Official Protocol Title:	A Phase-IV, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of Golimumab (MK-8259 [SCH 900259]) After Treatment Withdrawal, Compared With Continued Treatment (Either Full- or Reduced-Treatment Regimen), In Subjects With Non-Radiographic Axial Spondyloarthritis
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TITLE:

A Phase-IV, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of Golimumab (MK-8259 [SCH 900259]) After Treatment Withdrawal, Compared With Continued Treatment (Either Full- or Reduced-Treatment Regimen), In Subjects With Non-Radiographic Axial Spondyloarthritis

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
5.1.1	Inclusion Criteria	The Inclusion criterion #3 was updated to include male contraception language: **Current:** If a female subject of child-bearing potential, agree to abstain from heterosexual activity or use a medically accepted method of contraception prior to enrollment, while receiving protocol-specified medication and for 6 months after stopping the medication. Medically accepted methods of contraception include condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intrauterine device (IUD), inert or copper-containing IUD, hormone- releasing IUD, systemic hormonal contraceptive, and surgical sterilization (eg, hysterectomy or tubal ligation). Other methods may be used as required by local legislation. Postmenopausal women are not required to use contraception. Postmenopausal is defined as at least 12 consecutive months without a spontaneous menstrual period. **Revised:** Meet one of the following categories: a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition). b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) Postmenopausal is defined as at least 12 consecutive months without a spontaneous menstrual period; (2) has had a hysterectomy and/or bilateral	Male contraception language is needed in the protocol.

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
		oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing. c) The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner while receiving trial medication or within 6 months after the last dose of trial medication by complying with one of the following: (1) practice abstinence† from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are‡: • intrauterine device (IUD) • vasectomy of a female subject's male partner • contraceptive rod implanted into the skin • barrier method (includes diaphragm, cervical cap, and male or female condom) combined with spermicidal gel or foam • hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection †Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.	

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
		‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.	
5.1.3	Exclusion Criteria	The following new exclusion criterion (No. 3) was added. Intends to donate eggs (female subjects) or sperm (male subjects) while receiving trial medication or within 6 months after the last dose of trial medication.	Language regarding the egg and sperm donation is needed in the protocol.
7.1.3	Laboratory Procedures/Assessments	The title of the Section 7.1.3.2 was revised as follow: **Current:** Serum/Urine Pregnancy Test **Revised**: Serum/Urine Pregnancy Testing and Follow-up of Pregnancy The section was revised to include that male subjects must use a medically accepted method of contraception during the trial or within 6 months after the last dose of trial medication. The following language was also added for male subjects. Male subjects who may have fathered a child during the trial or within 6 months after stopping the trial medication must notify the site immediately.	Language regarding male contraception language and follow-up of pregnancy is needed in the protocol.

Section Number(s)	Section Title(s)	Description of Change (s)	Rationale
7.2.2	Reporting of Pregnancy and Lactation to Sponsor	The Section was updated as follow to collect pregnancy/lactation information from the partner of a male subject. Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial. Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/ randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/ randomization through 6 months following cessation of Sponsor's product must be reported. All reported pregnancies must be followed to the completion/ termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).	Language regarding follow-up of pregnancy to include female partners of male subjects is needed in the protocol.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.1	Study Flow Chart: Period 1: Open-Label Run-in	Scheduled Month for Safety F/U telephone call was updated from 13 to 12.	Typographical error
6.1	Study Flow Chart: Period 1: Open-Label Run-in	Two footnotes were updated to describe scheduling Visits 17 and 24 following assessments for disease activity at Month 7 (Visit 16) and at Month 10 (Visit 23): d. At Month 7 (Visit 16), subjects are assessed for Inactive Disease status (defined as ASDAS <1.3). Subjects who do not attain Inactive Disease status are discontinued; these subjects are to be scheduled for the DC visit to perform procedures (vital signs, Physician Global Disease Assessment, routine laboratory blood draw, and pregnancy test if required) that were not done at the Month 7 visit (Visit 16) but are required per DC visit. Subjects who attain inactive disease status (i.e., ASDAS <1.3) at Visit 16 will be scheduled for Visit 17 (within 2-7 days) to continue to receive open-label golimumab for self-administration at home in Period 1. e. At Month 10 (Visit 23), subjects complete Period 1 and are assessed for Period 2. Subjects who attain Inactive Disease (defined as ASDAS <1.3) status enter Period 2. Subjects who do not attain Inactive Disease status are discontinued, and all procedures outlined for the DC visit are to be performed. Subjects who attain inactive disease status (i.e., ASDAS <1.3) at Visit 23 will be scheduled for Visit 24 (within 2-7 days) to enter Period 2 and receive double-blind treatment.	Adds clarity for scheduling the clinic visits

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.2	Study Flow Chart: Period 2: Double-blind Withdrawal	The following footnote was added to the Flow Chart. c. If the subject discontinued from the trial during Period 2, trial medication will not be administered at the DC clinic visit.	All procedures to be performed at Visit 48 and discontinuation visits are the same, except for administration of trial medication. Trial medication will be administered at the last clinic visit (Visit 48) but will not be administered if subjects discontinued from Period 2 for any reason.
7.1.5.5	Unscheduled Visit(s) to confirm a "Flare" during Period 2	The timing between visits needed to confirm the "flare" was updated. **Current:** If this ASDAS shows absolute score ≥2.1 and/or post-withdrawal increase of ≥1.1, then the subject will be asked to come to the clinic, for an unscheduled visit, for an additional assessment for confirmation of a "flare". This additional assessment should occur within ideally < 10 days (but no more than 3 weeks); or this assessment can occur at a previously scheduled clinic visit, if the timing fits within ideally <10 days (but no more than 3 weeks) from the first assessment. **Revised:** If this ASDAS shows absolute score ≥2.1 and/or post-withdrawal increase of ≥1.1, then the subject will be asked to come to the clinic, for an unscheduled visit, for an additional assessment for confirmation of a "flare". This additional assessment should occur within ideally 2 to 10 days (but no more than 3 weeks); or this assessment can occur at a previously scheduled clinic visit, if the timing fits within ideally 2 to 10 days (but no more than 3 weeks) from the first assessment.	To clarify the timing between visits needed to confirm a flare

1.0 TRIAL SUMMARY

Abbreviated Title	Golimumab (MK-8259 / SCH 900259) in nr-axSpA: Withdrawal trial (GO-BACK)
Trial Phase	IV
Clinical Indication	Treatment of non-radiographic axial spondyloarthritis (nr-axSpA)
Trial Type	Interventional
Type of control	Placebo
Route of administration	Subcutaneous
Trial Blinding	Double-blind
Treatment Groups	• Treatment withdrawal: Placebo every month (QM) • Golimumab every month (QM) • Golimumab every 2 months (Q2M)
Number of trial subjects	Approximately 300 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 3.6 years from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject participates in the trial for up to approximately 27 months from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of no more than 2 months, each subject enters an approximately 10-month open-label run-in period, followed by an approximately 12-month double-blind withdrawal or continued treatment period. After the last dose of trial medication, each subject is followed for an additional 3 months.

Randomization Ratio	1:1:1

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, double-blind, parallel-group, withdrawal trial of golimumab (MK-8259) in subjects with nonradiographic axial spondyloarthritis (nr-axSpA) to be conducted in conformance with Good Clinical Practices (GCPs). In brief, subjects with active nr-axSpA are treated with open-label golimumab. Those subjects who attain inactive disease status when assessed after both 7 and 10 months on open-label therapy are then randomized to be either withdrawn from golimumab or continued on golimumab using either a full (every month [QM]) or a reduced (every 2 months [Q2M]) regimen. Randomized subjects are followed for approximately 12 months to characterize the incidence of a "flare" in disease activity. Those subjects who have a disease "flare" following randomization are then re-treated with open-label golimumab to characterize the clinical response to re-treatment after a "flare".

To be eligible for the run-in period (i.e., to receive open-label golimumab), subjects must have objective signs of inflammation, defined as elevated serum C-reactive protein (CRP) measured at the Screening visit (Visit 1), or evidence of active inflammation in the sacroiliac (SI) joints on magnetic resonance imaging (MRI) available at the Baseline visit (Visit 2). SI-joint MRIs and plain conventional x-rays must undergo central reading to determine study eligibility. A maximum of 40% of subjects may have a normal CRP level at the initial (i.e., Screening) visit.

Period 1: Open-label Run-in (approximately 10 months duration)

After a screening period (up to 2 months [60 days]), eligible subjects enter the run-in period to receive open-label golimumab 50 mg subcutaneous (SC) monthly, starting at Month 0. Subjects are assessed by the investigator at study visits scheduled at Months 0, 1, 4, 7, and 10. Additionally, during this open-label period, subjects must complete the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questionnaire twice monthly. Subjects who achieve a clinical response by Month 4 (or earlier) continue to receive golimumab monthly through Period 1 (i.e., for an additional 6 months). A clinical response is defined as an improvement in BASDAI score of ≥2 (on a numerical rating scale [NRS] from 0 to 10) or ≥50% improvement in BASDAI score when determined relative to the score at Month 0. Subjects who have not attained a clinical response by Month 4 of treatment with open-label golimumab are discontinued from the study at Month 4 (and will have a safety follow-up telephone call 3 months after their last dose of trial medication; see Section 7.1.5.2 for more details). At Month 7, evaluations will be performed to calculate Ankylosing Spondylitis Disease Activity Score (ASDAS). Subjects who attain inactive disease status (defined as ASDAS <1.3) continue to receive golimumab monthly through Period 1. Subjects who do not have inactive disease by Month 7 are discontinued from the study (and will have a safety follow-up telephone call 3 months after their last dose of trial medication; see Section 7.1.5.3 for more details).

Period 2: Double-blind Withdrawal Versus Continued Therapy (approximately 12 months duration)

At Month 10 (Visit 23; see also Trial Flow Chart – Section 6.1), evaluations are performed to calculate ASDAS. Subjects who have attained inactive disease status (defined as ASDAS <1.3) at both Months 7 and 10 of open-label treatment are eligible to enter the double-blind withdrawal period (see Section 7.1.5.4 for more details); only these subjects are to be scheduled for the next clinic visit (Visit 24), which begins Period 2. Eligible subjects undergo stratified randomization in a 1:1:1 ratio to one of the following 3 treatment arms: 1) treatment-withdrawal (i.e., monthly injections of matching-placebo for golimumab), 2) golimumab QM (i.e., a full-treatment regimen, per approved labeling), or 3) golimumab Q2M (i.e., a reduced-treatment regimen, via monthly injections that alternate between golimumab and matching-placebo for golimumab). Strata are defined by the presence or absence of elevated CRP (>6.0 mg/L vs. ≤6.0 mg/L) at the Screening visit. Eligible subjects receive their initial dose of blinded trial medication during Visit 24. Subjects who do not have inactive disease at Visit 23 do not enter Period 2; these subjects are discontinued from the study (and will have a safety follow-up telephone call 3 months after their last dose of trial medication).

Over the course of 12 months during Period 2, subjects return to the trial site for evaluation, including laboratory testing, approximately every 2 months (starting from the initial dose of double-blind trial medication). Subjects also continue to complete the BASDAI questionnaire twice monthly in order to rate disease activity. If there is an increase of ≥2 (on the 0 to 10 NRS) in BASDAI score compared to Month 10 (Visit 23), the trial site calls the subject to initiate a full evaluation of whether a "flare" (indicative of increased disease activity) is occurring; assessments include information obtained over the phone and/or at an unscheduled visit. A "flare" is defined by ASDAS collected at 2 consecutive assessments that both show absolute score ≥2.1 and/or post-withdrawal increase (i.e., change from Visit 23) of ≥1.1 (see Section 7.1.5.5 for details on confirming a "flare").

If a "flare" occurs during Period 2, then subjects discontinue blinded therapy (placebo, golimumab QM, or golimumab Q2M) and begin re-treatment with open-label golimumab QM. There should be an interval of at least 10 days between the last dose of Period-2 double-blind therapy and the first dose of open-label golimumab after a "flare" is confirmed. Thereafter, it is expected that re-treatment with open-label golimumab continues monthly through the end of Period 2. A clinical response to re-treatment is defined as a BASDAI score improvement of ≥2 or ≥50% improvement (measured relative to the mean of the 2 BASDAI scores that were collected at the 2 consecutive assessments that defined the "flare") that occurs within 3 months of restarting open-label treatment. If a subject shows insufficient improvement after 3 months of restarting open-label treatment for a "flare", the investigator may consider discontinuing this subject from the study (based on clinical judgment) and will ensure a safety follow-up telephone call 3 months after the last dose of trial medication. If the subject is determined to have experienced a first "flare" between Months 19 and 22, the subject then completes a course of re-treatment (i.e., 3 monthly open-label golimumab injections) and will have a safety follow-up telephone call 3 months after the last dose of open-label golimumab. Subjects who do not experience a "flare" during Period 2 are to complete the study at Month 22 and will have a safety follow-up telephone call 3 months after their last dose of blinded trial medication.

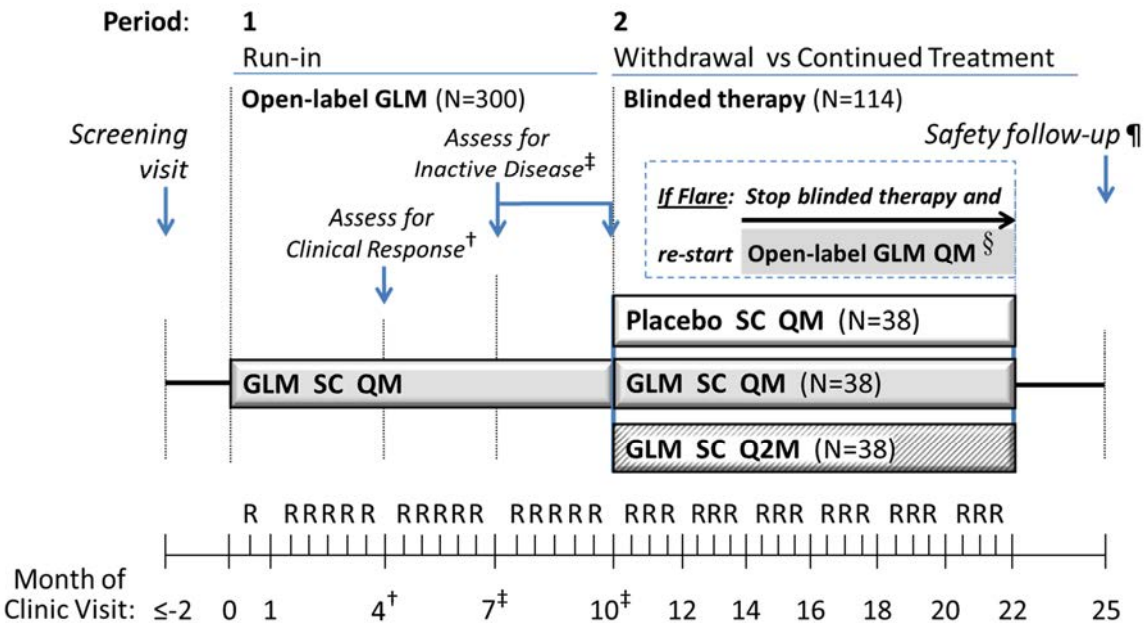
Approximately 300 subjects are expected to enter Period 1. Based on the response to golimumab observed in the recently completed GO-AHEAD trial (P07642) [1], approximately 114 subjects are expected to continue into Period 2, based on attaining inactive disease status (ASDAS <1.3) at both Months 7 and 10 of open-label golimumab. If the number of subjects who attain inactive disease is fewer than expected, additional subjects may need to enter Period 1 in order to randomize approximately 114 subjects with inactive disease status in Period 2.

