Product: MK-8259
Protocol/Amendment No.: 021
VEAP ID NO: 6189
Date: 15-January-2018

SPONSOR:

MSD Pharmaceuticals LLC, a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
Pavlovskaya street, 7, building 1
Moscow, 115093, Russian Federation

TITLE:

A Prospective Observational Study to Evaluate Clinical and Radiological Manifestations of Coxitis in Patients with Ankylosing Spondylitis treated with Simponi® (golimumab)

Summary of Changes

Summary of Changes for Amendment of 15 January 2018

Protocol Section	Change
Protocol Summary	Approximately 40 months (16 months recruitment, plus 24 months follow up with interim statistical analysis at 12 months of follow up) Sample size calculation is based on data from GO-RAISE registration study in which golimumab was evaluated in patients with AS. The baseline BASFI was 5.0 which changed by mean (± SD, standard deviation) −2.5 (± 2.12) at week 52 (approximately 12 months). The analysis of the data shows that the minimum necessary sample size should be 18 patients to show a statistically significant change of BASFI from baseline to 12 months. On this basis and considering that the dropout rate over the two years is expected to be 30%, we decided that the necessary number of patients to be included into protocol should be 39 individuals. It is expected that around 27 patients will be included in the patient set completing the study. Power of the study is 90% with formula evaluation P = 1-β where P is power and β is type 2 error = 10%.
6.1.2.3 Interim Statistical Analysis	Interim Statistical Analysis will be performed when at least 18 patients recruited are observed and have their tests done at 12 months.
6.1.2.4 Central collection and evaluation of X-ray, MR Images and US protocols	Central collection and evaluation will be performed when at least 18 patients recruited are observed and have their tests done at 12 and 24 months.
8.1.1 Interim Statistical Analysis	Interim Statistical Analysis will be performed when at least 18 patients recruited are observed and have their tests done at 12 months.
8.2.1 Methods to Minimize Bias	Bias from early drop out of patients from the study can be reduced with Interim Statistical Analysis which is to be performed when at least 18 patients recruited are observed and have their tests done at 12 months. Also, patients who drop out before final follow up visit are planned to enter an analysis of last-observation-carried forward (LOCF). Data recorded on the last visits of patients will contribute to the analysis.

Protocol Section	Change
8.2.2 Limitations	This study will collect data on patients being treated in real clinical Rheumatology practice. It is expected that the number of patients dropping out before completion of the whole course of observation will be about 30%. To minimize this limitation, the study will enroll 39 patients to ensure that the number of subjects entering the analysis *Per Protocol* will be enough (27 subjects). In addition, secondary analyses will evaluate data on completers vs patients dropping out before completion separately.
8.3 Sample Size and Power Calculations	Thus, the analysis of the data shows that the minimum necessary sample size should be at least 18 patients to show a statistically significant change of BASFI from baseline to 12 months. On this basis and considering that the dropout rate over the two years of the study is expected to be about 30% (ranging from 21% in a randomized controlled study [19] to 37% in real clinical practice [25]), it is decided that the necessary number of patients to be included into the study should be 39 individuals. It is expected that at least 27 patients will be included in the patient set completing the study.
11 List of References	Manara M. et al et al. Two-year retention rate of golimumab in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: data from the LORHEN registry. Clinical Experimental Rheumatology, 2017 Vol.35, N°5. Pg. 0804-0809

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PROTOCOL SUMMARY

Title	A Prospective Observational Study to Evaluate Clinical and Radiological Manifestations of Coxitis in Patients with Ankylosing Spondylitis treated with Simponi® (golimumab) – GO-COX
Vendor/Collaborator	Atlant Clinical Ltd
Rationale	Coxitis in AS is inflammation of hip(s) affecting significant number of patients. It is associated with worse function and more expressed axial disease requiring hip replacement at end-stage. Number of studies dedicated to coxitis treated with TNF alpha inhibitors is very limited. Simponi® (golimumab) has not been studied in hip disease in AS although it is registered for AS. This study will provide valuable data on clinical and radiological signs of coxitis in AS at baseline and its clinical and radiological evolution during treatment with golimumab in daily clinical practice.
Primary Objective(s)	To evaluate change of functional impairment in AS patients with coxitis from baseline to 12 months of therapy with golimumab by BASFI in daily clinical practice
Study Design	This study is a non-interventional prospective observational cohort study conducted in multiple centers across Russia.
Study Population	Patients with ankylosing spondylitis (according to the modified New York criteria) with coxitis newly prescribed golimumab during the course of usual clinical care will be enrolled and followed prospectively for 24 months with data collection at the approximate time points: baseline (pre-treatment) and consequent every 6 months.
Study Duration	Approximately 40 months (16 months recruitment, plus 24 months follow up with interim statistical analysis at 12 months of follow up)
Exposure and Outcome	Patients will receive golimumab as prescribed in regular clinical practice.
Statistical Methods	Quantitative variables will be tested for normal distribution using the Shapiro-Wilk test. The hypothesis of equality of variances will be tested using Levene's test. Quantitative variables matching a normal distribution will be described in terms of the mean ± standard deviation, and values outside of the normal distribution as medians, 25% and 75% quartiles. Qualitative variables will be presented in the form of percentages of the absolute value N.
Sample Size and Power Calculations	Sample size calculation is based on data from GO-RAISE registration study in which golimumab was evaluated in patients with AS. The baseline BASFI was 5.0 which changed by mean (± SD, standard deviation) −2.5 (± 2.12) at week 52 (approximately 12 months). The analysis of the data shows that the minimum necessary sample size should be 18 patients to show a statistically significant change of BASFI from baseline to 12 months. On this basis and considering that the dropout rate over the two years is expected to be 30%, we decided that the necessary number of patients to be included into protocol should be 39 individuals. It is expected that around 27 patients will be included in the patient set completing the study. Power of the study is 90% with formula evaluation P = 1-β where P is power and β is type 2 error = 10%.
Limitations	In this non-interventional study the quality of the data is important. Therefore, it is important for the sponsor or designee to monitor data completion and perform quality checks during the course of the study. To minimize missing data, a set of core variables is required to be available at enrollment as part of inclusion criteria.

