungal
Otitis media fungal
Pancreatitis fungal
Penicillium infection
Pericarditis fungal
Pericarditis histoplasma
Phaehyphomycosis
Pneumocystis jirovecii infection
Pneumocystis jirovecii pneumonia
Pneumocystis test positive
Pneumonia cryptococcal
Pneumonia cytomegaloviral
Pneumonia herpes viral
Pneumonia toxoplasmal
Polyomavirus-associated nephropathy
Presumed ocular histoplasmosis syndrome
Proctitis herpes
Progressive multifocal leukoencephalopathy
Progressive vaccinia
Pseudallescheria infection
Pseudallescheria sepsis
Pyelonephritis fungal
Respiratory moniliasis
Retinitis histoplasma
Retinitis viral
Rhodococcus infection
Rhodococcus test positive
Scedosporium infection
Sepsis pasteurella
Sinusitis aspergillus
Sinusitis fungal
Splenic candidiasis
Splenic infection fungal
Stomatococcal infection
Stomatococcus test positive
Strongyloidiasis
Systemic candida
Systemic mycosis
Tonsillitis fungal
Upper respiratory fungal infection
Varicella zoster gastritis
Varicella zoster oesophagitis
Varicella zoster pneumonia
Varicella zoster virus infection
Viral oesophagitis
Yersinia sepsis

Active TB

Adrenal gland tuberculosis
Bone tuberculosis
Choroid tubercles
Congenital tuberculosis
Conjunctivitis tuberculous
Cutaneous tuberculosis
Disseminated tuberculosis
Ear tuberculosis
Epididymitis tuberculous
Erythema induratum
Exposure to communicable disease
Extrapulmonary tuberculosis
Female genital tract tuberculosis
Joint tuberculosis
Lymph node tuberculosis
Male genital tract tuberculosis
Meningitis tuberculous
Oesophageal tuberculosis
Pericarditis tuberculous
Peritoneal tuberculosis
Prostatitis tuberculous
Pulmonary tuberculoma
Pulmonary tuberculosis
Renal tuberculosis
Salpingitis tuberculous
Silicotuberculosis
Spleen tuberculosis
Thyroid tuberculosis
Tuberculoma of central nervous system
Tuberculosis
Tuberculosis bladder
Tuberculosis gastrointestinal
Tuberculosis liver
Tuberculosis of central nervous system
Tuberculosis of eye
Tuberculosis of genitourinary system
Tuberculosis of intrathoracic lymph nodes
Tuberculosis of peripheral lymph nodes
Tuberculosis ureter
Tuberculous abscess central nervous system
Tuberculous endometritis
Tuberculous laryngitis
Tuberculous pleurisy
Tuberculous tenosynovitis

Latent TB

Latent tuberculosis
Mycobacterium test positive
Mycobacterium tuberculosis complex test positive
Tuberculin test false negative
Tuberculin test positive

Herpes zoster infection

Colitis herpes
Gastritis herpes
Genital herpes zoster
Herpes oesophagitis
Herpes ophthalmic
Herpes pharyngitis
Herpes sepsis
Herpes virus infection
Herpes zoster
Herpes zoster cutaneous disseminated
Herpes zoster disseminated
Herpes zoster infection neurological
Herpes zoster meningitis
Herpes zoster meningoencephalitis
Herpes zoster meningomyelitis
Herpes zoster necrotising retinopathy
Herpes zoster oticus
Herpes zoster pharyngitis

Meningitis herpes

Meningomyelitis herpes

Ophthalmic herpes zoster

Pneumonia herpes viral

Proctitis herpes

Varicella zoster gastritis

Varicella zoster oesophagitis

Varicella zoster pneumonia

Varicella zoster virus infection

Malignancies
Malignancies standardized MedDRA query (SMQ) (Narrow)

Hypersensitivity reactions (including anaphylaxis and angioedema)
Anaphylactic reaction SMQ (Narrow)

Angioedema SMQ (Narrow)

Hypersensitivity SMQ (Narrow)

Gastrointestinal (GI) perforation
Gastrointestinal perforation SMQ (Narrow)

Demyelinating disorders
Demyelination SMQ (Narrow)

Major adverse cardiac events (MACE)
Cardiac failure SMQ (Narrow)

Cerebrovascular disorders SMQ (Narrow)

Ischemic heart disease SMQ (Narrow)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past week</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!