It is anticipated that most of the subjects who enter Period 2 will participate in the trial for up to approximately 27 months from the time the subject signs the ICF through the final contact. For subjects determined to have experienced a "flare" for the first time between Months 19 and 22, the duration of participation in the trial may exceed 27 months (i.e., up to 30 months) to allow completion of a 3-month course of re-treatment after the "flare".

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



† If a Clinical Response (defined as: BASDAI improvement of ≥2 or ≥50%, on a 0–10 numerical rating scale, relative to Month 0) is not shown by Month 4, subject must discontinue.
‡ Only subjects with Inactive Disease (defined as ASDAS <1.3 score) are eligible to proceed beyond this visit.
§ Clinic visits are reset to occur every 2 months after the first Open-label dose (for a Flare) is administered.
¶ Subjects have a follow-up phone call 3 months after the final dose of trial medication.

GLM: golimumab; SC: subcutaneous; QM: every month; Q2M: every 2 months; R: Remote completion of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score; ASDAS: Ankylosing Spondylitis Disease Activity Score

Figure 1 Trial Schematic

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In adults with active nr-axSpA who attain inactive disease after receiving open–label golimumab during a 10-month run-in (Period 1):

Primary Objective: To evaluate the effect of treatment withdrawal vs continued treatment with golimumab (either QM or Q2M) on the incidence of a "flare" during up to 12 months of Period 2.

Hypothesis: Continued treatment with golimumab is superior to treatment withdrawal, based on the proportion of subjects without a "flare" during up to 12 months of Period 2.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects who withdraw from or continue treatment with golimumab during Period 2:

(1) **Objective**: To characterize the proportion of subjects with a "flare" in the treatment-withdrawal group or the reduced-treatment group who then show a clinical response after retreatment with open-label golimumab.

(2) **Objective**: To evaluate the time to first "flare" after withdrawal of golimumab vs continuous treatment with golimumab (either QM or Q2M).

(3) **Objective**: To evaluate the symptoms and signs of nr-axSpA (e.g., Assessment of SpondyloArthritis international Society [ASAS]20, ASAS40, BASDAI50, ASAS partial remission and ASDAS <1.3) after withdrawal of golimumab vs continuous treatment with golimumab (either QM or Q2M) and after re-treatment with open-label golimumab if needed for a "flare".

(4) **Objective:** To characterize the safety and tolerability of golimumab treatment.

3.3 Exploratory Objectives

For subjects who withdraw from or continue treatment with golimumab during Period 2:

(1) **Objective**: To explore baseline demographic and disease characteristics as predictors of a "flare".

(2) **Objective**: To characterize the clinical response after re-treatment for a "flare".

(3) **Objective**: To characterize the clinical response as measured by patient-reported symptoms, C-reactive protein, and based on a global assessment of disease by the investigator.

(4) **Objective**: To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome may be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) and approved product labeling for detailed background information on golimumab MK-8259.

4.1.1 Pharmaceutical and Therapeutic Background

Golimumab is a human monoclonal antibody (mAb) that is directed against tumor necrosis factor alpha (TNFα) and is referred to as a TNF inhibitor. Golimumab, administered SC, is registered for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis (AS), ulcerative colitis, and nr-axSpA indications.

The ASAS has recommended use of TNF inhibitors, following failure of 2 nonsteroidal anti-inflammatory drugs (NSAIDs) or intolerance to such agents [2]. TNF inhibitors such as adalimumab, certolizumab, etanercept, and golimumab have proven to be highly effective in the treatment of nr-axSpA when NSAIDs have failed to provide adequate efficacy.

A recent trial has assessed golimumab as treatment for nr-axSpA. Results in the GO-AHEAD (P07642) trial demonstrated that golimumab is efficacious in subjects with nr-axSpA. In Part 1 of this trial, which was through 16 weeks of double-blind treatment, golimumab was shown to be superior to placebo, as measured by the proportions of subjects achieving ASAS20, ASAS40, BASDAI50, ASAS Partial Remission and by the change from baseline in SI-joint inflammation on MRI using the SPARCC score [1]. Furthermore, golimumab provided substantial benefits to subjects with nr-axSpA by improving multiple aspects of range of motion, physical function, and health-related quality of life. In Part 2 of the GO-AHEAD trial, which was an open-label long-term extension through 52 weeks of treatment, improvements in disease activity were retained, both in the subjects who received golimumab in Part 1 and Part 2 and in the subjects who switched from placebo in Part 1 to golimumab in Part 2. The incidence of serious adverse events (SAEs) and other significant adverse events (AEs) was comparable between the subjects treated with golimumab and those treated with placebo during Part 1. No new safety signals were identified with golimumab treatment for nr-axSpA during Part 1 or Part 2 of the trial. These results demonstrate a favorable benefit:risk profile for golimumab treatment in subjects with nr-axSpA.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The current paradigm for treatment of nr-axSpA with TNF inhibitors is to maintain treatment on a chronic basis. Data regarding alternate treatment paradigms with TNF inhibitors for the long-term management of nr-axSpA are not available. An example of an alternate treatment paradigm is to adjust the dosing regimen, guided by clinical symptoms and signs. The purpose of this trial is to evaluate the effects of golimumab treatment withdrawal, compared with continued golimumab treatment (either QM or Q2M), during approximately up to 12 months. Efficacy and safety results of this trial will provide investigators and clinicians with important information regarding dose optimization of golimumab for treatment of nr-axSpA, especially for subjects who show a good response to golimumab within 4 months and then have inactive disease status after both 7 and 10 months of open-label treatment in Period 1.

The subject population in this trial is aligned with the population for which golimumab is approved for use in the European Union (EU). Namely, subjects to be enrolled must have active nr-axSpA with objective signs of inflammation who are either intolerant of, or have

demonstrated a lack of response to, NSAIDs. Subjects are adults (i.e., age ≥18 years) who are ≤45 years of age; excluding older adults is consistent with guidance from ASAS classification criteria for axial spondyloarthritis (SpA).

4.2.2 Rationale for Dose Selection/Regimen

The dose and regimen of golimumab selected for open-label treatment in this study is consistent with its approved use:

- Golimumab 50 mg is given SC monthly.
- For subjects with a body weight more than 100 kg who do not achieve an adequate clinical response after up to 3 doses, increasing the dose of golimumab to 100 mg SC monthly may be considered (as described in Section 5.2.1.2).

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Inactive disease status and a disease "flare" in this trial are defined using the ASDAS. The ASDAS was developed by ASAS as an index for disease activity measurement in axial SpA that includes subjective measures (rated by the subject) and objective measure (CRP) to create a well-balanced index [3]. This score combines 5 disease activity variables that have only partial overlap, resulting in one single score with better validity, enhanced discriminative capacity, and improved sensitivity to change as compared with single-item variables. Cutoffs to identify "disease activity states" and "response criteria" using the ASDAS were first identified in 2011 [4]. This trial will use the cutoffs defined by ASAS:

- Level of ASDAS to identify subjects with inactive disease: ASDAS <1.3;
- Level of ASDAS to identify subjects with a "flare": ASDAS ≥2.1 (which defines high disease activity) and/or a change in ASDAS by ≥1.1 (which is considered a clinically important change).

The BASDAI score, which combines 6 questions that are self-assessed by subjects, is used to define a clinical response in this trial, both to open-label treatment with golimumab and to re-treatment with open-label golimumab after a "flare". Clinical response is defined as a BASDAI score improvement by ≥2 (on a 0 to 10 scale) and/or score improvement by ≥50%. This definition of a "responder" is from the ASAS recommendations for use of TNF inhibitors in subjects with Axial SpA [2]. To assess the response to open-label golimumab, the response is compared with the BASDAI score at Month 0; to assess the response to re-treatment, the response is compared with the mean of the 2 BASDAI scores obtained when the "flare" was diagnosed.

To characterize the symptoms and signs of nr-axSpA in subjects treated with golimumab or withdrawn from golimumab, other secondary endpoints will be assessed in this trial. These include ASAS20, ASAS40, BASDAI50, and ASAS Partial Remission. All of these endpoints have been studied in many previous studies of axial SpA. Of note, in the GO-AHEAD

(P07642) trial in subjects with nr-axSpA, golimumab was shown to be superior to placebo for each of these endpoints [1].

4.2.3.2 Safety Endpoints

The analysis of safety results will follow a tiered approach; the tiers differ with respect to the analyses that will be performed (as described in Section 8.6.2). Adverse events (AEs) refer to both clinical and laboratory AEs. The safety tiers are defined as follows:

Tier 1: Serious Infections, serious opportunistic infections, active tuberculosis, malignancies, and serious systemic hypersensitivity (including anaphylactic reaction) are prespecified as “Tier-1” events (for analysis of differences between treatments) in double-blind Period 2; and as “Select safety endpoints of interest” (for display as listings) in open-label Period 1.

Any AEs (specific terms, as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the numbers of events observed.

Tier 2: Treatment-emergent AEs that occur with at least 4 events in at least one treatment group)
Tier 3: Treatment-emergent AEs that occur with inadequate frequency to qualify as Tier-2 AEs, predefined limits of change for laboratory test results, routine safety measures including vital signs.

4.2.3.3 Planned Exploratory Biomarker Research

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with treatments in this study.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens collected for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational

material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Golimumab has been shown to be effective and generally safe and well-tolerated in subjects for the treatment of nr-axSpA, and it is currently approved for use in this disease. The risks of golimumab include serious infections (including opportunistic infections and tuberculosis), congestive heart failure, lymphoma (and other malignancies), infusion-related reactions, and other risks as detailed in the current product labeling.

In this trial, subjects who have insufficient benefit from the approved regimen of golimumab, after approximately 4 months of open-label treatment, are to be discontinued from the study, so they can seek alternative therapy. Subjects are also discontinued from the study if they have not attained inactive disease status after either 7 or 10 months of open-label treatment. Subjects who attain inactive disease after both 7 and 10 months of open-label golimumab can then be randomly withdrawn from treatment or continued on treatment using a full regimen (golimumab QM) or a reduced regimen (golimumab Q2M). All randomized subjects are monitored for the risk of a worsening in their disease: subjects are closely followed (using self-ratings of their disease, collected twice monthly) and closely observed (at clinic visits every 2 months). The risk of this investigational treatment paradigm is that subjects may experience worsening of their symptoms upon withdrawal of golimumab and may not respond as effectively to golimumab when it is reinitiated to treat a "flare".

The benefits of this investigational treatment paradigm are that subjects will receive golimumab at the approved dose and regimen for the first 10 months of the trial and can reasonably expect to experience adequate control of their disease. The trial may demonstrate that control of symptoms is adequate following withdrawal of golimumab for a period of time and that continuous use (whether using a full regimen or a reduced regimen) is not necessary in all subjects. The benefit of this paradigm will be less exposure to golimumab and potentially the reduction in established risks associated with use of a TNF-inhibitor, such as serious infections and malignancies.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and ICF documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Adult subjects with active nr-AxSpA, who have objective signs of inflammation and intolerance or inadequate response to NSAIDs, will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be male or female and must be ≥18 to ≤45 years of age.

2. Be able to provide written informed consent for the trial and may also provide consent for Future Biomedical Research. However, the subject may participate in the trial without participating in Future Biomedical Research.

3. Meet one of the following categories:

   a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

   b) The subject is a female who is not of reproductive potential, defined as a female who either: (1)Postmenopausal is defined as at least 12 consecutive months without a spontaneous menstrual period; (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

   c) The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner while receiving trial medication or within 6 months after the last dose of trial medication by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity.

   Acceptable methods of contraception are[‡]:

   - intrauterine device (IUD)
   - vasectomy of a female subject's male partner
   - contraceptive rod implanted into the skin
   - barrier method (includes diaphragm, cervical cap, and male or female condom) with spermicidal gel or foam
   - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

   [†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

4. Have chronic back pain of ≥3 months duration by history.

5. Have a physician's diagnosis of active nr-axSpA with disease duration ≤5 years.

   Note: Disease duration is defined as the length of time since onset of symptoms

6. Meet either criterion "**a**" or "**b**" as adopted from ASAS classification criteria:

   a. Active inflammation on MRI highly suggestive of sacroiliitis associated with spondyloarthropathy and 1 or more of the following spondyloarthritis characteristics:

   - Inflammatory back pain, defined as having at least 4 out of the 5 following parameters:
     - age at onset <40 years;
     - insidious onset;
     - improvement with exercise;
     - no improvement with rest;
     - pain at night (with improvement upon getting up);
   - Arthritis diagnosed by a physician;
   - Enthesitis (heel) diagnosed by a physician: Spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus;
   - Dactylitis diagnosed by a physician;
   - Psoriasis diagnosed by a physician;
   - History of inflammatory bowel disease (IBD) diagnosed by a physician;
   - History of uveitis confirmed by an ophthalmologist;
   - Good response to NSAIDs: (Good response is defined as "24-48h after a full dose of NSAID the back pain is not present anymore or is much better");
   - Family history for SpA: Presence in first-degree (mother, father, sisters, brothers, children) or second-degree (maternal and paternal grandparents, aunts, uncles, nieces and nephews) relatives of any of the following: (1) AS; (2) psoriasis; (3) acute uveitis; (4) reactive arthritis; (5) IBD;
   - Elevated CRP (based on values obtained through a central laboratory);
   - Human leukocyte antigen B27 (HLA-B27)+ gene

OR

b. HLA-B27+ gene and 2 or more of the following spondyloarthritis characteristics:

- Inflammatory back pain, defined as having at least 4 out of the 5 following parameters:
  - age at onset <40 years;
  - insidious onset;
  - improvement with exercise;
  - no improvement with rest;
  - pain at night (with improvement upon getting up);
- Arthritis diagnosed by a physician;
- Enthesitis (heel) diagnosed by a physician:

  Spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus;
- Dactylitis;
- Psoriasis diagnosed by a physician;
- History of inflammatory bowel disease (IBD) diagnosed by a physician
- History of uveitis confirmed by an ophthalmologist;
- Good response to NSAIDs;

  Note: Good response is defined as "24-48h after a full dose of NSAID the back pain is not present anymore or is much better"
- Family history for SpA:

  Presence in first-degree (mother, father, sisters, brothers, children) or second-degree (maternal and paternal grandparents, aunts, uncles, nieces and nephews) relatives of any of the following: (1) AS; (2) psoriasis; (3) acute uveitis; (4) reactive arthritis; (5) IBD;
- Elevated CRP (based on values obtained through a central laboratory).

7. Have elevated CRP at the Screening visit or evidence of active inflammation in the SI joints on MRI.

   Note: Elevated CRP is defined as a value that is >6.0 mg/L; a maximum of 40% of enrolled subjects may have normal CRP at the Screening visit. All MRIs must undergo central reading to determine study eligibility.
8. Have ASDAS ≥2.1 at the Screening visit.
9. Show high disease activity at Screening and Baseline of both a Total Back Pain score of ≥4 and a BASDAI score of ≥4 (each on a NRS of 0 to 10).

10. Have an acceptable history of use of NSAIDs: either an inadequate response, as assessed by the investigator, with maximal recommended daily doses of at least 2 NSAIDs; or must be unable to receive maximal NSAID therapy because of intolerance, toxicity, or contraindications to NSAIDs. (Note: It is possible that a subject had a good response initially to NSAIDs but subsequently had inadequate response or developed intolerance to NSAIDs therapy).
11. Have acceptable current use of NSAIDs at Screening:
    - If currently using an NSAID, must be on a stable daily dose for at least 14 days prior to Screening

      Note: Such use of NSAIDs is allowed and will be monitored during the study.
    - If not currently using an NSAID, short-term use is allowed (up to 1 week) during Period 1 and is allowed as needed during Period 2.