1 Background and Rationale

1.1 Background

Ankylosing Spondylitis (AS) is a chronic autoimmune disease characterized by back pain caused by inflammation of the sacroiliac joints and spine. In Europe, prevalence of AS ranges from 0,08% to 1,8% , while incidence is 1,5-7,3 per 100 000 depending on population studied [1,2]. In Russia, an absolute number of AS patients was reported as 39800 (approximate prevalence 0,028%) and the incidence was 5 438 patients per year (approximate incidence 3,9 per 100 000) in 2010. Also, it was noted that the number of patients is increasing. Thus, approximate prevalence was 0,022% and 0,024% in 2004 and 2008, respectively. Approximate incidence was 2,5 per 100 000 in 2006 [3].

The grow of prevalence and incidence of AS in Russia might be related to arrangement of national educational campaign across the country in 2010-2014. This campaign has been led by a Spondyloarhritis Research Taskforce of the National Research Rheumatology Institute n.a. V.A.Nosonova. MSD is one of the main sponsors of the educational campaign. Thus, MSD sponsored 20 and 18 regional spondyloarthritis schools (local conferences) in different regions of Russia in 2012 and 2013, respectively [MSD data].

Involvement of hip joint (coxitis) occurs in 24-36% of AS patients [4]. The joint can be affected by synovitis, enthesial inflammation and bone marrow involvement. The clinical pattern of coxitis includes typical inguinal pain with impaired and painful movement of the hip [9]. Coxitis is associated with more severe AS. It is recognized that patients with hip disease have worse BASFI scores than patients without hip involvement [4,5,9]. These higher BASFI scores might be associated with all BASFI questions of which many appear to be directly related to the hip (e.g. difficulty with getting up off the floor or out of a chair, tying shoes, climbing stairs) [5], but also with questions related to functions with no hip involvement (e.g. looking over the shoulder without turning your body) [4,5]. Moreover, there is clear evidence that coxitis is associated with more pronounced axial disease, clinically and radiologically: patients with clinical hip involvement are more prone to have severely limited cervical rotation [4] and patients with hip scores of 2 or greater (BASRI hip scores) have median BASRI spine scores that are more than two points higher than those of patients with a hip score of 0 [6]. Coxitis is associated with earlier beginning of AS including juvenile onset [4,7] and its longer duration [5]. The combination of the stiff spine and hip can severely affect physical status of patients and their quality of life, psychosocial status and employability [8].

Radiography, ultrasonography (US) and MRI are used to confirm clinical manifestation of coxitis in AS patients [9]. The most widely used and best validated radiological index is the bath ankylosing spondylitis radiology index (BASRI hip). In this score, the hips hip radiographs are graded on a scale of 0–4 (0 – no change; 1 – suspicious: focal joint space narrowing; 2 – mild: circumferential joint space narrowing >2mm; 3 – moderate: circumferential joint space narrowing ≤ 2mm or bone-on-bone apposition of <2 cm; and 4 – severe: bone deformity or bone-on-bone apposition of ≥2 cm) [9].

US can reveal synovial hypertrophy, synovial hypervascularization and joint effusion [9].

MRI can detect soft tissue and bone inflammation of hip. There was a recent Chinese study investigating inflammatory MRI changes in AS patients investigating pattern of hip involvement. Active inflammatory changes included subchondral bone marrow edema, joint effusion, abnormal synovial enhancement, enthesitis at sites where ligaments and tendons are attached to bone. They are visualized

best by STIR (short tau inversion recovery) sequence and fat-saturated contrast-enhanced T1-weighted sequence. Chronic inflammatory changes were fatty degeneration, erosive destruction, joint space narrowing, sclerosis, ankylosis. They are best seen by using a T1-weighted TSE sequence [10]. The proportion of hip involvement according to MR imaging, radiographs, and clinical symptoms was:

	Proportion of hip involvement
MRI	74,1% (86/116)
Radiography	20,7% (24/116)
Clinical symptoms	30,2% (35/116)

MRI yielded higher values than radiographs and clinical symptoms in the detection of hip involvement in patients with AS ($P < 0.05$). The frequency of MRI changes in 81 hips (42 patients) have been shown to be: acute changes alone – 43,1%, chronic and acute changes – 26,7%, normal – 25,9%, chronic changes – 4,3%. The rates of acute MRI inflammatory changes have been shown to be:

	Rates of acute MRI inflammatory changes
Synovitis alone	48,1%
Synovitis + bone edema	21,0%
Synovitis + bone edema + enthesithis	18,5%
Synovitis + enthesitis	8,6%
Bone edema alone	3,7%
Enthesitis alone	0
Bone edema and enthesitis	0

There are no studies investigating correlation of different radiological manifestations over time.

According to current international guidelines, management of AS patients with coxitis does not differ from management of AS patients without hip involvement and includes physiotherapy, pharmacological therapy (NSAIDs, sulfasalazine, TNF alpha inhibitors) and surgery [8,11,12,13]. The latter is total hip replacement which is used in cases of end-stage disease [9]. In analysis of three databases of AS patients (Belgian database ASPECT, n=847, Spanish database REGISPONSER, n=1405 and Ibero-American database RESPONDIA, n=466), it was shown that 5-8% of the AS patients undergo hip replacement surgery, 47% of them have bilateral hip replacement. After >30 years of disease duration, the chance of having at least one replaced hip is 12-25% [4]. Investigators who were analyzing Norwegian

Arthroplasty Register noticed that in 2003-2010 there was a trend towards a reduced frequency of hip replacement procedures in the AS group when compared to osteoarthritis group. It was hypothesized that this trend was related to broader introduction of TNF alpha inhibitors [14].

According to the ASAS/EULAR recommendations for the management of ankylosing spondylitis, anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments [11]. Literature search identifies three publications on efficacy of TNF alpha inhibitors in hip disease in AS patients.

The first one, by Wang D. et al, describes results of follow-up in 56 patients with AS with coxitis treated with etanercept in combination with MTX. It was shown that Harris hip score, BASDAI, BASFI, ESR, CRP improved after 12 weeks of therapy (p<0,001 for all measurements). No radiological data were provided [15].

The second one, by Lian F. et al, presents results of 12-month treatment of coxitis in 92 AS patients with etanercept in combination with MTX. It was shown that Harris hip score, BASDAI, BASFI, ESR, CRP improved after 12 months of therapy (p<0,05 for all measurements). In the whole population of patients BASRI-hip remained with no changes (baseline vs. 12 month of treatment). MRI proved a total of 93 hip joints (51%) had joint fluid synovitis in MRI at baseline and 13 positive hip joint fluid synovitis at the 12th month [16]. Other MRI symptoms were not described by the authors.

The third one, by Konsta M. et al, contains results of retrospective study analyzing clinical (BASDAI, BASFI) and radiographical (BASRI hip, mean joint space width) in 23 patients being treated with infliximab for 6±2,5 years (mean±SD). BASDAI and BASFI improved over time (from 6.3 and 6.9 to 1.67 and 3.3, respectively), while individual BASRI-hip scores at baseline (2.50±0.86, mean±SD) remained unchanged as well as the average width of the whole joint space in these patients (3.59±0.79 mm) was not reduced at end of follow-up. Authors assume that TNF inhibitors are able to inhibit structural progression of hip disease in AS but state that prospective studies with at least 2-years follow-up are required to investigate structural progression of coxitis in AS [17].

The novel TNF alpha inhibitor Simponi® (golimumab) has sophisticatedly been studied in AS in GO-RAISE study. It was shown that golimumab provides clinical and radiological response. At week 24, ASAS 20 response was registered in 55,8% (p<0,001 *vs.* placebo) of patients taking golimumab 50 mg subcutaneously once per 4 weeks. During a 5-years follow-up, response was maintained: BASDAI at week 52 and 256 was 2.6 and 2.2, respectively (baseline BASDAI was 6.6); BASFI at week 52 and 256 was 2.5 and 2.0, respectively (baseline BASFI was 5.0). Spine MRI inflammation index (ASspiMRI-a) decreased from 9,3 at baseline by 5.9 (p=0,011 *vs.* placebo) and 7.1 at week 14 and 104, respectively [18,19,20,21]. Based on data provided by GO-RAISE study, Simponi® (golimumab) has been registered in AS and can be recommended for daily clinical practice in Russia [22]. But patients with coxitis were not included in GO-RAISE study.

In EULAR 2014, the first data from real clinical practice on Simponi® (golimumab) were presented - GO.A.RE.L. (Golimumab in Apulian real-life patients). According to the abstract, 76 patients with axial-SpA has been treated with golimumab and followed up for up to 24 months. Disease activity characteristics are presented in the table:

	BASDAI	ASDAS-CRP

Baseline	5.9	3.9
6 months	2.76	1.6
12 months	2.96	1.9
24 months	2.32	1.5
p	0.0021	NS

These preliminary results confirmed a good effectiveness of golimumab in patients with axial SpA in standard care settings [23]. But patients with coxitis were not included in GO.A.RE.L. study.

1.2 Rationale

Coxitis in AS is inflammation of hip(s) affecting significant number of patients. It is associated with worse function and more expressed axial disease requiring hip replacement at end-stage. Clinical symptoms (pain and affected movement) should be confirmed with imaging (X-ray and MRI). Synovitis and its combination with bone edema and enthesitis are the most frequent MRI manifestations. There are no data on change of these manifestations over time with or without treatment. US imaging can reveal inflammatory changes in hips but there are no data on change of US manifestations over time.

Number of studies dedicated to coxitis treated with TNF alpha inhibitors is very limited: one of them is a retrospective study with 23 patients, two others are prospective but with short follow-up for 12 months (when at least two years are recommended as a follow-up in AS to investigate the radiographic progression) and without conclusive imaging data (MRI and/or US). Simponi® (golimumab) has not been studied in hip disease in AS although it is registered for AS.

Hip disease in ankylosing spondylitis is understudied. This study will provide valuable data on clinical and radiological signs of coxitis in AS at baseline and its clinical and radiological evolution during treatment with TNF alpha inhibitors in daily clinical practice. Collection of radiological data will include US and MRI which have not been widely explored as evaluation of coxitis in AS in previous studies.

Based on data from studies described in the Background section it can be expected that the TNF alpha inhibitor golimumab will be effective clinically and radiologically:

1) it is expected significant improvement of BASFI at 12 months from the baseline;
2) it is expected that there will be no structural progression of coxitis at 12 and 24 months from the baseline expressed as stable BASRI hip index.