      Note: Such use of NSAIDs will be monitored during the study.
12. Tuberculosis Assessment (see also Section 7.1.3.3):
    a. Have no history of untreated latent or active tuberculosis (TB) prior to screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB prior to first administration of study agent, or have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first dose of administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation.
    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluations and receive appropriate treatment for latent TB prior to the first administration of study agent.

d. Within 6 weeks prior to the first administration of study agent, have a negative QuantiFERON®-TB Gold test result, or have a newly identified positive QuantiFERON®-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent. Within 6 weeks prior to the first administration of study agent, a negative tuberculin skin test, or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent, is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

- If, based on the investigator's judgment of a subject's high risk of latent TB infection, the QuantiFERON®-TB Gold test and the tuberculin skin test are both performed, and if either is positive, and if active TB has been ruled out, then appropriate treatment for latent TB must be initiated prior to the first administration of study agent.
- Subjects with persistently indeterminate QuantiFERON®-TB Gold test results may be enrolled without treatment for latent TB, if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.
- The QuantiFERON®-TB Gold test and the tuberculin skin test are not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; subjects with documentation of having completed adequate treatment as described above **are not** required to initiate additional treatment for latent TB.

e. Have a chest radiograph (both posterior-anterior and lateral views) within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

13. Be judged to be medically stable, other than nr-axSpA, based on medical history, physical examination, and routine laboratory tests.

14. Undergo screening for hepatitis B virus (HBV), which at a minimum includes testing for HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and HBV core antibody (anti-HBc total), and demonstrate to be eligible based on the following results:

Action	Hepatitis B Surface Antigen(HBsAg)	Hepatitis B Surface Antibody(anti-HBs)	Hepatitis B Core Antibody(anti-HBc Total)
Exclude	+	– ***or*** +	– ***or*** +
Include	–	+	+
Include	–	+	–
Include	–	–	–
Require Hepatitis B viral DNA (HBV DNA) testing*	–	–	+
* If HBV DNA is detectable or there is evidence of chronic liver disease, exclude from clinical trial. If the HBV DNA test is negative, the subject is eligible for this trial. In the event the HBV DNA test cannot be performed, the subject is not eligible for this trial.			

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has bilateral sacroiliitis Grade 2 or unilateral sacroiliitis Grade 3 or Grade 4 on conventional x-rays (to exclude subjects who meet modified New York criteria for AS).

   Note: SI-joint x-rays must undergo central reading to determine study eligibility. Subjects who have a SI joint x-ray performed within 6 months prior to Screening do not need to have a SI joint x-ray repeated at Screening.

2. If female, is nursing, pregnant, or intending to become pregnant within 6 months after receiving the last administration of trial medication.
3. Intends to donate eggs (female subjects) or sperm (male subjects) while receiving trial medication or within 6 months after the last dose of trial medication.
4. Has any clinically significant condition or situation, other than those listed as exclusion criteria that, in the opinion of the investigator, would interfere with the trial evaluations or participation in the trial.
5. Has ever received any cytotoxic drugs, including but not limited to chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents.

6. Has received any treatment listed in the table below more recently than the indicated off-drug period prior to Screening.

Medications, Supplements, and Other Substances that are Prohibited for Trial Entry

Prohibited Medications, Supplements, and Other Substances	Off-Drug Period Prior to Screening
Disease modifying anti-rheumatic drugs such as but not limited to: Methotrexate Sulfasalazine Leflunomide Hydroxychloroquine Steroids (oral, parenteral, intra-articular) Cyclosporine (Note: ophthalmic use is allowed) Mycophenolate mofetil Azathioprine.	30 days (8 weeks for leflunomide unless subject undergoes standard cholestyramine or activated charcoal washout)
Live vaccinations	3 months
Investigational medications	30 days or 5 half lives (whichever is longer)
Bacille Calmette-Guerin (BCG) vaccination	12 months

7. Has ever received TNF-α targeted therapy or any other biological agents intended to treat immune-mediated diseases, including but not limited to infliximab, etanercept, adalimumab, certolizumab, golimumab, alefacept, efalizumab, rituximab, natalizumab, secukinumab, ixekizumab, ustekinumab, or vedolizumab.
8. Has an allergy/sensitivity to golimumab or its excipients.
9. Has any systemic inflammatory condition from Screening up to Baseline with signs and symptoms including, but not limited to:
    a. psoriatic arthritis,
    b. active Lyme disease,
    c. systemic lupus erythematosus,
    d. infectious arthritis,
    e. vasculitis,
    f. parvovirus infection,
    g. rheumatoid arthritis,
    h. active uveitis,
    i. active IBD**.**
10. Has a history of latent or active granulomatous infection, including histoplasmosis, or coccidioidomycosis, prior to Screening.
11. Had a nontuberculous mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, Pneumocystis jirovecii [carinii], aspergillus) within 6 months prior to Screening.
12. Has a history of an infected joint prosthesis, or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

13. Had a serious infection (including but not limited to, hepatitis, pneumonia, sepsis, or pyelonephritis), or has been hospitalized for an infection, or has been treated with IV antibiotics for an infection within 2 months prior to Baseline. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.
14. Had a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (e.g., bronchiectasis), sinusitis, recurrent urinary tract infection (e.g., recurrent pyelonephritis, chronic nonremitting cystitis), an open, draining, or infected skin wound, or an ulcer.
15. Is known to be infected with human immunodeficiency virus (HIV) or seropositive for hepatitis C virus (HCV).

    Note: Subject infected with HCV is eligible if there are 2 negative HCV RNA test results 6 months apart prior to Screening and there is a third negative HCV RNA test result at Screening.
16. Has a chest x-ray within 2 months prior to Screening that shows an abnormality suggestive of a current active infection or malignancy.
17. Has a history of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease such as lymphadenopathy of unusual size or location and/or clinically significant splenomegaly, or monoclonal gammopathy of undetermined significance.
18. Has had a malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin that have been treated, with no evidence of recurrence for at least 3 months prior to Baseline; and carcinoma in situ of cervix that has been surgically cured).
19. Has a history of known demyelinating diseases such as multiple sclerosis or optic neuritis.
20. Has a history of or concurrent congestive heart failure ([CHF] of any grade [I-IV]), including medically controlled, asymptomatic CHF.
21. Has a transplanted organ (with the exception of a corneal transplant performed ≥3 months prior to baseline).
22. Has current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, cardiovascular, metabolic, ophthalmological, respiratory, hematologic, gastrointestinal, endocrine, pulmonary, neurologic, psychiatric, cerebral, or other significant medical illness or disorder that, in the judgment of the investigator, could interfere with the trial, or require treatment that might interfere with the trial. Other conditions that are well controlled and stable will not prohibit participation if deemed appropriate per the investigator's judgment. The Sponsor's medical monitor should be consulted if there are any questions regarding a specific medical condition.
23. Is a user of recreational or illicit drugs or has or had a substance abuse (drug or alcohol) problem within the previous 2 years.

24. Has participated in any other interventional clinical trial within 30 days, inclusive, of signing the informed consent form of the current trial.
25. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 1.

Table 1 Trial Treatment

Biologic	Dose/Potency	Dose Frequency	Route of Administration	Regimen (Treatment Period)	Use
Golimumab	Per approved label: 50 mg (or 100 mg)†	Every month (QM)	Subcutaneous (SC)	Open-label from Month 0 to Month 9 (Period 1); switch to open-label golimumab upon "flare" (Period 2)	Standard of Care
Golimumab (full-treatment regimen)	Per approved label: 50 mg (or 100 mg)†	Every month (QM)	Subcutaneous (SC)	Double-blind monthly injections of active golimumab for 12 months (or until "flare")	Experimental
Golimumab (reduced-treatment regimen)	50 mg (or 100 mg)†	Every 2 months (Q2M)	Subcutaneous (SC)	Double-blind monthly injections of active golimumab, alternating with placebo for golimumab, for 12 months (or until "flare")	Experimental
Matching placebo for golimumab		Every month (QM)	Subcutaneous (SC)	Double-blind monthly injections of placebo for golimumab for 12 months (or until "flare")	Experimental
† For subjects with body weight more than 100 kg, increasing the dose of golimumab to 100 mg may be considered during the Open-label Period 1 (and would continue during Period 2, depending on the randomization schedule).					

The frequency of SC injections is monthly during the entire trial. After an initial dose has been given, administration then continues preferably on the same day of every month (consistent with approved labeling) with an allowed window of ±5 days. As the trial progresses, the day of the month that is targeted for dosing can be re-set, if needed (see Section 7.1.1.10). Depending on the period of the trial (open-label Period 1 or double-blind Period 2) and on the randomization schedule for treatment withdrawal or continued treatment (during Period 2), an individual injection may contain active golimumab or a matching placebo.

The first dose of golimumab 50 mg SC is administered at the study center by site personnel on the day of enrollment at Visit 2 (considered "Month 0"). If allowed by local guidelines and after proper training in injection technique, subjects may self-inject if determined by their physician that it is appropriate and with medical follow-up as necessary. For subjects with a body weight of more than 100 kg, increasing the dose of golimumab to 100 mg SC may be considered; see Section 5.2.1.2.

Open-label golimumab is administered monthly during Period 1. After 10 months on open-label therapy, eligible subjects will be randomized, in a double-blind manner, to 1 of 3 treatment arms to receive either matching-placebo for golimumab (i.e., treatment withdrawal), continued treatment with golimumab every month (as a full-treatment regimen), or continued treatment with golimumab every 2 months (as a reduced-treatment regimen), via monthly injections that alternate between golimumab and matching placebo. If a "flare" is confirmed, subjects are treated with open-label golimumab monthly until Month 22 (end of Period 2). There should be an interval of at least 10 days between the last dose of Period-2 assigned double-blind therapy and starting open-label golimumab.

All supplies indicated in Table 1 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification (Escalation)

For subjects with body weight more than 100 kg who, based on the investigator's clinical judgment, do not achieve an adequate clinical response after up to 3 doses, increasing the dose of golimumab to 100 mg SC may be considered. This may require an unscheduled visit at Month 2 or Month 3, to enable a clinical evaluation by the investigator at that time for the decision to increase the dose to 100 mg SC. No other dose modifications for escalation are permitted during the trial. If a decision is made to increase to 100 mg (which requires 2 injections of 50 mg) for a given subject in Period 1, then administration of 2 injections at the time of each dose administration is also expected to continue for this subject through Period 2.

5.2.2 Timing of Dose Administration

There are no specific instructions for the time of day for dosing. General considerations regarding the monthly schedule for dosing are described in Section 5.2.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used during Period 2. Golimumab (MK-8259) and placebo will be packaged identically so that blind/masking is maintained. The subject, the investigator, and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

During Period 2, subjects assigned to receive golimumab Q2M will receive monthly injections that alternate between golimumab and matching placebo.

5.3 Randomization or Treatment Allocation

Period 1: Subjects in Period 1 are assigned an allocation number using an interactive voice response system / integrated web response system (IVRS/IWRS) and will receive open-label golimumab by non-random assignment.

Period 2: Random assignment of eligible subjects to double-blind treatment occurs centrally using an IVRS/IWRS. Only subjects who qualify for Period 2 are to be randomly assigned to 1 of the 3 treatment arms in 1:1:1 ratio: treatment withdrawal (i.e., placebo QM), golimumab QM, or golimumab Q2M.

The allocation number assigned for Period 1 is maintained during Period 2.

5.4 Stratification

The following entry criterion is used as the stratification factor for randomization in Period 2:

- CRP category at Screening (>6.0 mg/L *or* ≤6.0 mg/L, as reported by the central laboratory).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Prohibited Medications

The following therapies are prohibited during the course of the trial:

- Disease modifying anti-rheumatic drugs such as but not limited to:
  - Methotrexate
  - Sulfasalazine
  - Leflunomide
  - Hydroxychloroquine
  - Steroids (oral, parenteral)
  - Cyclosporine (Note: ophthalmic use is allowed)
  - Mycophenolate mofetil
  - Azathioprine
- Live vaccinations
- Investigational medications
- Drugs of abuse/recreational use of drug
- Bacille Calmette-Guerin (BCG) vaccination
- TNF-α targeted therapy or any biological agents used for treatment of immune-mediated diseases, including but not limited to infliximab, etanercept, adalimumab, certolizumab, alefacept or efalizumab, rituximab, natalizumab, secukinumab, ixekizumab, ustekinumab, or vedolizumab.

Allowed Medications

The following are specific instructions regarding concomitant NSAID use during the course of the trial:

- If the subject is a NSAID user at the time of screening, the use of NSAIDs is allowed to continue during the study (Period 1 and Period 2).
- If the subject is not a NSAID user at the time of screening, short-term use (up to a week) is allowed during Period 1, then NSAID use is allowed as needed during Period 2.

All use of NSAIDs will be monitored, and the data will be collected in the database.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

There are no diet restrictions. Subjects should maintain a normal diet and activity level.

The subject will receive a paper comment card to assist in capturing information regarding AEs and use of concomitant medication between visits.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Discontinuation from treatment is "permanent". Once a subject is discontinued, he/she shall not be allowed to restart treatment.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment and followed for approximately 3 months after the last dose of trial medication for any of the following reasons:

- Subject initiates medications prohibited during this trial that will alter evaluation of safety or efficacy. The Sponsor's trial physician should be consulted if there are any questions regarding a specific medication.
- Investigator or Sponsor's trial physician deems treatment discontinuation is in the subject's best interest.
- Subject does not attain clinical response (based on BASDAI) by end of Month 4.
- Subject does not attain inactive disease status (ASDAS <1.3) by end of Month 7 or by end of Month 10.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- Subject becomes pregnant.
- Subject develops reaction resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a ≥40mm Hg decrease in systolic blood pressure that occurs following a trial medication injection.
- Subject develops reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of trial medication. These may be accompanied by other events including pruritus; facial, hand, or lip edema; dysphagia; urticaria; sore throat; and/or headache.
- Subject develops severe opportunistic infection.
- Subject develops malignancy, excluding nonmelanoma skin cancer.
- Subject develops congestive heart failure.
- Subject develops demyelinating disease.