2 Objectives

2.1 Primary Objective

- To evaluate change of functional impairment in AS patients with coxitis from baseline to 12 months of therapy with golimumab by BASFI in daily clinical practice

2.2 Secondary Objectives

- To evaluate change of functional impairment in AS patients with coxitis from baseline to 24 months of therapy with golimumab by BASFI in daily clinical practice
- To evaluate change of mobility impairment in AS patients with coxitis from baseline to 12 and 24 months of therapy with golimumab by BASMI in daily clinical practice
- To evaluate change of disease activity in AS patients with coxitis from baseline to 12 and 24 months of therapy with golimumab by ASDAS-CRP in daily clinical practice
- To evaluate change of BASRI-hip from baseline to 12 and 24 months of therapy with golimumab
  To evaluate change of disease activity in AS patients with coxitis from baseline to 12 and 24 months of therapy with golimumab by BASDAI in daily clinical practice

2.3 Exploratory objectives

- To evaluate change of MRI signs of coxitis in AS from baseline to 12 months of therapy with golimumab in daily clinical practice
- To evaluate change of US signs of coxitis in AS from baseline to 12 months of therapy with golimumab
- To evaluate mean clinical scores (BASFI, BASMI, ASDAS-CRP, BASDAI) in subgroups of patients with or without MRI/US signs at baseline and their change at 12 months
- To evaluate occupational status of AS patients with coxitis at 12 and 24 months of therapy with golimumab in daily clinical practice

  Data collected at 12 and 24 months are to be used for statistical analysis. But if these data is unavailable (e.g. due to early drop out before the final follow-up) data collected at 6 and 18 months are to be used according to analysis of last-observation-carried forward (LOCF) to minimize bias – section 8.2.1.

3 METHODOLOGY

3.1 Summary of Study Design

This study is a non-interventional prospective observational cohort study. Patients participating after signing informed consent form will receive treatment and diagnostic procedures according to daily clinical practice conducted by his/her physician.

Visits during the study will include collection of data if already available. There are no procedures that are required as part of this study.

The study is to be conducted in multiple centers across Russia. AS patients with coxitis newly prescribed golimumab during the course of usual clinical care, will be enrolled and followed prospectively for 24 months with data collection at the approximate time points: baseline (pre-treatment) and consequent every 6 months. A time window of approximately ± 6 weeks is envisaged for follow-up visits.

Patients will be screened and selected according to inclusion and exclusion criteria prior to enrollment. The study centers will maintain a list of all screened patients with the reasons for excluding patients being enrolled into the study.

Baseline data will be extracted from medical records (MR), if available at each treatment center. No additional interventional tests or medical procedures such as additional blood samples, X-ray or other technical investigations will be performed as a part of this study. If any data element is not available it will be reported as missing.

At baseline, data on age, gender, occupational status, AS and coxitis symptoms duration, concomitant disease, will be collected according to usual clinical practice.

C-reactive protein (CRP) is usually measured as part of the normal screening for patients prior to the initiation of a biologic agent in clinical practice. The results of this measurements will be collected. No additional blood withdrawals will be necessary for the study. CRP will be collected at baseline and at 6, 12, 18, 24 months if the measurements are available in regular clinical practice. Human leukocyte antigen B27 (HLA-B27) status (i.e. positive or negative) will be collected at baseline if available. Most AS patients will have this test performed as part of the diagnostic work-up in clinical practice.

For disease activity the following instruments recommended for daily clinical practice will be used: BASFI, BASMI, ASDAS-CRP. These scores will be evaluated at baseline and at 6, 12, 18, 24 months.

Radiography of hip joint is used in clinical practice. BASRI hip will be collected at baseline and at 12, 24 months.

MRI (STIR (short tau inversion recovery) sequence and fat-saturated contrast-enhanced T1-weighted sequence) and ultrasonography (US) are used in clinical practice. Usually patients have either US or MRI, but sometimes physician may administer both radiology test if one of them is unsatisfactory as a diagnostic tool. Data of these tests will be collected at baseline and at 6, 12 months.

3.2 Study Population

All patients enrolled must be newly prescribed golimumab per the usual standard of care of the investigator.

In patients who have been prescribed these agents the moment of prescription is normally separated from the moment the agents are administered (e.g. administrative procedures, day-clinic visit to be scheduled, retrieval of the medicine at the pharmacist, etc.). Patients will be enrolled after the decision to treat with golimumab is made, but before the initiation of the newly prescribed medicine, i.e. patients must not have initiated treatment prior to the baseline data collection (enrollment).

Patient's data are to be collected after signing informed consent form and till the end of the study. If patient discontinues participation earlier, the data before discontinuation will be collected.

Patient can withdraw the informed consent form for any reason for any time. Investigator can decide to discontinue participation of patient for safety, lack of efficacy or any other reason.

3.3 Inclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

All patients need to meet all of the following inclusion criteria:

1. Adult patients (>18 years of age) with definite AS (as per modified New York criteria)
2. Coxitis with BASRI-hip score 0-2
3. Newly prescribed golimumab according to usual clinical practice
4. Naïve to anti-TNFs or other biologic agents prior to initiation of golimumab as indicated by the patient's medical records
5. Patient is enrolled after the investigator's decision to treat with golimumab, but before initiation of treatment with golimumab
6. Patient was informed of the benefits and risks of golimumab as per normal practice using the product leaflet
7. Signed informed consent form

3.4 Exclusion Criteria

Patients meeting the following criteria must not be enrolled in the study:

Prior or current use of an anti-TNF or other biologic agents for any disease

1. Any contraindication to golimumab in accordance to the label of Simponi®
2. BASRI-hip score 3-4
3. Any contraindication to MRI, e.g. previous hip joint replacement, heart pace maker.

3.5 Patients Enrollment

The principles of non-interventional studies (NIS) will be used. These principles include the following regarding the enrollment and monitoring of patients:

- Patient population: AS patients with coxitis followed in normal practice, in whom golimumab has been newly prescribed, will be asked to participate in the study. In patients who have been prescribed these agents the moment of prescription is normally separated from the moment the agents are administered (e.g. administrative procedures, day-clinic visit to be scheduled, retrieval of the medicine at the pharmacist, etc.). For the study, the informed consent form (ICF) will be presented at the visit during which the medicine is administered. After signing the ICF those patients agreeing to participate will be followed for approximately 24 months following the initiation of the newly prescribed medicine
- Informed consent form: Patients who have received a prescription for golimumab can be included after signing an ICF and after receiving responses to all his/her questions from the imvestigator proposing participation in the study. As the decision to treat the patient with a medicine of interest in this study falls within routine practice and has to be completed prior to the decision to include the patient in the study, the ICF will not provide any information on potential benefits or risks of the drug prescribed. The patient should have been informed about drug benefits and risks as per normal practice using the drug leaflet with data from actual registered label of Simponi® (golimumab) prior to inclusion in the NIS.

4 Variables and Epidemiological Measurements

4.1 Patient Demographics

The following demographic parameters will be recorded at baseline:

- Age
- Gender
- Weight
- Employment status

4.2 Treatment of golimumab and end of treatment

Data on golimumab usage as well as reasons for discontinuation of treatment will be collected at baseline and at 6, 12, 18, 24 months.

Reasons for discontinuation are withdrawal of the informed consent form by the patient for any reason, decision of the investigator to stop administration of golimumab due to safety concerns and/or due to lack of efficacy.

4.3 Clinical and Behavioral Variables

The following clinical parameters will be recorded:

- AS diagnosis duration at baseline
- Coxitis symptoms duration at baseline
- BASFI at baseline and 6, 12, 18, 24 months
- BASMI at baseline and 6, 12, 18, 24 months
- ASDAS-CRP at baseline and 6, 12, 18, 24 months
- BASDAI at baseline and 6, 12, 18, 24 months
- Radiologic stage of sacroiliitis at baseline
- Hip(s) X-ray imaging (BASRI hip index) at baseline and 12, 24 months
- Hip MRI and/or US at baseline and 6, 12 months
- Concomitant medication at baseline and at 6, 12, 18, 24 months
- Comorbidities at baseline

These parameters are described in more detail in the following sections. It should be noted that clinical variables collected in this non-interventional study are recommended for daily-practice clinical record keeping for the management of AS in Russia. Thus these variables are available for the majority of the AS patients in regular clinical practice and can be collected within locally applicable legal and ethical framework for non-interventional research.

4.3.1 AS diagnosis duration and coxitis symptom duration

AS diagnosis duration is defined as the time since date of first diagnosis of definite AS per modified New York criteria and will be recorded in number of months and years.

Coxitis symptom duration is defined as the time since date of first hip pain symptoms in a patient with AS and will be recorded in number of months and years.

4.3.2 Bath AS Functionality Index (BASFI)

The BASFI is a self-assessment instrument for defining and monitoring functional ability (physical functioning) in patients with AS. Contains 10 items: 8 items concerning activities referring to the functional anatomy of the patients (bending, reaching, changing position, standing, turning, and climbing steps) and 2 items assessing the patients' ability to cope with everyday life.

The BASFI is administered as a patient's self-report questionnaire. Consists of Numeric response scale (0–10) or Visual analog scale (0–10 cm) anchored by adjectival descriptors "easy" and "impossible." Are used to answer the questions which are practical for use in clinical practice. The mean of the 10 individual scales (scores) gives the BASFI score – a value between 0 and 10 with 0 reflecting no functional impairments and 10 reflecting maximal impairment. Numerical response scale is expected to be used by the physicians participating in the study.

The BASFI is a valid measure of physical function in AS patients and has good discrimination between groups and interventions. It is simple and easy touse and score, takes < 3 minutes to complete. The tool was designed for use in AS, but can also be used in the other spondylarthritides.

The BASFI is Endorsed by the Assessment of SpondyloArthritis International Society. The BASFI is the most widely used functional index for assessment of AS patients, primarily in studies of disease impact and in clinical trials. [22, 24]

4.3.3 Bath AS Metrological Index (BASMI)

The BASMI is an instrument that is typically used to assess mobility of spine and hip joints.

The BASMI consists of 5 items which are clinical measures of cervical rotation, tragus to wall distance, lumbar flexion, lumbar side flexion, and intermalleolar distance. Each item is scored from 0 to 10 based on individually defined cut points. Ranges are given as cervical rotation (>85.0° to ≤8.5°), tragus to wall (<10 cm to ≥38 cm), lumbar flexion (>7.0 cm to ≤0.7 cm), lumbar side flexion (>20.0 cm to <1.2 cm), and intermalleolar distance (≥120 cm to <30 cm).

The BASMI score is a sum of the 5 measures. The results can be graded as 0 – normal, 1 – moderate impairment, 2 – severe impairment. Every patient is given two attempts for every movement. The best results out of two is used for the BASMI.

The BASMI is included in the ASAS core sets as the preferred measure of spinal mobility. It has been used in clinical trials of anti–tumor necrosis factor agents in AS patients

The BASMI is valid, reproducible, and easy to perform with minimal training, giving valuable information about spinal mobility due to inflammation or structural damage. It is the measure of choice put forward by ASAS to measure spinal mobility in clinical trials. [22, 24]

4.3.4 ASDAS-CRP

ASDAS (AS Disease Activity Score) is an instrument to measure disease activity in AS based on a composite score.

The score includes patient-reported assessments of back pain, duration of morning stiffness, peripheral joint pain and/or swelling, general well-being, and a serologic marker of inflammation (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]). The ASDAS including CRP has been presented as the preferred version and the one including ESR as the alternative version.

Patient response items and a serologic measure of inflammation are mathematically combined to give the ASDAS. Score ranges from zero (reflecting no disease activity) with the upper end of the scale being determined by the level of the CRP or ESR.

The time for the patient to complete the items is very short (estimated at <1 minute) with only 4 single-item questions. The score is most easily calculated using an online calculator or a hand-held calculator.

The ASDAS has been endorsed by the ASAS. The ASDAS has been validated in several observational cohorts and trial populations. It is emerging as the best measure of disease activity in AS on the basis of including both patient-generated items and objective measures of inflammation and on having, to date, equivalent or superior performance when compared to the BASDAI. [22, 24]

4.3.5 BASDAI

BASDAI (Bath AS Disease Activity Index) is an instrument to measure disease activity in AS based on a composite score.