- Subject develops active TB.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

6.1 Period 1: Open-Label Run-in

Trial Period:	Screening		Period 1: Open-Label Run-in									
Visit Number/ Title:	1/ Screening	2/ Enrollment	3/ RC[a]	4	5-9/ RC[a]	10	11-15/ RC[a]	16	17	18-22/ RC[a]	23 or DC	Safety F/U[b] TC
Scheduled Month:	-2	0	0.5	1	1.5; 2; 2.5; 3; 3.5	4[c]	4.5; 5; 5.5; 6; 6.5	7[d]	7	7.5; 8; 8.5; 9; 9.5	10[e]	12
Scheduling Window Days:			± 7 days for clinic visit; ± 3 days for remote completion of BASDAI									
Screening/Administrative												
Informed Consent	X											
Informed Consent For Future Biomedical Research	X											
Demographic	X											
Inclusion/Exclusion Criteria	X	X										
Medical History	X											
Prior and Concomitant Therapy Review	X	X		X		X		X			X	X
Subject Identification Card[f]	X											
Contact IVRS/IWRS[g]	X	X		X		X			X		X	
Trial Medication Accountability		X		X		X		X			X	
Dispense Trial Medication for Monthly Self-administration at Home[h]				X		X			X			
Issue/Review Trial Medication Injection Log				X		X		X			X	
Issue/Review Comments Card	X	X		X		X		X			X	
Clinical Procedures/ Assessments												
Physical Examination[i]	X	X		X		X		X			X	
Vital Signs (BP, Temp, HR)[j]	X	X									X	
Chest x-ray[k]	X											
X-rays of SI Joints[l]	X											
MRI of SI Joints[m]	X											

Trial Period:	Screening		Period 1: Open-Label Run-in									
Visit Number/ Title:	1/ Screening	2/ Enrollment	3/ RC[a]	4	5-9/ RC[a]	10	11-15/ RC[a]	16	17	18-22/ RC[a]	23 or DC	Safety F/U[b] TC
Scheduled Month:	-2	0	0.5	1	1.5; 2; 2.5; 3; 3.5	4[c]	4.5; 5; 5.5; 6; 6.5	7[d]	7	7.5; 8; 8.5; 9; 9.5	10[e]	12
Scheduling Window Days:			± 7 days for clinic visit; ± 3 days for remote completion of BASDAI									
BASDAI[n]	X	X	X	X	X	X	X	X		X	X	
BASFI	X	X		X		X		X			X	
Patient Global Disease Assessment (PGD_N)	X	X		X		X		X			X	
Total Back Pain[n] (TBP)	X	X		X		X		X			X	
Global Assessment of Disease by Investigator (GADI)		X									X	
Assess Eligibility to Continue in Period 1[c,d]						X		X				
Assess Eligibility for Period 2[e]											X	
Adverse Events		X		X		X		X			X	X
Administer Trial Medication in Clinic		X		X								
Clinical Laboratory Assessments												
Routine Laboratory (Hematology, Chemistry)	X	X									X	
C-reactive Protein (CRP)	X	X						X			X	
Serum Pregnancy Test[o]	X										X	
Urine Pregnancy Test		X		X		X		X				
QuantiFERON®-TB Gold test (tuberculin skin test also, only if needed)[p]	X											
HLA-B27 Gene Status[q]	X											
HBV/HCV Screening	X											
Sample for PK[r]		X		X		X		X			X	
Serum Sample for Analysis of Antibodies to GLM, and Neutralizing Antibody[r,s]		X		X		X		X			X	
Blood for Genetic Analysis[t]		X										

AE=adverse event; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BP=Blood Pressure; CRP=C-reactive protein; DC=discontinuation; DNA= Deoxyribonucleic Acid; FBR=future biomedical research; F/U=Follow Up; GLM=golimumab; HBV=hepatitis-B virus; HLA-B27=Human Leukocyte Antigen B27; HR=Heart Rate; IVRS=interactive voice response system; IWRS=interactive web response system; MRI=magnetic resonance imaging; PK=Pharmacokinetic; RC=remote completion; SI joint=sacroiliac joint; TB=Tuberculosis; TC=telephone call.

a. Remote completion (e.g., at home) of the BASDAI questionnaire by subjects, twice monthly, using an electronic device.
b. The telephone call for safety follow-up is made approximately 3 months after the last dose of trial medication.
c. At Month 4 (Visit 10), subjects are assessed for Clinical Response (BASDAI improvement ≥2 or ≥50% since start of re-treatment). Subjects who do not attain Clinical Response are to be discontinued from the study. All procedures outlined for the DC visit are to be performed.
d. At Month 7 (Visit 16), subjects are assessed for Inactive Disease status (defined as ASDAS <1.3). Subjects who do not attain Inactive Disease status are discontinued; these subjects are to be scheduled for the DC visit to perform procedures (vital signs, Physician Global Disease Assessment, routine laboratory blood draw, and pregnancy test if required) that were not done at the Month 7 visit (Visit 16) but are required per DC visit. Subjects who attain inactive disease status (i.e., ASDAS <1.3) at Visit 16 will be scheduled for Visit 17 (within 2-7 days) to continue to receive open-label golimumab for self-administration at home in Period 1.
e. At Month 10 (Visit 23), subjects complete Period 1 and are assessed for Period 2. Subjects who attain Inactive Disease (defined as ASDAS <1.3) status enter Period 2. Subjects who do not attain Inactive Disease status are discontinued, and all procedures outlined for the DC visit are to be performed. Subjects who attain inactive disease status (i.e., ASDAS <1.3) at Visit 23 will be scheduled for Visit 24 (within 2-7 days) to enter in Period 2 and to receive double-blind treatment.
f. Also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication in emergency situations when the investigator is not available.
g. Sites to call IVRS to register the subject at V1; to assign allocation number at V2; to assign trial medications from V2 to V23; to update subject disposition at DC visit.
h. After proper training, subjects may self-inject trial medication monthly ± 5 days, if their physician determines it is appropriate and with medical follow-up as necessary.
i. The first physical exam (PE) (performed at Screening) will be a complete PE, including a full skin examination and excluding genital and urinary. Subsequent PEs would include a full skin assessment and would be directed to evaluate signs and symptoms of potential AEs.
j. Height (with the shoes removed) and weight (in street clothing with jacket/coat and shoes removed) should be collected at the screening visit only.
k. Subjects who have chest x-ray performed within 3 months prior to Screening with no clinically significant findings do not need to have chest x-ray repeated at Screening
l. For subjects who have a SI joint x-ray performed within 6 months prior to Screening, the site can send the x-ray for central reading. If these x-rays are evaluable by central reading, then these subjects do not need to have a SI joint x-ray repeated at Screening
m. Screening MRI should be performed for subjects only if the CRP value is normal and subject is otherwise deemed to be eligible for the study. For subjects who have MRI performed within 6 months prior to Screening, the site can send MRI films for central reading. If these films are evaluable by central reading, then these subjects with clinical evidence of inflammation do not need to have a MRI repeated at Screening.
n. Each subject must show high disease activity at Screening and Baseline as measured by Total Back Pain score ≥4 and a BASDAI score ≥4 on 0 to 10 NRS.
o. If local law requires more frequent pregnancy testing, the site will perform the assessments as per local requirement.
p. The tuberculin skin test is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in the country participating in the trial or the tuberculin skin test is mandated by local health authorities. If, based on the investigator's judgment, the subject is at high risk of latent TB infection, the QuantiFERON®-TB Gold test and the tuberculin skin test may both be performed.
q. HLA-B27 status only has to be assessed at Screening, and if previously documented, it is not necessary to assess again for this trial.
r. At all visits, samples MUST be collected BEFORE the administration of trial medication.
s. The same sample will be used for detection of antibodies to golimumab and neutralizing antibody analysis.
t. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but the FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

6.2 Period 2: Double-blind Withdrawal

Trial Period:	Period 2: Double-blind Withdrawal															
Visit Number/ Title:	24[a]	25-27/ RC[b]	28	29-31/ RC[b]	32	33-35/ RC[b]	36	37-39/ RC[b]	40	41-43/ RC[b]	44	45-47/ RC[b]	48/ DC[c]	Uns TC[d]	Uns[e,f]	Safety F/U[g] TC
Scheduled Month:	10	10.5; 11; 11.5	12	12.5; 13; 13.5	14	14.5; 15; 15.5	16	16.5; 17; 17.5	18	18.5; 19; 19.5	20	20.5; 21; 21.5	22			25
Scheduling Window Days:	± 7 days for clinic visit; ± 3 days for remote completion of BASDAI															
Administrative																
Concomitant Therapy			X		X		X		X		X		X			X
Contact IVRS/IWRS[h]	X		X		X		X		X		X		X		X	
Trial Medication Accountability			X		X		X		X		X		X			
Dispense Trial Medication for Self-administration at Home[i]	X		X		X		X		X		X					
Issue/Review Comments Card	X		X		X		X		X		X		X			
Issue/Review Trial Medication Log	X		X		X		X		X		X		X			
Clinical Procedures/Assessments																
Physical Examination[j]			X		X		X		X		X		X			
Vital Signs (BP, Temp, HR)													X			
BASDAI		X	X	X	X	X	X	X	X	X	X	X	X		X	
BASFI			X		X		X		X		X		X		X	
Patient Global Disease Assessment (PGD_N)			X		X		X		X		X		X	X	X	
Total Back Pain (TBP)			X		X		X		X		X		X		X	
Global Assessment of Disease by Investigator (GADI)													X		X	
Adverse Events			X		X		X		X		X		X			X
Administer Trial Medication in Clinic	X		X		X		X		X		X		X		X	
Clinical Laboratory Assessments																
Serum Pregnancy Test[k]													X			
Urine Pregnancy Test			X		X		X		X		X					
Routine Laboratory (Hematology, Chemistry) Testing							X						X			
C-reactive Protein (CRP)			X		X		X		X		X		X		X	
Sample for PK[l]			X		X		X		X		X		X			
Serum Sample for Analysis of Antibodies to GLM, and Neutralizing Antibody[l,,m]			X				X						X			

AE = adverse event; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BP = Blood pressure; CRP = C-reactive protein; DC=discontinuation; F/U=Follow up; GLM = golimumab; HR = Heart Rate; IVRS = interactive voice-response system; IWRS = interactive web-response system; PK = Pharmacokinetic; RC=remote completion; TC= Telephone call; Uns= Unscheduled.

a. Subjects who attain Inactive Disease Status (i.e., ASDAS <1.3) at Visit 23 will be scheduled for Visit 24 so that they can be randomized in Period 2 and receive the first dose of Period 2 double-blind trial medication.
b. Remote completion of the BASDAI questionnaire by subjects, twice monthly, using an electronic device.
c. If the subject discontinued from the trial during Period 2, trial medication will not be administered at the DC clinic visit.
d. If subjects report an increase of ≥2 BASDAI score compared with Month 10 (Visit 23), site is to call subject to obtain Patient Global Disease Assessment, and then use the CRP value from the previous clinic visit to calculate ASDAS. See Section 7.1.5.4 for more details.
e. If "flare" (defined as ASDAS absolute score ≥2.1 and/or post-withdrawal increase (i.e., change from Visit 23) of ≥1.1 at 2 consecutive visits) is confirmed *during* a "flare confirmation" visit (based on the BASDAI and PGD_N obtained at that visit), subject will begin re-treatment with open-label golimumab for the confirmed "flare" at that visit. Clinic visits are then to be scheduled every 2 months from the date of the initial re-treatment with open-label golimumab
f. If "flare" is confirmed *after* a "flare confirmation" visit (based on the CRP result as eventually received from that visit), then the subject is asked to return to the clinic to begin re-treatment with open-label golimumab for the "flare". Clinic visits are then to be scheduled every 2 months from the initial re-treatment with open-label golimumab.
g. The safety follow-up phone call is made approximately 3 months after the last dose of trial medication.
h. When it is confirmed at Visit 23 that a subject is eligible for Period 2, site to call IVRS/IWRS to randomize the subject into Period 2 (Double-blind) prior to administering the trial medication; assign trial medication at all clinic visits; update the subject status at V48/DC visit.
i. During Period 2, site personnel will administer the trial medication (± 5 days) during clinic visits. If subjects are self-injecting, the monthly dose to be administered (± 5 days) between clinic visits will be dispensed for subjects to self-inject at home.
j. PEs would include a full skin assessment and would be directed to evaluate signs and symptoms of potential AEs assessment.
k. If local law requires more frequent pregnancy testing, the site will perform the assessments as per local requirement
l. At all visits, samples MUST be collected BEFORE the administration of trial medication.
m. The same sample will be used for detection of antibodies to golimumab and neutralizing antibody analysis.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria specified in Section 5.1 will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial. All appropriate medications and washout periods will be discussed with the subject, including those that will be prohibited and allowed throughout the duration of the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history should be obtained by the investigator or qualified designee. Subject history should include information on clinically significant personal history including identification of major cardiovascular risk factors, current and past smoking history, current alcohol use, past history of infections (including hepatitis, serious infection requiring hospitalization or IV antibiotics, tuberculosis), malignancies, and major cardiovascular conditions (including myocardial infarction, cardiac revascularization, angina [stable or unstable], stroke [ischemic or hemorrhagic] or transient ischemic stroke [TIA], congestive heart failure, arrhythmias, hypertension, diabetes, hyperlipidemia, and peripheral vascular disease [venous or arterial]). Any clinically relevant changes found at any time during the study will be recorded as adverse events. On the medical history form, nr-axSpA will be recorded as the primary condition.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

At the Screening visit, the investigator or qualified designee should review all appropriate prior and prohibited medications and the necessary medication off-drug times with the subject. A record of prior medications taken by the subject within 3 months before screening is to be obtained. In addition, the use of BCG vaccine should be captured within 12 months before screening. All medications used for the treatment of nr-axSpA at any time prior to Screening should be recorded on the electronic case report form (eCRF).

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee should record medication, if any, taken by the subject at all visits after the subject consent is obtained until the conclusion of the protocol-specified follow-up period.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 randomization number.

Subjects will be randomized to 1 of the 3 treatment arms in the double-blind Period 2. The randomization for Period 2 treatments will be based on a randomization schedule; however, each subject will retain his/her original allocation number.

7.1.1.8 Trial Compliance (Medication)

At all protocol-specified visits, the investigator or qualified designee must record whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing noncompliance must be recorded.

During Periods 1 and 2, the investigator staff will contact each subject during each dosing window to remind the subject to administer trial medication.

7.1.1.9 Trial Medication Injection Administration

After an initial injection has been given, administration is generally expected to continue preferably on the same day of every month, with an allowed window of ±5 days. As the trial progresses, the day of the month that is targeted for dosing can be re-set, if needed. If a dose is administered outside the ±5-day window (and assuming there is no other reason the subject must discontinue trial medication in the trial), then the day of that month when the dose was administered becomes the new target day for subsequent administration, again with a ±5-day window. For example, if a subject receives the initial dose on March 10, the next target day of administration will be April 10. If this second dose is instead administered on April 15 (which is delayed, but still within the allowed time window), then the next target day is May 10. If the second dose is administered on April 18 (which is outside the ±5-day window [e.g., rescheduling due to an AE or other concerns]), then the new target day is May 18.

During Period 1, the first injection of open-label golimumab SC will be administered in the clinic by the appropriate site personnel at the Month-0 visit (Visit 2). After proper training in injection technique, subjects may self-inject the next dose in the clinic in the presence of site personnel at the Month-1 visit. If allowed by the local guidelines, subjects may self-inject the subsequent doses of trial medication at home between clinic visits, or subjects may opt to continue receiving trial medication at the study center after the Month 1 visit. Each injection of golimumab should be given at a different location of the body than the previous injection. Injections should be done in the abdomen, thigh or upper arm. Injections in the upper arm should be done by someone other than the subject. If subjects will be self-injecting at home, then enough trial medication to last until the next visit will be provided to the subjects to take home. The final dose of open-label golimumab during Period 1 will be administered at Month 9; response will be assessed at Month 10 (Visit 23) after approximately 10 months of open-label therapy to determine if the subject has attained inactive disease status.

During Period 2, eligible subjects will be randomly allocated to receive either a full regimen of golimumab (50 mg QM), a reduced regimen of golimumab (50 mg Q2M), or treatment withdrawal (placebo QM) in a double-blind manner. The blinded trial medication will be administered by the site personnel during the clinic visits, which are scheduled to occur every 2 months. If subjects are self-injecting at home, the monthly dose to be administered between the clinic visits will be dispensed.

Verbal and written instructions for proper storage, handling and administration of the trial medication will be given to subjects and will include instructions to contact the study site immediately if they experience problems with the trial medication administration.

Interruptions from the protocol specified treatment for ≥60 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.1.10 Trial Medication Injection Log

If subjects opt to self-administer injections at home, each subject will be provided with a Trial Medication Injection Log at the Month-1 visit to collect the date and time of each dose of self-administered trial medication. This information will be recorded on the log by the subject for all trial medication doses administered away from the clinic, or by site personnel when trial medication is administered at the site. The subject must bring his/her injection log to all trial visits. At each visit, the site will review the log, record the new information in the eCRF, and return the log to the subject. Subjects will be instructed to return the completed injection log at their final visit.