The index includes patient-reported levels of back pain, fatigue, peripheral joint pain and swelling, localized tenderness, and the duration and severity of morning stiffness.

It contains 6 items with numeric response scales (0–10) or visual analog scales (VAS, 0–10 cm) anchored by adjectival descriptors “none” and “very severe.” Duration of morning stiffness is anchored by a time scale (0–2 or more hours).

The BASDAI has been endorsed by the Assessment of SpondyloArthritis international Society (ASAS) for the measurement of disease activity. The BASDAI has been the most frequently used measure of disease activity in in AS patients. [22, 24]

4.3.6 X-ray imaging of the Hip(s)

Information on hip(s) X-ray will be collected for patients based on availability in the patient charts at baseline and at 12, 24 months. Focus will be to gather information on coxitis on conventional X-rays to determine BASRI-hip score:

0: no change;

1 - suspicious: focal joint space narrowing;

2 - mild: circumferential joint space narrowing >2mm;

3 - moderate: circumferential joint space narrowing ≤ 2mm or bone-on-bone apposition of <2 cm;

4 - severe: bone deformity or bone-on-bone apposition of ≥2 cm.

4.3.7 MRI of hip(s)

Information on hip(s) MRI (STIR (short tau inversion recovery) sequence and fat-saturated contrast-enhanced T1-weighted sequence) will be collected for patients based on availability. If MRI done at screening, information on MRI is not required at baseline.

Information on hip(s) MRI (STIR (short tau inversion recovery) sequence and fat-saturated contrast-enhanced T1-weighted sequence) will be collected for patients based on availability in the patient charts at 6, 12 months to evaluate changes of inflammation parameters.

The following parameters of active inflammation will be determined:

- No lesions suggesting inflammation
- Subchondral bone marrow edema (expressed as Yes or No)
- Joint effusion (expressed as Yes or No)
- Enthesitis at sites where ligaments and tendons are attached to bone in structures adjacent to the hip joint (expressed as Yes or No)
- Fatty degeneration (expressed as Yes or No)
- Change of a parameter from previous examination (Positive change or No change or Negative change)

At the moment, there is no standardized MRI scores available for hips. This is the reason for collecting information on each individual MRI sign of inflammation and for placing change of MRI signs in the Exploratory objectives.

4.3.8 US of hip(s)

Information on hip(s) US will be collected for patients based on availability in the patient charts. If US done at screening, information on US is not be required at baseline.

Information on hip(s) US will be collected for patients based on availability in the patient charts at 6, 12 months to evaluate changes of inflammation parameters.

The following parameters of active inflammation will be determined:

- Joint effusion (expressed as Yes or No)
- Distance between lower margin of femoral neck and lower part of joint capsule expressed in millimeters
- Enthesitis at sites where ligaments and tendons are attached to bone in structures adjacent to the hip joint (expressed as Yes or No)
- Change of enthesitis from previous examination (Positive change or No change or Negative change)

At the moment, there is no standardized US scores available for hips. This is the reason for collecting information on each individual US sign of inflammation and for placing change of US signs in the Exploratory objectives.

4.3.9 Concomitant medications

Data will be captured on medication given for the treatment of AS. These medications include: NSAIDs, disease-modifying antirheumatic drugs (DMARDs) (e.g. Sulfasalazine and methotrexate), corticosteroids, medications for comorbidities and medications for other extra-articular manifestations. For medications, the categories of medications will be recorded.

4.3.10 Comorbidities

Information on comorbidities, which is part of routine medical assessment of AS patients, will be collected at baseline. They will include:

- Inflammatory bowel disease
- Uveitis
- Psoriasis
- Hypertension
- Stroke
- Ischemic heart disease (angina pectoris and/or myocardial infarction)
- Lung Disease
- Asthma
- Chronic obstructive pulmonary disease
- Pulmonary fibrosis
- Renal disease
- Liver disease
- Peptic ulcer disease
- Thyroid disease
- Depression
- Cerebrovascular accident
- Demyelinating disease
- Epilepsy
- Diabetes
- Tuberculosis
- Malignancy
- Mental illness other than depression
- Gastrointestinal disease
- Anemia or other blood disorder

- Fibromyalgia
- Other

4.4 Laboratory Variables

4.4.1 HLA-B27 Genotyping

HLA-genotype will be recorded as HLA-B27 positive or negative. The information will be obtained from the patients' medical records and no additional genetic testing will be required as part of the study.

5 Study Flow Chart

Study period	**Screening**	**Observation**				
Visit Number/ Title	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6
Study Day/Month	Days -28 thru 0	Day 1	Month 6	Month 12	Month 18	Month 24
Scheduling Window	-	-	±6 weeks	±6 weeks	±6 weeks	±6 weeks
Informed Consent	X[a]	X[a]				
Subject Identification Card		X				
Inclusion/Exclusion Criteria	X	X				
Age	X	X				
Gender		X				
Weight		X				
Occupational status		X	X	X	X	X
AS diagnosis duration		X				
Radiographic stage of sacroiliitis		X				
Coxitis symptoms duration		X				
Golimumab administration registration		X	X	X	X	X
BASFI		X	X	X	X	X
BASMI		X	X	X	X	X
ASDAS-CRP		X	X	X	X	X
BASDAI		X	X	X	X	X
BASRI-hip	X	X[c]		X		X
MRI signs	X[b]	X[c]	X	X		
US signs	X[b]	X[c]	X	X		
CRP		X	X	X	X	X
HLA-B27		X				
Comorbidities	X	X				
Concomitant Medications		X	X	X	X	X
Adverse Events		X	X	X	X	X

a - Informed consents form is provided after the treating physician has made the decision to prescribe golimumab but before the patient receives the treatment
b – Coxitis can be confirmed with MRI and/or US at Screening
c – If Hip X-rays and MRI/US done at screening, information on Hip X-ray and MRI/US is not required at baseline

6 STUDY PROCEDURES

The Study Diagram in Section 5 summarizes the study procedures to be performed at each visit. Individual study 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 Sponsor for reasons related to subject safety.

6.1 Study Procedures

The Study Diagram in Section 5 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below.

6.1.1. Administrative procedures

6.1.1.1 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 study.

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 study. 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 study and the study 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.

6.1.2. Other Procedures

6.1.2.1. Withdrawal/Discontinuation

The patient may withdraw his/her consent to participate in the study at any time for any reason. This decision will not have any consequences for his/her future medical care.

The investigator may exclude a patient from the study at any time if he/she finds that continuation of participation in the study might be harmful or does not meet interests of the patient: for safety, lack of efficacy or any other reason.

The sponsor may stop the study at any time. In such case, all investigators will be informed in advance.

6.1.2.2 Data Collection

Data will be collected from multiple centers. Based on the protocol, a CRF will be developed for data collection. Each local center will be asked to enter the data into the CRFs. All the data entered in the CRF will be entered into a single database stored centrally and analyzed.

6.1.2.3 Interim Statistical Analysis

Interim Statistical Analysis will be performed when at least 18 patients recruited are observed and have their tests done at 12 months.

6.1.2.4 Central collection and evaluation of X-ray, MR Images and US protocols

Radiographs, MR images and US protocols will be collected and analyzed centrally in the Rheumatology Research Institute after being evaluated by the radiologists and rheumatologists of the investigational sites.

Central collection and evaluation will be performed when at least 18 patients recruited are observed and have their tests done at 12 and 24 months.

Central collection of images will not interfere with daily clinical practice as it will take place after local evaluation.

6.1.3 Clinical Procedures/Assessments

6.1.3.1. Collection of Demographic data.

The demographic parameters including age, gender, weight, employment status will be recorded at baseline.

6.1.3.2. Duration of AS diagnosis and coxitis symptoms.

Time from AS diagnosis and from the beginning coxitis symptoms will be recorded at baseline.

6.1.3.3. Radiographic stage of sacroiliitis

Radiological stage of sacroiliitis (I, II, III, IV) will be recorded at baseline.

6.1.3.4. Golimumab administration registration.

Data on golimumab usage as well as reasons for discontinuation of treatment will be collected at baseline and at 6, 12, 18, 24 months.

Reasons for discontinuation are withdrawal of the informed consent form by the patient for any reason, decision of the investigator to stop administration of golimumab due to safety concerns and/or due to lack of efficacy.

6.1.3.5. BASFI

Level of BASFI (Bath AS Functionality Index) at baseline and at 6, 12, 18, 24 months.

6.1.3.6. BASMI

Level of BASMI (Bath AS Metrological Index) will be recorded at baseline and at 6, 12,18, 24 months.

6.1.3.7. ASDAS-CRP

Level of ASDAS-CRP will be recorded at baseline and at 6, 12, 18, 24 months.

6.1.3.8. BASDAI

Level of BASDAI will be recorded at baseline and at 6, 12, 18, 24 months.

6.1.3.9. BASRI-hip

BASRI-hip score determined based on hip(s) conventional X-ray will be recorded at screening as one of the inclusion criterion, at baseline and at 12, 24 months.

6.1.3.10. Hip(s) MRI

Information on hip(s) MRI (STIR (short tau inversion recovery) sequence and fat-saturated contrast-enhanced T1-weighted sequence) will be recorded at screening as one of the inclusion criterion (confirmation of coxitis) or at baseline and at 12 months.

6.1.3.11. Hip(s) US

Information on hip(s) US will be recorded at screening as one of the inclusion criterion (confirmation of coxitis) or at baseline and at 6, 12 months.

6.1.3.12. Concomitant medications

Information on medication (name and category) given for the treatment of AS will be recorded at baseline and at 6, 12, 18, 24 months.

6.1.3.13. Comorbidities

Information on comorbidities, which is part of routine medical assessment of AS patients, will be recorded at baseline.

6.1.4 Laboratory Procedures/Assessments

6.1.4.1. HLA-B27 Genotyping

HLA-genotype will be recorded as HLA-B27 positive or negative at baseline. This information will be obtained from the patients' medical records.

6.1.4.2. C-reactive protein.

Level of CRP will be recorded in mg/l at baseline and at 6, 12, 18, 24 months.

7 Safety Reporting and Related Procedures

Introduction

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

7.1 Adverse Event Reporting

7.1.1 INVESTIGATOR RESPONSIBILITY:

If the investigator becomes aware of any serious adverse event (SAE), including death due to any cause, or non-serious adverse reaction (NSAR) following the use of Simponi®, or any other MSD product, the

event must be reported according to Table 1. The investigator must evaluate each SAE for causality and record causality on the AE form for each event reported.

Similarly, pre-specified Health Outcomes of Interest (HOIs) that meet criteria for SAE/NSAR, special situations, and any spontaneously reported AEs must be reported according to Table 1.

Table 1: AE Reporting Timeframes and Process for Investigators

EVENT TYPE	**INVESTIGATOR TIME FRAME**
	Investigator to MSD [1], [2]
• SAE, regardless of causality • Serious pre-specified Health Outcome of Interest (HOI) • Serious Special Situation, regardless of causality	24 hours from receipt
• Non-serious Adverse Reaction (NSAR) • Non-Serious pre-specified HOI if NSAR • Non-serious Special Situation, regardless of causality	10 calendar days from receipt
• Spontaneously reported adverse events for MSD products-submit using above timeframes • If the investigator elects to submit AEs for **non-MSD products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations	
Follow-up to any event-submit using above timeframes	
[1] AE reports from investigators must be transmitted via fax, secure email (if available), or entered directly into vendor's electronic data collection (EDC) platform, if utilized. **[2] Investigator to Merck:** Applies to studies that do not have a vendor managing AEs.	