7.1.1.11 Issue and Review Comments Card

The subject will receive a separate paper comment card to assist in capturing information regarding AEs and use of concomitant medication between visits. The comment card should be returned at each visit, and the information should be discussed with the investigator and/or qualified designee. If the data from the card reflect a change in concomitant medication, occurrence of AEs, explanation of non-compliance, or other relevant information pertaining to a subject's involvement in this trial, it should be captured in the appropriate section of the eCRF. Card comments that are not considered to be relevant to the investigator should be indicated as such, during the site's review of the card, in the space provided. All comments cards should be initialed and dated by the reviewer at the time of collection from the subject. The comment card will be collected from each subject at his/her final clinic visit and will remain at the site as a source.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

The first physical exam (PE) (performed at Screening) will be a complete PE, excluding genitourinary system. This complete PE should also include a full skin examination. Subsequent PEs will be symptom-directed as determined by the investigator. These directed PEs should also include a full skin assessment as clinically indicated based upon symptoms and signs. If the subject is discontinued for any reason during Period 1 or 2, every attempt should be made to perform a final PE, which will also be a PE that is symptom-directed.

7.1.2.2 Vital Signs

Systolic and diastolic blood pressure (mmHg); oral, axillary or tympanic temperature (°C or °F); and pulse (beats per minute) will be recorded while the subject is seated.

Note: Vital signs should be evaluated and recorded at any other time before, during, or after the trial medication injection if required by local regulations and/or local clinical practice, or when medically indicated.

Any clinically significant abnormalities in vital signs noted after the subject signs the ICF will be recorded as an AE in the eCRF.

Height and weight should be collected at the Screening visit only.

Height should be taken without shoes.

Weight should be taken in street clothing with jacket/coat and shoes removed.

7.1.2.3 Chest X-ray (CXR)

For this protocol, a chest x-ray is mandatory to assess the tuberculosis (TB) screening eligibility criterion. Subjects should have a chest x-ray within 3 months prior to the screening visit with no evidence of current active TB or old inactive TB. If a negative chest x-ray is not available, then the subject must have a chest x-ray performed during screening showing no evidence of active or inactive TB.

7.1.2.4 X-Rays of Sacroiliac Joints

Subjects will undergo x-rays of SI joints at screening. The x-rays will be read by the central vendor for determination of subject eligibility according to exclusion criterion #1 (See Section 5.1.3). The central vendor eligibility report regarding the SI-joint x-rays must be received before a subject may undergo the Magnetic Resonance imaging (MRI) for screening purposes (in the scenario that the C-reactive protein [CRP] test is normal at the Screening visit).

Note: For subjects who have a SI joint x-ray performed within 6 months prior to screening, the site can send the x-ray for central reading. If these x-rays are evaluable by central reading, then these subjects do not need to have a SI joint x-ray repeated at the Screening visit.

7.1.2.5 Magnetic Resonance Imaging of Sacroiliac Joints

An MRI of the SI joints should be performed at Screening only if the CRP value is normal and the subject is otherwise deemed to be eligible for the trial. In this situation, the central vendor's MRI report must be received prior to a subject being allowed to receive open-label golimumab in Period 1.

For subjects who have had an MRI performed within 6 months prior to the Screening visit, the site can send these MRI films for central reading. If these MRI films are evaluable by central reading, the central reader will report the presence or absence of active inflammation of SI joints, highly suggestive of sacroiliitis. These subjects with clinical evidence of inflammation do not need to have an MRI repeated at Screening.

Separately, historical MRI results can also be used to help document the medical diagnosis of nr-axSpA. If subjects have had historical MRI films taken within 3 years prior to the Screening visit, the site will send them to central reader. If these MRI films are evaluable by central reading, the presence or absence of SI-joint inflammation will be reported.

Note: The evaluation of MRI results obtained >6 months prior to the Screening visit will be used only as historical information to help document the diagnosis of the disease; MRI results obtained >6 months before the Screening visit will not be used to assess the presence or absence of active inflammation of SI joints at the Baseline (i.e., not to determine eligibility to receive open-label golimumab in Period 1, in the scenario that the CRP test is normal at the Screening visit).

7.1.2.6 Bath Ankylosing Spondylitis Disease Activity Index (Patient Reported Outcome)

Subjects will complete the BASDAI by answering 6 questions at all clinic visits, as well as twice monthly between clinic visits, using the 0 to 10 NRS. Subjects will be instructed by site personnel on how to use an electronic device to record their ratings for each question; subjects will also be able to use an electronic device remotely (i.e., at home) to record their ratings between clinic visits.

Q1. Fatigue/tiredness	Over past week: 0 *to* 10 = None *to* Very severe
Q2. Neck, back, or hip (spinal) pain	Over past week: 0 *to* 10 = None *to* Very severe
Q3. Pain/swelling in joints other than neck, back, or hip	Over past week: 0 *to* 10 = None *to* Very severe
Q4. Tenderness	Over past week: 0 *to* 10 = None *to* Very severe
Q5. Level of morning stiffness	Since awakening: 0 *to* 10 = None *to* Very severe
Q6. Duration of morning stiffness	Since awakening: 0 *to* 10 = Zero *to* 2-or-more hours

Calculation of the BASDAI score is described in Section 8.4.3. Three of the questions on the BASDAI are also components of the ASDAS, as described in Section 8.4.3. Details on scales and questions are provided in Appendix 12.6 [9].

7.1.2.7 Bath Ankylosing Spondylitis Functional Index (Patient Reported Outcome)

Subjects will complete the BASFI by answering 10 questions using the 0 to 10 NRS at all clinic visits. Eight of the questions relate to the functional capacity of the subject and 2 relate to the subject's ability to cope with everyday life. An increase along the scale indicates a worsening condition, ranging from "Easy" to "Impossible." Details on scales and questions are provided in Appendix 12.7 [9].

7.1.2.8 Patient Global Disease Assessment (Patient Reported Outcome)

Subjects will be asked to make an overall global assessment of their disease activity over the past week using the 0 to 10 NRS, with 0 being not active to 10 being extremely active. The Patient's Global Disease assessment (on Numeric scale) (PGD_N) is one of the domains of the ASDAS (see Section 8.4.3). Details are provided in Appendix 12.8 [9].

7.1.2.9 Total Back Pain (Patient Reported Outcome)

Subjects will be asked to assess their average total back pain (TBP) over the past week using the 0 to 10 NRS, with 0 being no pain to 10 being extreme pain. Total Back Pain is one of the domains of the ASAS. Details are provided in Appendix 12.9 [9].

7.1.2.10 Global Assessment of Disease by Investigator

A Global assessment of disease by investigator (GADI) will be recorded using a Likert scale (Very Well, Well, Fair, Poor, Very Poor). Details are provided in Appendix 12.10.

7.1.2.11 Record Adverse Events

At all visits after the subject consent is obtained until the conclusion of the protocol-specified follow-up period, the investigator or designee will solicit from the subject information concerning AEs. All AEs experienced since the previous visit or contact will be recorded on the eCRF. Flares of uveitis, psoriasis, IBD should be recorded. For instructions regarding AEs, see Section 7.2 Assessment and Reporting of Adverse Events.

7.1.2.12 Monitoring Malignancies

There will be follow-up communications between the Sponsor and the investigator regarding all malignancies that occur in subjects ages 30 years or younger. Twice a year, the Sponsor will review the AE database for possible premalignant conditions occurring in subjects ages 30 years or younger. If any are reported, the Sponsor will contact the investigator with a dedicated follow-up request that needs to be completed. This will be done via a dedicated Malignancy Follow-up Questionnaire. Within 2 weeks of receiving the questionnaire from the Sponsor, the investigator(s) must complete the questionnaire and submit it to the Sponsor via a designated fax number. In case a pre-malignant condition has progressed to a malignancy, the investigator will also need to complete the Malignancy Follow-Up Questionnaire. To obtain the information necessary to complete the Malignancy Follow-up Questionnaire, the investigator must make at least 2 attempts to contact the subject or guardian. If the attempts are not successful, the reason for each unsuccessful attempt must be documented (e.g., subject lost-to-follow-up, subject refuses to supply the additional information, etc.).

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Other Tests)

Laboratory tests for hematology, chemistry and additional tests are specified in Table 2.

Table 2 Laboratory Tests

Hematology	Chemistry	Additional Tests
Basophils	Albumin	CRP
Eosinophils	Alkaline phosphatase	Serum Pregnancy
Hematocrit	ALT	QuantiFERON®-TB Gold Test
Hemoglobin	AST	HCV
Lymphocytes	Bilirubin	HLA-B27
Monocytes	Blood urea nitrogen	HBV surface antigen (HBsAg),
Neutrophils	Calcium	HBV surface antibody(anti-HBs)
Platelets	Chloride	HBV core antibody(anti-HBc total)
Red blood cell count	GGT	HBV DNA testing*
White blood cell count	Potassium	
	Serum Creatinine	
	Sodium	
	Total protein	
*HBV DNA test will be performed only if HBs Ag and anti-HBs are negative and anti-HBc total is positive.		

Note: Routine laboratory examinations should be performed, evaluated, and recorded at any other time if required by local regulations and/or local clinical practice, or when medically indicated.

Nonclinically significant laboratory data will be kept in the subject's source document but any clinically significant abnormalities in laboratory data noted after the subject signs the ICF will be recorded as AEs in the eCRF.

7.1.3.2 Serum/Urine Pregnancy Testing and Follow-up of Pregnancy

Female subjects of childbearing potential will have serum and urine pregnancy tests performed at visits specified in Trial Flow Charts - Section 6.0. If local law requires more frequent pregnancy testing, the site will perform the assessments.

In order to be eligible for the trial, female subjects of childbearing potential and male subjects must agree to use a medically accepted method of contraception prior to enrollment, while receiving trial medication or within 6 months after stopping the medication (Section 5.1.2). Female subjects who become pregnant during the trial must discontinue treatment (Section 5.8). Male subjects who may have fathered a child during the trial or within 6 months after stopping the trial medication must notify the site immediately. The site will report pregnancies to the Sponsor's designee via appropriate eCRF within 24 hours as described in Section 7.2.2.

7.1.3.3 Tuberculosis (TB) Screening

For this protocol, a chest x-ray AND a QuantiFERON®-TB Gold test are mandatory, regardless of local guideline preferences. In addition, all subjects must undergo all additional applicable tests for TB (such as tuberculin skin test) and latent TB screening in accordance with local guidelines and protocol requirements.

Subjects who have negative diagnostic TB test results are considered eligible for the trial. A subject with a positive result for active TB should not be included in the current trial. The TB testing should be completed during the Screening visit and the results must be reviewed to assess subject eligibility prior to the Baseline visit. Tests include, but are not limited to posterior-anterior and lateral chest x-rays (unless a chest x-ray has been performed within 3 months prior to first treatment administration) and QuantiFERON®-TB Gold test (unless performed within 6 weeks prior to the first treatment administration), and tuberculin skin test.

Within 6 weeks prior to first administration of trial medication, subjects should have:

- negative diagnostic TB test results (defined as a negative QuantiFERON-TB Gold test [and a negative tuberculin skin test, but only if tuberculin skin test is needed]), OR

- a newly identified positive TB test result (defined as positive QuantiFERON-TB Gold test [and/or a positive tuberculin skin test, but only if tuberculin skin test is needed]) during Screening for which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of trial medication. The duration of the treatment before the first administration should be in accord with local guidelines, if any.

Investigators have the option to use both the QuantiFERON-TB Gold test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated in order to evaluate a subject who has high risk of having latent TB. Local guidelines specifically directed to high risk and/or immunocompromised subjects should be used for screening and interpreting positive test results for TB.

QuantiFERON-TB Gold testing (and tuberculin skin testing also, but only if needed) must be performed and read by experienced, trained, and licensed personnel according to published local guidelines, either at the participating trial site, a local public health clinic, or a primary care physician's office. If this testing was performed at any site other than the investigator's facility, the results must be made available in written form as source documentation.

7.1.3.4 HLA-B27 Gene Status

HLA-B27 gene testing will be done at Screening to document a subject's HLA-B27 status. If previously documented, it is not necessary to perform this assessment for this trial; however, actual results need to be captured in the subject's medical records.

7.1.3.5 Screening for Hepatitis B Virus (HBV)

Each subject must undergo a screening for hepatitis B virus (HBV), which at a minimum includes testing for HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and HBV core antibody total (anti-HBc total), and demonstrate to be eligible based on the following results:

a. Subjects who test **positive** for surface antigen (HBsAg+) ***are not eligible*** for this trial, regardless of the results of other hepatitis B tests.

b. Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this trial.

c. Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this trial.

d. Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject ***is not eligible*** for this trial. If the HBV DNA test is **negative**, the subject ***is eligible*** for this trial. In the event the HBV DNA test cannot be performed, the subject ***is not eligible*** for this trial.

Action	Hepatitis B Surface Antigen(HBsAg)	Hepatitis B Surface Antibody(anti-HBs)	Hepatitis B Core Antibody(anti-HBc Total)
Exclude	+	– ***or*** +	– ***or*** +
Include	–	+	+
Include	–	+	–
Include	–	–	–
Require Hepatitis B viral DNA (HBV DNA) testing*	–	–	+
* If HBV DNA is detectable or there is evidence of chronic liver disease, exclude from clinical trial. If the HBV DNA test is negative, the subject is eligible for this trial. In the event the HBV DNA test cannot be performed, the subject is not eligible for this trial.			

7.1.3.6 Pharmacokinetic (PK) and Immunogenicity Evaluations

7.1.3.6.1 Blood Collection for Plasma MK-8259

Analyses for MK-8259 (golimumab) concentration will be performed using a validated method. It is important to accurately record the date/time of administration of the trial medication as well as the date/time that each sample was collected for PK analysis. Sample collection, storage and shipment instructions for plasma samples will be provided in the central operations/laboratory manual.

7.1.3.6.2 Blood Collection for Antibodies to Golimumab (MK-8259)

Serum samples will be used to evaluate the antibodies to golimumab. Instructions for the collection, handling, and shipping of blood samples are provided in the Laboratory manual.

7.1.3.7 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research

7.1.3.8 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for planned genetic analysis samples will be provided in the central operations/laboratory manual.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the discontinuation visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events and subjects will have a safety follow-up telephone call 3 months after their last dose of trial medication.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Weight scale
- Centrifuge

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening and Baseline Eligibility (Visit 1 and Visit 2)

All screening procedures (including MRI) required to assess subjects' eligibility for the trial should be completed within the 2 months (60 days) prior to administration of the first dose of open-label golimumab at Visit 2. IVRS/IWRS should be used beginning with the Screening visit and ending with completion/discontinuation visit.

Subjects in this study may be rescreened once prior to receiving open-label golimumab, with prior approval by the Sponsor trial physician. If a subject is rescreened, the same screening number must be used.

When it is confirmed at Baseline (Visit 2 or "Month 0") that a subject is eligible to enter Period 1 (to receive open-label golimumab), the subject should be assigned an allocation number using the IVRS/IWRS. Refer to the IVRS/IWRS user manual for additional details.

7.1.5.2 Month-4 Clinic Visit (Visit 10)

At Month 4 (Visit 10), all subjects will be assessed for clinical response based on BASDAI score. Subjects who attain a clinical response by Month 4 (or earlier) will continue to receive golimumab monthly during Period 1. A clinical response is defined as a BASDAI score improvement of ≥2 (on a NRS from 0 to 10) or ≥50% improvement, when determined relative to the score at Month 0. Subjects who have not attained a clinical response by Visit 10 will be discontinued from the study and will have a safety follow-up telephone call 3 months after their last dose of trial medication.

7.1.5.3 Month-7 Clinic Visit (Visit 16)

At Month 7 (Visit 16), all assessments listed in Trial Flow Chart - Section 6.0 will be performed including those required to calculate ASDAS: BASDAI, PGD_N and CRP testing. Trial medication will <u>not</u> be administered at Visit 16. Once the Visit-16 CRP test result is available (from the central laboratory), the site will determine the ASDAS in order to assess for inactive disease status (defined as ASDAS <1.3).

- Subjects who show ASDAS <1.3 at Visit 16 are to continue in the trial and complete Period 1. Sites will schedule <u>only</u> these eligible subjects for the next clinic visit (Visit 17, which should occur about 2 to 7 days after Visit 16) to dispense open-label golimumab to complete Period 1.
- Subjects who show ASDAS ≥1.3 at Visit 16 will be discontinued from the trial. Sites will call these subjects for an unscheduled visit to perform procedures that are required at the Discontinuation (DC) visit but were not performed at Visit 16. These procedures include obtaining vital signs, GADI, routine laboratory blood testing, and pregnancy test (if required). These subjects will have a safety follow-up telephone call 3 months after their final dose of trial medication.

7.1.5.4 Month-10 Clinic Visit (Visit 23)

After approximately 10 months of open-label therapy (with the final dose of open-label golimumab during Period 1 administered at Month 9), assessments at Visit 23 will be performed, including those required to calculate the ASDAS: BASDAI, PGD_N and CRP testing. Trial medication will not be administered at Visit 23. Once the Visit-23 CRP test result is available (from the central laboratory), the site will determine the ASDAS in order to assess for inactive disease status (defined as ASDAS <1.3).

- Subjects who show ASDAS <1.3 at Visit 23 are eligible to enter Period 2 and receive double-blind treatment. Sites will schedule only these eligible subjects for the next clinic visit (Visit 24, which should occur about 2 to 7 days after Visit 23). At Visit 24, subjects will receive their initial dose of blinded trial medication and thereafter will continue monthly administration during Period 2. The next clinic visit (Visit 28) should be scheduled about 2 months after Visit 24.
- Subjects who show ASDAS ≥1.3 at Visit 23 will be discontinued from the trial. These subjects will have a safety follow-up telephone call 3 months after their final dose of trial medication.

7.1.5.5 Unscheduled Visit(s) to Confirm a "Flare" during Period 2

Evaluations by Telephone Contact(s) during Period 2

As obtained (via electronic device) during Period 2, if the BASDAI score is increased by ≥2 (on the 0 to 10 NRS) compared to Month 10 (Visit 23), then sites will call subjects to also obtain a Patient Global Disease assessment (on Numeric scale) (PGD_N) score. (Subjects may also contact the clinic if they believe a "flare" is occurring, regardless of their BASDAI score. In this situation, sites will call the subject to obtain both the BASDAI and the PGD_N. Similarly, if the BASDAI increase by ≥2 is observed at a regularly scheduled clinic visit, then this situation can initiate the additional assessments to confirm a "flare".) Using these values obtained for BASDAI and PGD_N, sites will also use the last available CRP value (i.e., the CRP result from the previous clinic visit) to determine the ASDAS. Based on this ASDAS, there are 2 possible decisions:

(1) If this ASDAS shows absolute score <2.1 and post-withdrawal increase (i.e., change from Visit 23) of <1.1, then this assessment is not consistent with a "flare". The subject is expected to continue the double-blind trial-medication administration and the scheduled clinic visits without change.

(2) If this ASDAS shows absolute score ≥2.1 and/or post-withdrawal increase of ≥1.1, then the subject will be asked to come to the clinic, for an unscheduled visit, for an additional assessment for confirmation of a "flare". This additional assessment should occur within ideally 2 to 10 days (but no more than 3 weeks); or this assessment can occur at a previously scheduled clinic visit, if the timing fits within ideally 2 to 10 days (but no more than 3 weeks) from the first assessment.

Evaluations during a Clinic Visit needed to Confirm a "Flare"

During a "flare-confirmation" visit, evaluations required to calculate ASDAS (BASDAI, PGD_N, CRP testing) will be performed. Using the BASDAI and PGD_N obtained *during* this "flare-confirmation" visit (and understanding that the result of the CRP test collected during this visit is not yet available), the investigator will determine the ASDAS using the BASDAI and PGD_N scores and assuming the minimum value of CRP that is defined for use in calculating ASDAS, which is CRP = 2 mg/L [8]. This ASDAS determines the decision among the following:

(1) If the ASDAS shows absolute score ≥2.1 and/or post-withdrawal increase (i.e., change from Visit 23) of ≥1.1, then this will confirm that a "flare" is occurring. The subject will begin re-treatment with open-label golimumab, which is then to be continued monthly through the end of Period 2. The next clinic visit should be scheduled about 2 months after the first dose of re-treatment with open-label golimumab.

(2) If the ASDAS shows absolute score <2.1 and post-withdrawal increase of <1.1, the subject will not be treated with the open-label golimumab at this unscheduled visit. However, when the CRP value becomes available from the sample collected at this "flare-confirmation" visit, the investigator must then re-calculate the ASDAS.

   (2a) If the re-calculation of ASDAS (now using the new CRP value) shows absolute score ≥2.1 and/or post-withdrawal increase of ≥1.1, then this will confirm that a "flare" is occurring. Once it is confirmed that a "flare" is occurring, the subject will be asked to return for a second unscheduled visit in order to begin re-treatment with open-label golimumab, which should then continue monthly through the end of Period 2. The next clinic visit should be scheduled about 2 months after the first dose of re-treatment with open-label golimumab.

   (2b) If the re-calculation of ASDAS (now using the new CRP value) shows absolute score <2.1 and post-withdrawal increase of <1.1, then this second assessment does not confirm a "flare". The subject is expected to continue the double-blind trial-medication administration and the scheduled clinic visits without change.

Note: In a scenario in which the BASDAI increase by ≥2 is observed at a regularly scheduled clinic visit and the "flare-confirmation" visit is then scheduled within ideally 2 to 10 days (but no more than 3 weeks), the CRP obtained at the regularly scheduled clinic visit can be used in the confirmatory determination of the ASDAS during the "flare-confirmation" visit. In this scenario, decisions (1) or (2b) above will pertain.

7.1.5.6 Safety Follow-Up Telephone call

All subjects who have either completed the trial or discontinued from the trial will have a safety follow-up phone call approximately 3 months after the last dose of trial medication.

7.2 Assessing and Recording Adverse Experiences

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 90 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than the dose specified in Section 5.2 of this protocol.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 6 months following cessation of Sponsor's product must be reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 3 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. Clinically significant opportunistic infections and TB.

3. Clinically significant hypersensitivity reactions.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 3. The investigator's assessment of causality is required for each adverse event. Refer to Table 3 for instructions in evaluating adverse events.

Table 3 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**
Yes, there is a reasonable possibility of Sponsor's product relationship.		There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
No, there is not a reasonable possibility of Sponsor's product relationship		Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor’s product. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	Phase IV, randomized, double-blind withdrawal study to evaluate the efficacy and safety of golimumab (MK-8259, GLM) after treatment withdrawal, compared with continuous treatment (either full- or reduced-treatment regimen), in subjects with nr-axSpA
Treatment Assignment	In Period 1, all subjects receive open-label GLM. In Period 2, subjects who attained inactive disease status (at both Month 7 and Month 10 of open-label golimumab treatment) in Period 1 undergo stratified randomization, in a 1:1:1 ratio (Placebo QM : GLM QM : GLM Q2M).
Analysis Populations	Efficacy: The primary efficacy population is: subjects who are randomized in Period 2 and take at least one dose of trial medication in Period 2. Safety: All Subjects as Treated (ASaT).
Primary Endpoint(s)	Proportion of subjects without a "flare" during up to 12 months in Period 2.
Key Secondary Endpoints	None
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by comparing treatment withdrawal (PBO) versus continued treatment with either GLM QM or GLM Q2M in the proportion of subjects without a "flare", using a stratified Miettenen and Nurminen (M&N) test.
Statistical Methods for Safety Analyses	Percentages of subjects with AEs in Period 2 will be summarized, using 95% CIs based on the M&N method, for broad AE categories (subjects with: Any AE, a Drug-related AE, a Serious AE, an AE that is both Drug-related and Serious, and Discontinuation due to AE).
Interim Analyses	No interim analysis is planned.

Multiplicity	The Type-I error rate over the multiple treatment comparisons will be controlled by a sequential (step down) testing procedure.
Sample Size and Power	Approximately 300 subjects will be enrolled to yield approximately 114 subjects eligible for randomization in Period 2 of the study, assuming the proportion of subjects with inactive disease in Period 1 at both Months 7 and 10 is about 38% in GLM-treated subjects (based on study P07642). Using a randomization ratio of 1:1:1 into the PBO, GLM QM, and GLM Q2M arms, there will be 38 subjects in each treatment arm. Based on the results of prior studies, the proportion without "flare" during the 12 months following randomization is expected to be approximately 80% in subjects on continued monthly GLM and 30% in subjects in the treatment withdrawal (PBO) arm. Under these assumptions, the power to detect a difference between treatment withdrawal (PBO) and continued GLM treatment (QM or Q2M) in the proportions of subjects without a "flare" exceeds 99%, given α=0.05 (2-sided). As the "flare" rates may differ from those observed in prior studies, the targeted sample sizes of 38 subjects per arm will provide 88% power to detect differences of 75% vs. 40% in the continued GLM (QM or Q2M) vs. PBO treatment arms.

8.2 Responsibility for Analyses / In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the designee/ Clinical Biostatistics department of the Sponsor.

Period 1 is conducted using an open-label design, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. Period 2 is conducted using a double-blind design under in-house blinding procedures. The official, final database for Period 2 will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Results of both periods will be presented in the CSR.

The interactive voice response system (IVRS) will generate and implement the randomized allocation schedule(s) for study treatment assignment.

8.3 Hypotheses / Estimation

The hypothesis and objectives of the study are stated in Section 3.0.

8.4 Analysis Endpoints

Efficacy and safety endpoints to be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints. Additional exploratory endpoints to characterize the clinical response after re-treatment for a "flare" during Period 2 (such as time to response and extent of response), as well as disease control during Period 2, will be fully described in the supplemental SAP.

The baseline value will be defined as the latest measurement collected prior to the first dose of golimumab in Period 1 (Visit 2).

8.4.1 Efficacy Endpoints

8.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this trial is the proportion of subjects without a disease activity "flare" during up to 12 months in Period 2 (in subjects who attained inactive disease status after receiving open-label golimumab in Period 1).

A "flare" is defined as ASDAS at two consecutive visits that both show *either* absolute score ≥2.1 *or* post-withdrawal increase (i.e., change from Visit 23) of ≥1.1.

8.4.1.2 Secondary Efficacy Endpoints

During Period 2:

- Proportion of subjects with a "flare" in the treatment-withdrawal group or the reduced-treatment group who then show a clinical response after re-treatment with open-label golimumab;
- Time to a first "flare";
- Proportion of subjects achieving ASAS20 response;
- Proportion of subjects achieving ASAS40 response;
- Proportion of subjects achieving BASDAI50 response;
- Proportion of subjects achieving ASAS partial remission;
- Proportion of subjects achieving inactive disease status: ASDAS <1.3 score.

8.4.1.3 Exploratory Endpoints

- Predictors of "flare" after withdrawal of GLM.
- Time to clinical response after re-treatment with golimumab for a "flare";
- Extent of clinical response after re-treatment with golimumab for a "flare" (including at 12 weeks after re-treatment)
- Proportion of subjects with disease control (subjects without "flare" or who attain clinical response after re-treatment for a "flare");
- Change from Baseline in components of the (composite) secondary endpoints:
  - BASDAI (0 to10 NRS);
  - Total Back Pain (0 to10 NRS);
  - Morning Stiffness (0 to10 NRS);
  - BASFI (0 to10 NRS);
  - Patient's Global Disease Assessment (0 to10 NRS);
  - ASDAS;
  - CRP (mg/L).
- Global Assessment of Disease by Investigator

8.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.3.2.

Serious infections, serious opportunistic infections, active tuberculosis, malignancies, and serious systemic hypersensitivity (including anaphylactic reaction) are prespecified as "Tier-1" events (for analysis of differences between treatments) in double-blind Period 2.

8.4.2.1 Events of Clinical Interest

The following serious and non-serious AEs are considered events of clinical interest (ECI) and monitored for this trial:

- Elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
- Clinically significant opportunistic infections and TB
- Clinically significant hypersensitivity reactions

8.4.2.2 Other Safety Endpoints:

- Change from baseline for laboratory safety parameters and vital signs;
- Proportion of subjects with clinical AEs, laboratory AEs, and anti-GLM antibodies;
- Markedly abnormal (MA) laboratory values

8.4.2.3 PK and Immunogenicity Endpoints

- GLM concentrations (PK endpoints/analyses are described in a supplemental SAP)
- Antibody status (positive/negative) for antibodies to GLM

8.4.3 Derivations of Efficacy Endpoints

8.4.3.1 Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI is defined as follows:

Subject self-assessment of 6 questions, on a NRS from 0 to 10: Q1. Fatigue/tiredness Q2. Neck, back, or hip (spinal) pain Q3. Pain/swelling in joints other than neck, back, or hip Q4. Tenderness Q5. Level of morning stiffness Q6. Duration of morning stiffness

BASDAI score = 0.2 (Q1+Q2+Q3+Q4 + 0.5 [Q5+Q6])

- BASDAI50 is defined as at least 50% improvement from baseline in the BASDAI score.

8.4.3.2 Ankylosing Spondylitis Disease Activity Score

The ASDAS is a composite index to assess disease activity in axial spondyloarthropathies.

The ASDAS is defined by calculating the following formula:

0.12 x Back Pain + 0.06 x Duration of Morning Stiffness + 0.11 x Patient Global + 0.07 x Peripheral Pain/Swelling + 0.58 x Ln(CRP+1)
1. Back pain – BASDAI question 2: "How would you describe the overall level of neck, back or hip pain you have had?" 2. Duration of Morning Stiffness – BASDAI question 6: "How long does your morning stiffness last from the time you wake up?" 3. Patient Global – Patient global disease assessment (PGD_N) "How active was your spondylitis on average during the last week?" 4. Peripheral Pain/Swelling – BASDAI question 3: "How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?" 5. Ln(CRP+1): natural logarithm of the C-reactive protein (mg/L) + 1

Back pain, duration of morning stiffness, patient global, and peripheral pain/swelling are all assessed on a NRS from 0 to 10 to calculate the ASDAS. When the CRP level is below the limit of detection (or when the CRP level is <2 mg/L), a value of 2 mg/L is used to calculate the ASDAS [8].

8.4.3.3 Assessment in SpondyloArthritis international Society-related Endpoints

- ASAS20: A 20% improvement in response on the Assessment in SpondyloArthritis international Society (ASAS) scale is defined as meeting both criteria:

    1. An improvement of ≥20% from Baseline and an absolute improvement from Baseline of ≥1 score (0 to10 NRS) in at least 3 of the following 4 domains:

        a) Pain: Total Back Pain score

        b) Morning Stiffness (average of questions 5 & 6 of the BASDAI concerning morning stiffness)

        c) Function: Bath Ankylosing Spondylitis Functional Index (BASFI)

        d) Patient Global Disease assessment (on Numeric scale) (PGD_N)

    2. Absence of deterioration from Baseline (≥20% and an absolute change of ≥1 score (0 to 10 NRS) in the potential remaining domain.

- ASAS40: An ASAS40 response is defined as meeting ≥40% improvement (with absolute improvement of ≥2 score (0 to10 NRS) in at least 3 of the 4 domains and no worsening at all in the potential remaining domain.

- ASAS Partial Remission: ASAS partial remission is defined as reaching ≤2 score (0 to 10 NRS) in all 4 ASAS domains.

8.4.3.4 Bath Ankylosing Spondylitis Functional Index

The BASFI is calculated as the mean of 10 NRSs (0 to 10 score). Eight of the scales relate to functional capacity of subjects, while the other 2 relate to a subject's ability to cope with everyday life. An increase along the scale indicates a worsening condition.

8.4.3.5 Morning Stiffness

Morning stiffness is defined as the mean of questions 5 and 6 of the BASDAI concerning morning stiffness.

8.4.3.6 Patient's Global Disease Assessment

The PGD_N is completed as follows:

Subjects make an overall assessment of disease activity over the past week on NRS from 0 to 10, with 0 being not active to 10 being extremely active.

8.4.3.7 Total Back Pain

The TBP is completed as follows:

Subjects assess their average total back pain over the past week on a NRS from 0 to 10, with 0 being no pain to 10 being extreme pain.

8.4.4 Derivations of Safety Endpoints

Levels of laboratory values that are considered to be markedly abnormal have been defined for each laboratory parameter in Table 4.

Table 4 Markedly Abnormal Criteria for Laboratory Parameters

Hematology laboratory parameters	
Test	**Criteria Value**
Hemoglobin (g/dL)	Decrease > 2.0 and Value < 8.0
Hematocrit (%)	Value < 27
Total WBC ($x10^3/\mu L$)	Value < 2.0 or Value > 20.0
Eosinophils, absolute ($x10^3/\mu L$)	Percent increase ≥ 100 and Value > 0.8
Lymphocytes, absolute ($x10^3/\mu L$)	Percent decrease ≥ 33 and Value < 1.0
Neutrophils, absolute ($x10^3/\mu L$)	Percent decrease ≥ 33 and Value < 1.5
Platelets ($x10^3/\mu L$)	Percent decrease ≥ 50 and Value < 75
Clinical chemistry laboratory parameters	
Test	**Criteria Value**
Albumin (g/dL)	Decrease ≥ 1.0 and Value < 2.5
Alkaline phosphatase (IU/L)	Percent increase ≥ 100 and Value > 250
ALT (IU/L)	Percent increase ≥ 100 and Value > 150
AST (IU/L)	Percent increase ≥ 100 and Value > 150
BUN (mg/dL)	Percent increase ≥ 66 and Value > 40
Calcium (mg/dL)	(Increase ≥ 2.0 and Value > 11.5) or (Decrease ≥ 1.5 and Value < 7.5)
Chloride (mEq/L)	Value < 85 or Value > 120
Creatinine (mg/dL)	Percent increase ≥ 66 and Value > 2.5
Potassium (mEq/L)	(Increase ≥ 0.8 and Value > 5.5) or (Decrease ≥ 0.8 and Value < 3.0)
Sodium (mEq/L)	(Increase ≥ 10 and Value > 150) or (Decrease ≥ 5 and Value < 125)
Total Bilirubin (mg/dL)	Percent increase ≥ 100 and Value > 1.5
Total protein (g/dL)	Value < 4.5 or Value > 10.0

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

Period 2: The Full Analyses Set (FAS) population consists of all randomized subjects who received at least one dose of post-randomization study treatment. The "flare" Full Analyses Set ("flare" FAS) population is defined as all FAS subjects in the Treatment Withdrawal (PBO) arm or in the GLM Q2Mdose interval arm who "flare" during Period 2.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

Period 1 safety data will be analyzed separately from Period-2 safety data.

Period 2: The ASaT population consists of all Period 2 randomized subjects who receive at least one dose of post-randomization study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

8.6 Statistical Methods

Statistical approaches for efficacy analyses are described in Section 8.6.1. Statistical approaches for safety analyses are described in 8.6.2. Ninety-five percent confidence intervals will be generated for response rates of various endpoints as detailed below. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives and related to analyses of data during Period 1 will be described in the supplemental SAP.

Efficacy data for continuous and categorical endpoints from Period 1 and Period 2 will be summarized separately. In Period 2, efficacy data will be summarized for each treatment comparison (GLM QM vs. withdrawal [PBO] and GLM Q2M vs. withdrawal [PBO]). In case of re-treatment following a "flare", efficacy data will also be summarized for the time before re-treatment vs. the time after re-treatment.

The primary efficacy endpoint, the proportion of subjects without a "flare" (comparing between the PBO and GLM QM arms and between the PBO and GLM Q2M arms) will be analyzed using the stratified Miettinen and Nurminen (M&N) method [5], with stratification based on CRP level (>6.0 mg/L *or* ≤6.0 mg/L) and weighting scheme based on sample-size weights.

In addition, a comparison of GLM QM vs. GLM Q2M will be conducted as an exploratory analysis.

The exact binomial method of Clopper and Pearson [6] will be used to calculate a 95% CI on the proportion of subjects re-treated with golimumab after a "flare" who show a clinical response.

Missing data for the primary endpoint will be handled as follows:

- Discontinuations: Subjects who enroll in Period 2 but discontinue prior to a "flare" will be counted as having a "flare".
- Missing components: If partial data are missing for the components of ASDAS (BASDAI questions 2, 3, 6, PGD_N, and CRP), then a multiple imputation (MI) procedure will be used to calculate the ASDAS. Details of the MI procedure will be provided in the sSAP.

Missing data for the secondary endpoint of proportion of subjects with a clinical response to re-treatment with GLM for a "flare" will be handled as follows:

- Discontinuations: Subjects who "flare" in Period-2 but do not undergo re-treatment or discontinue prior to re-attainment of inactive disease will be counted in the group having "flare" without clinical response to re-treatment.
- Missing components data will be handled similarly as for the primary endpoint.

Time to first "flare" and time to clinical response after a "flare" will be summarized using a Kaplan-Meier (K-M) analysis and a stratified log rank test. The time to first "flare" analysis will be conducted in the FAS. Day 1 for the K-M analysis will be the start date of Period 2. Subjects who do not "flare" will be censored at the time of study discontinuation; subjects who are lost-to-follow-up will be censored at the time of last data available. For the time to first "flare" analysis, missing component data will be imputed as specified for the primary endpoint. Summaries may include the pooled dose-reduction arms (Treatment Withdrawal [PBO] arm plus GLM Q2M arm) vs. GLM QM arm, as well as the 3 treatment arms separately.

The proportion of subjects with a clinical response to re-treatment with GLM for a "flare" and the time to clinical response after re-treatment with GLM for a "flare" analysis will be conducted in the "flare" FAS.

Other binary-response endpoints will be summarized by time point with 95% confidence intervals calculated using the exact binomial method of Clopper and Pearson (Period 1) and stratified M&N (Period 2). These summaries will be based on observed data; no missing data will be imputed.

Continuous endpoints will be summarized by time point using descriptive statistics. These summaries will be based on observed data; no missing data will be imputed.

Table 5 summarizes the key efficacy analyses.

Table 5 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Objective				
Proportion of subjects *without* a disease activity "flare", in subjects who attained inactive disease status in Period 2	Primary	Stratified M&N‡	FAS	Non-responder imputation for early discontinuations, MI§ for missing components
Secondary Objectives				
Proportion of subjects with a clinical response to re-treatment with golimumab after a "flare" in Period 2	Primary	Clopper and Pearson	Flare FAS	Non-clinical response imputation for early discontinuations or "flare" without re-treatment, MI§ for missing components
Time to first "flare" in Period 2	Primary	Kaplan-Meier	FAS	MI§ for missing components

‡ Miettenen and Nurminen.
§ MI=Multiple Imputation of ASDAS individual components used to determine Inactive Disease status.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests and vital signs measurements.

The analysis of safety results will follow a tiered approach (Table 6). The tiers differ with respect to the analyses that will be performed.

Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI	Descriptive Statistics
Tier 1‡	Serious infections, serious opportunistic infections, active tuberculosis, malignancies, and serious systemic hypersensitivity (including anaphylactic reaction)	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs or MA lab values (incidence ≥4 subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or MA lab values (incidence <4 subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
‡ Applies to Period 2 only.
Note: SOC=System Organ Class; MA=Markedly Abnormal; X = results will be provided.

Tier 1 analysis will be performed in Period 2 only if there are at least 4 events in one of the treatment arms, using the Miettinen and Nurminen method for between-treatment differences in the percentage of subjects with events. In the case of less than 4 events in each treatment arms, the Tier 1 events will be listed by subject, treatment and period. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided; only point estimates are provided for Tier 3 safety parameters. Adverse experiences (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3. For this protocol, broad clinical and laboratory AE categories (consisting of the percentage of subjects with: Any AE, a Drug-related AE, a Serious AE, an AE that is both Drug-related and Serious, and Discontinued due to an AE) will be considered Tier 2 endpoints. Using the exact binomial method of Clopper and Pearson (Period 1) and Miettenen and Nurminen (Period 2), 95% confidence intervals will be provided for the percentages of subjects with events.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Safety data from Period 1 and Period 2 will be summarized separately. Period-2 safety data will be summarized for each treatment group (GLM QM, GLM Q2M, and PBO); in the case of re-treatment, safety data will also be summarized for the time before re-treatment vs. the time after re-treatment.

Continuous measures, such as changes from baseline in laboratory and vital signs parameters, will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Events of clinical interest will be listed by subject. Other selected safety endpoints of interest will be listed by subject, treatment and period; these endpoints include: serious infections, serious opportunistic infections, active tuberculosis, malignancies, and serious systemic hypersensitivity (including anaphylactic reaction).

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, enrolled in Period 1, enrolled in Period 2, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, race), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

8.6.3.2 Antibodies to Golimumab

Blood samples will be collected to examine the formation of antibodies to GLM at the visits specified in the flow chart. Antibody data will be summarized as follows:

- Antibody status (positive/negative) of subjects will be summarized by treatment group. Further details about defining the treatment groups and approach to summarizing the data are described in a supplemental SAP.
    - GLM QM (both before and after Re-treatment, if needed);
    - GLM Q2M (both before and after Re-treatment, if needed);
    - PBO (both before and after Re-treatment, if needed).

In general, incidences of broad category AEs and injection-site reactions will be summarized by antibody status and treatment group.

- The proportion of subjects who show clinical response following re-treatment with GLM for a “flare” will be summarized by antibody status. The proportion of subjects who do not “flare” after withdrawal of GLM, or after reduction to GLM Q2M dosing, will also be summarized by antibody status. Efficacy endpoints (for example, ASDAS, ASAS20 response, ASAS40 response, and BASDAI50 response), occurrence of “flare”, clinical response after re-treatment for a “flare”, and antibody status will be listed by time point for subjects with positive antibody status.

8.6.3.3 Pharmacokinetic Data

The approach to summarizing the PK data is described in a supplemental SAP.

8.7 Interim Analyses

No interim analyses are planned for this study.

8.8 Multiplicity

The Type-I error rate over the multiple treatment comparisons will be controlled by a sequential (step down) testing procedure. Testing of the primary hypotheses will begin with comparison of the GLM QM versus PBO. The GLM Q2M versus PBO comparison will be performed only if the primary efficacy GLM QM versus PBO analysis is statistically significant at two-sided $\alpha = 0.05$.

All other efficacy analyses will be considered supportive and/or exploratory.

8.9 Sample Size and Power Calculations

A total of approximately 300 subjects will be enrolled. Assuming the proportion of subjects who attain inactive disease in Period 1 at both Months 7 and 10 is about 38% (based on the GO-AHEAD study, P07642 [1]), 300 enrolled subjects would result in approximately 114 subjects eligible for Period 2 of the study. With 114 subjects randomized in a ratio of 1:1:1 into the PBO, GLM QM, and GLM Q2M arms, 38 subjects are expected in each treatment arm.

Based on an expected proportion who do not "flare" of 80% in the GLM QM arm (based on study P07642) and 30% in the PBO arm (based on studies of subjects with early axial spondyloarthritis [7]), the power to detect a difference between treatment withdrawal (PBO) vs. continued treatment with GLM QM in the proportion of subjects who do not "flare" exceeds 99%, given α=0.05 (2-sided). (See the bold text in Table 6 below.) If the primary hypothesis is rejected for the GLM QM vs. PBO (treatment withdrawal) comparison, then tests of GLM Q2M vs. PBO will be conducted. It is not known if the proportion who do not "flare" for the GLM Q2M arm will be similar to that for the GLM QM arm; but with a sample size of 38 per arm, the study will have 88% power to detect differences of 75% vs. 40% in the proportions of subjects who do not "flare", should the estimates of absence of "flare" differ from what has been observed in prior studies [7]. (See the bold italic text in Table 7 provides estimates of power for several response scenarios.

Table 7 Power for the Primary Endpoint, Comparing Two Treatment Arms

Treatment withdrawal: Placebo arm	Continued golimumab: QM or Q2M arm	
Proportion who Do not "flare" (N=38)	Proportion who Do not "flare" (N=38)	Power†
20%	80%	99%
	75%	99%
	70%	99%
	65%	98%
	60%	96%
30%	**80%**	**99%**
	75%	98%
	70%	95%
	65%	87%
	60%	75%
40%	80%	96%
	75%	***88%***
	70%	75%
	65%	59%
	60%	41%
†Assumes α=0.05 and 2-sided test QM=every month; Q2M=every 2 months		

8.10 Subgroup Analyses and Effect of Baseline Factors

To explore whether the treatment effect is consistent across various subgroups, the estimate of the treatment effect (with a nominal 95% CI) for the primary endpoint, the proportion of subjects without a "flare" during up to 12 months, will be estimated and plotted within each category of each subgroup. The following are examples of classification variables:

- CRP category (>6.0 mg/L *or* ≤6.0 mg/L)
- MRI category for SI joint sacroiliitis (positive *or* negative)
- Gender (male *or* female)
- Age (≤30 years *or* >30 years)

In addition, a Forest plot will be produced, which provides the point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.11 Compliance (Medication Adherence)

Drug accountability data for GLM will be collected during the study. Compliance (also termed "medication adherence") rates will be summarized (N, mean, median, standard deviation, range [min and max]) by period and by treatment group and overall in Period 2. The compliance rate for a subject will be defined as the total number of doses taken divided by the total number of doses the subject was supposed to take during the treatment period.

The number of injections (administrations) will be summarized similarly as described above for the compliance rates. In addition, descriptive statistics (counts and percentages) will be provided for the number of injections administrated by period and by treatment group and overall in Period 2.

8.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary statistics (N, mean, median, and standard deviation) for the "Number of Days on Therapy" by Period and treatment group. A summary of total GLM exposure across Periods 1 and 2 will also be provided.

Period-2 duration of exposure will be calculated as follows:

- GLM QM group = the number of days from the first dose of GLM at Month 10 to the last dose + 30 days;
- GLM Q2M group = the number of days from the first dose of GLM at Month 10 to the last dose of GLM + 30 days;
- Placebo (withdrawal) group = number of days from Month 10 to the first dose of GLM given as re-treatment for a "flare" or to study discontinuation for subjects who don't undergo re-treatment with GLM.

Due to the long half-life of GLM, the above subject-time computations will ignore the missing doses. The total subject-time of exposure for a group will be the sum of the subject-time of exposure of all subjects in the group.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
golimumab 50mg/0.5mL	Injection
placebo for golimumab 50mg/0.5mL	Injection

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

During Period 1 Open-label Run-in phase, subjects will receive open-label, kitted golimumab 50mg/0.5mL. Each kit will contain a single pre-filled syringe and each subject will receive 1 kit at the first dispensing visit followed by 3 kits at all subsequent dispensing visits. During Period 2 Double-blind, subjects will receive blinded, kitted golimumab 50mg/0.5mL or placebo. Each subject will be dispensed 2 kits every 2 months and each kit will contain 1 pre-filled syringe.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment identity for the double-blind Period 2 of this trial. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned, and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the

Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol,

the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to

pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.7 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained.

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

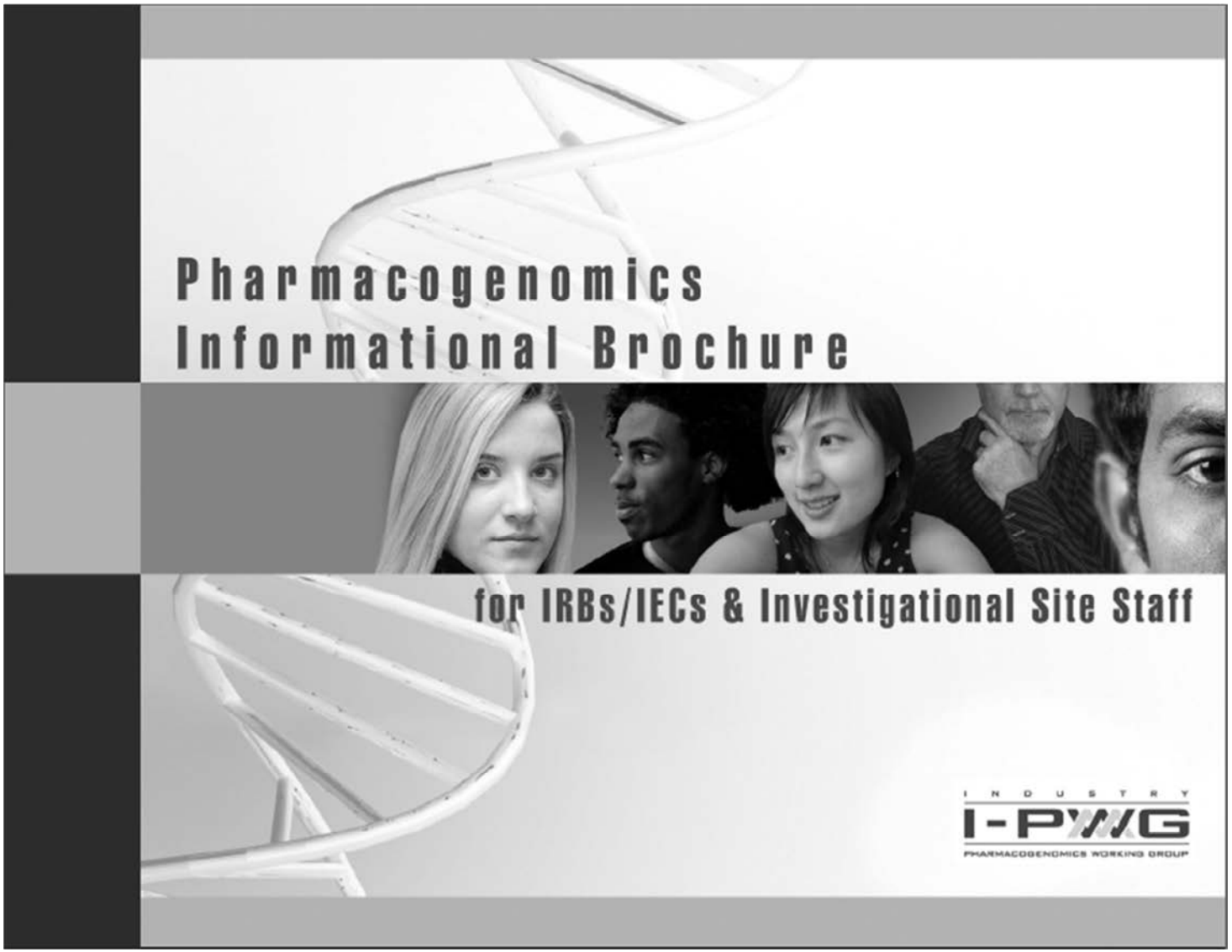
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



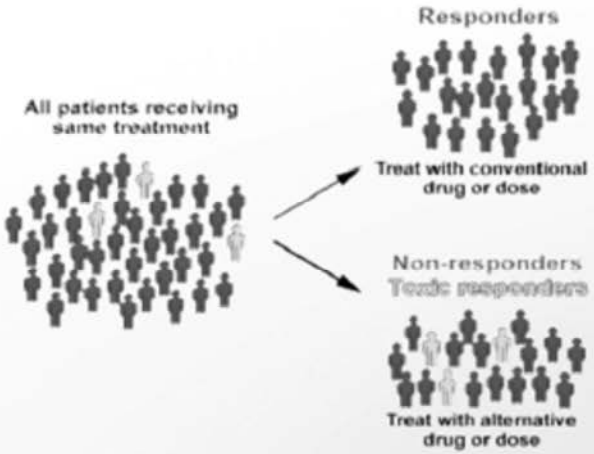
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid (DNA)**. DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

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Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[3].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-Identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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http://www.i-pwg.org

12.4 Approximate Blood Volumes Drawn/Collected

Blood Volumes in milliliters (mL) by Trial Visit and by Sample Types

	Screening Visit	***Visit 2***	***Visits 4, 10, 16***	***Visit 23***	***Visits 28, 32, 40, 44***	***Visits 36, 48, Uns.***
Blood Parameter	**Approximate Blood Volume (mL)**					
Hematology	5	5		5		5x2=10
Serum Chemistry	5	5		5		5x2=10
CRP	5	5	5 (V16 only)	5	5x4=20	5x3=10 (V36, V48, and Uns.)
Serum β-Human Chorionic Gonadotropin (β-hCG)	5			5		5 (V48 only)
Hepatitis B Virus Screen (Per site SOPs)/ Tuberculosis Test/HLA B-27	15					
Blood for Genetic Analysis		8.5				
Pharmacokinetic (PK)		5	5 x 3 visits =15	5	5x4=20	5x2=10
Anti-drug (MK-8259) antibody		5	5 x 3 visits =15	5	5x1=5 (V28 only)	5x2=10
Expected Total (mL)	**35 mL**	**33.5 mL**	**Visits 4 and 10 = 10 mL; Visit 16=15 mL**	**30 mL**	**V28=15 mL V32, V40, and V44=10 mL**	**V36=25 mL; V48 =30 mL; Uns.=5 mL**

12.5 List of Abbreviations

Term	Definition
AE	Adverse Event
ALT	ALanine aminoTransferase (also known as SGPT)
AS	Ankylosing Spondylitis
ASAS	Assessment of the SpondyloArthritis international Society
ASaT	All Subjects as Treated
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	ASpartate aminoTransferase (also known as SGOT)
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BCG	Bacille Calmette-Guerin vaccination
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
DC	Discontinuation
DMARDs	Disease Modifying Anti-Rheumatic Drugs
DNA	DeoxyriboNucleic Acid
ECI	Event of Clinical Interest
eCRF	electronic Case Report Form
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration, USA
GADI	Global Assessment of Disease by Investigator
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLM	Golimumab
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen B27
IB	Investigator’s Brochure

Term	Definition
IBD	Inflammatory Bowel Disease
IEC	Independent Ethics Committee
ICF	Informed Consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
IRB	Institutional Review Board
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K-M	Kaplan-Meier
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NA, N/A	Not applicable
nr-axSpA	Non-radiographic axial SpondyloArthritis
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PE	Physical Exam
PGDN	Patient Global Disease assessment (on Numeric scale)
QM	Every Month
Q2M	Every 2 Months
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SI joints	SacroIliac joints
SOP	Standard Operating Procedure
SpA	SpondyloArthritis
SPARCC	SPondyloArthritis Research Consortium of Canada
TB	TuBerculosis
TNFα	Tumor Necrosis Factor alpha

12.6 Bath Ankylosing Spondylitis Disease Activity Index

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Please tick the box which represents your answer. (i.e. ☒)
All questions refer to **last week**.

1. How would you describe the overall level of fatigue/tiredness you have experienced?

none very severe

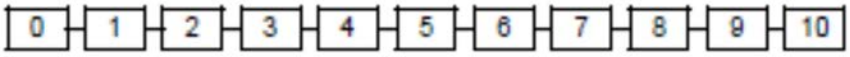
2. How would you describe the overall level of AS **neck, back or hip** pain you have had?

none very severe

3. How would you describe the overall level of pain/swelling in joints **other than** neck, back or hips you have had?

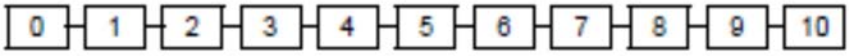
none very severe

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?



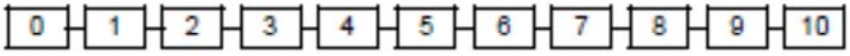
none very severe

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?



none very severe

6. How long does your morning stiffness last from the time you wake up?



0 hr 1 hr 2 or more hrs

BASDAI - United Kingdom/English - Mapi Research Institute.
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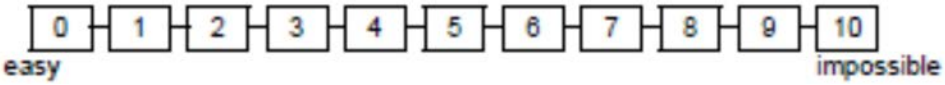
12.7 Bath Ankylosing Spondylitis Functional Index

Bath Ankylosing Spondylitis Functional Index (BASFI)

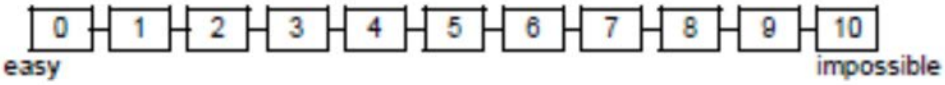
Please indicate your level of ability with each of the following activities during **the last week**. (i.e. [redacted])

(An aid is a piece of equipment which helps you to perform an action or movement)

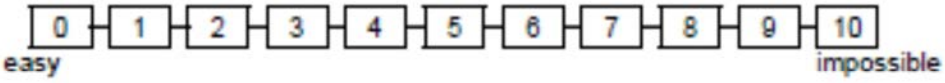
1. Putting on your socks or tights without help or aids (e.g. sock aid).



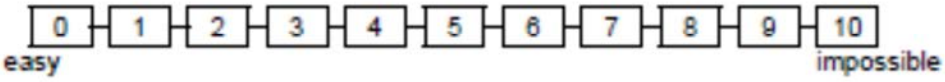
2. Bending forward from the waist to pick up a pen from the floor without an aid.



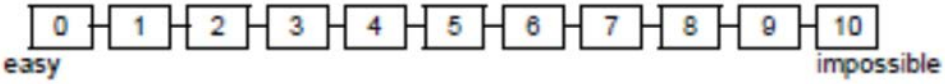
3. Reaching up to a high shelf without help or aids (e.g. helping hand).



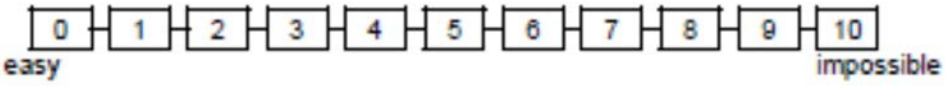
4. Getting up out of an armless dining room chair without using your hands or any other help.



5. Getting up off the floor without help from lying on your back.



6. Standing unsupported for 10 minutes without discomfort.



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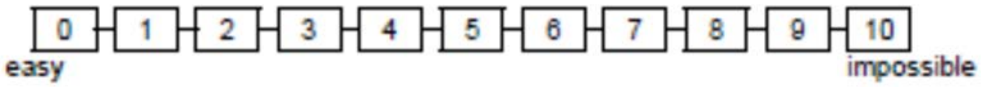
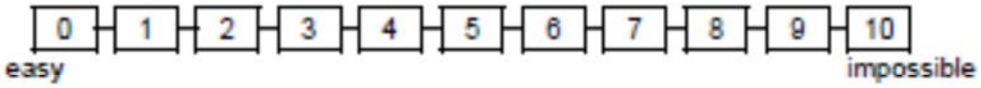
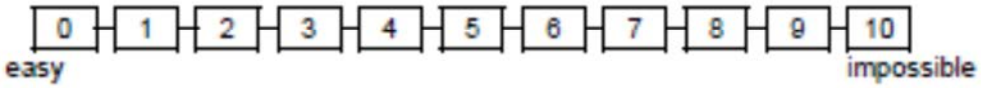
7. Climbing 12-15 steps without using a handrail or walking aid. **One foot at each step.**



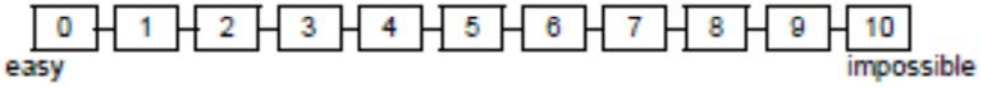
8. Looking over your shoulder without turning your body.



9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).



10. Doing a full day's activities, whether it be at home or at work.



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12.8 Patient Global Disease Assessment

GOLIMUMAB (MK-8259 / SCH 900259) IN NR-AXSPA: WITHDRAWAL TRIAL (GO-BACK)

PGDN

Compound	Protocol	Visit	Screening No. (Site - Sequence No.)	Randomization No.
MK-8259	038			

PATIENT GLOBAL DISEASE ASSESSMENT

THIS SECTION FOR USE BY STUDY PERSONNEL ONLY.

Specify completion date: _____
DD-Mon-YYYY

Comments:

Only the subject should enter information onto this questionnaire

On average during the last 7 days how active was your spine arthritis?

Please mark the box that represents your answer, for example (☒)

Numeric Rating Scale

0	1	2	3	4	5	6	7	8	9	10
Not Active										Very Active

I confirm this information is accurate.	Subject's Initials:	Date:

I have reviewed this information	Staff Initials:	Date:

12.9 Total Back Pain

GOLIMUMAB (MK-8259 / SCH 900259) IN NR-AXSPA: WITHDRAWAL TRIAL (GO-BACK)

TBP

Compound	Protocol	Visit	Screening No. (Site - Sequence No.)	Randomization No.
MK-8259	038			

TOTAL BACK PAIN ASSESSMENT

THIS SECTION FOR USE BY STUDY PERSONNEL ONLY.

Specify completion date: _____
DD-Mon-YYYY

Comments:

Only the subject should enter information onto this questionnaire

On average during the last 7 days, how severe was your spine pain due to spine arthritis?

Please mark the box that represents your answer, for example (5)

Numeric Rating Scale

0	1	2	3	4	5	6	7	8	9	10
No Pain										Most severe pain

I confirm this information is accurate.	Subject's Initials:	Date:

I have reviewed this information	Staff Initials:	Date:

12.10 Global Assessment of Disease by Investigator

GOLIMUMAB (MK-8259 / SCH 900259) IN NR-AXSPA: WITHDRAWAL TRIAL (GO-BACK)

GADI

Compound	Protocol	Visit
MK-8259	038	

Screening No. (Site - Sequence No.)	Randomization No.

GLOBAL ASSESSMENT OF DISEASE ACTIVITY SCALE (INVESTIGATOR)

Specify completion date: _____
DD-Mon-YYYY

NOTE: *The following assessment is to be completed by the* ***same*** *investigator throughout the complete duration of the study.*

Make a global assessment of the patient's disease status by marking an "X" in one box below.

- ☐ Very Well
- ☐ Well
- ☐ Fair
- ☐ Poor
- ☐ Very Poor

I confirm this information is accurate.	Staff Initials:	Date:

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	