Submitting AE reports to Merck Global Safety: All AEs must be submitted to the local MSD Russia Office via FAX # +7-495-228-3239 and email DPOC.Russia@merck.com**, in English using an AE form (attached) for reporting to worldwide regulatory agencies as appropriate. Then, from the local MSD Russia Office, the AE form is to be submitted to the PAEL Mailbox within 1 business day.**

Enhanced Malignancy Reporting

All malignancies occurring in patients 30 years of age or younger who received Golimumab must be reported to sponsor or designee within 24 hours using the same method described in the protocol for SAE reporting.

In addition, there will be follow-up from the Sponsor or designee (CRO) to the Investigator using a dedicated Malignancy Follow-up Questionnaire that needs to be completed by the Investigator and submitted to the Sponsor or designee within 2 weeks of receipt, using the same method described above for SAE reporting. The Investigator must make at least 2 attempts to contact the patient or guardian to complete the Malignancy Follow-up Questionnaire. If the attempts are not successful, the reason for

each unsuccessful attempt must be documented (e.g., patient lost-to-follow-up, patient refuses to supply the additional information, etc.).

The Sponsor or designee (CRO) will review the study AE database for possible premalignant conditions twice a year. If any are reported, the Sponsor or designee will contact the Investigator with a dedicated follow-up request that needs to be completed. In case a pre-malignant condition has progressed to a malignancy, the Investigator will need to complete the Malignancy Follow-Up Questionnaire.

7.1.2 STUDY REPORT

The final study report, and any planned interim analysis, will include aggregate listings of all events collected for Simponi® and will be provided to regulatory agencies by the sponsor as required.

7.1.3 PERIODIC SAFETY UPDATE REPORTS

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

7.2 DEFINITIONS

7.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. 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 product, is also an adverse event.

7.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

7.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

7.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 7.2.3.

7.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent

7.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are pre-specified clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnosis, treatment or procedures. Examples of HOIs include syncope or hypoglycaemia collected as study endpoints. HOIs must be assessed as part of AE collection and may meet criteria for AE reporting. Specifically, the investigator must assess each HOI for serious criteria and causality. If the HOI meets criteria specified in the protocol for AE reporting, then it must be reported as such.

7.2.7 Sponsor's product

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

7.2.8 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): 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.

8 Statistical Analysis Plan

8.1 Statistical Methods

Quantitative variables will be tested for normal distribution using the Shapiro-Wilk test. The hypothesis of equality of variances will be tested using Levene's test. Quantitative variables matching a normal distribution will be described in terms of the mean ± standard deviation, and values outside of the normal distribution as medians, 25% and 75% quartiles. Qualitative variables will be presented in the form of percentages of the absolute value N.

Quantitative variables that meet normal distribution criteria and equality of variances will be compared using Student's paired t-criteria. The Wilcoxon signed rank will be used to compare quantitative variables that do not meet normal distribution or equality of variance criteria.

Comparative analysis of qualitative variables will use a Chi-square test. If at least one of the absolute rates is less than 5, an exact two-sided Fischer's test is to be used.

Descriptive analysis will be used for the following:

1) description of the study population at the baseline;
2) data completeness;
3) distributions of reasons for discontinuation for the study population;
4) attrition of the study population;
5) durability and variability of responses.

Descriptive analysis is to be done via completion of standard tables and creation of graphical representation of each patient over time as his/her own line connecting each data point.

8.1.1 Interim Statistical Analysis

Interim Statistical Analysis will be performed when at least 18 patients recruited are observed and have their tests done at 12 months.

8.1.2 Primary Objective: Calculation of Epidemiological Measure of Interest

- Change of BASFI score from baseline to 12 months of therapy

8.1.3 Secondary Objectives: Calculation of Epidemiological Measures of Interest

- Change of BASFI score from baseline to 24 months of therapy
- Change of BASMI score from baseline to 12 and 24 months of therapy
- Change of ASDAS-CRP score from baseline to 12 and 24 months of therapy
- Change of BASDAI score from baseline to 12 and 24 months of therapy
- Change of BASRI-hip score from baseline to 12 and 24 months of therapy

8.1.4 Exploratory Objectives: Calculation of Epidemiological Measures of Interest

- Change of MRI signs from baseline to 6 and 12 months of therapy (will be presented descriptively)
- Change of US signs from baseline to 6 and 12 months of therapy (will be presented descriptively)
- Mean clinical scores (BASFI, BASMI, ASDAS-CRP, BASDAI) in subgroups of patients with or without MRI/US signs at baseline and their change at 12 months
- Change of employment status of patients at 12 and 24 months of therapy (will be presented descriptively)

8.2 Bias

8.2.1 Methods to Minimize Bias

Potential sources of bias are errors in recruitment, early drop out of patients from the study, deviation of administration of golimumab from the label of Simponi®.

Bias from errors in recruitment of patients can be reduced with rigorous adherence to inclusion/exclusion criteria when recruiting patients for the study.

Bias from early drop out of patients from the study can be reduced with Interim Statistical Analysis which is to be performed when at least 18 patients recruited are observed and have their tests done at 12 months. Also, patients who drop out before final follow up visit are planned to enter an analysis of last-observation-carried forward (LOCF). Data recorded on the last visits of patients will contribute to the analysis.

Deviation from the label of Simponi® are determined as delays of injections for more than 2 weeks at least 2 times per year. Data from patients with such delays are to be analyzed separately.

8.2.2 Limitations

In this non-interventional study the quality of the data is important. Therefore, it is important for the sponsor or designee to monitor data completion and perform quality checks during the course of the study. To minimize missing data, a set of core variables is required to be available at enrollment as part of inclusion criteria.

This study will collect data on patients being treated in real clinical Rheumatology practice. It is expected that the number of patients dropping out before completion of the whole course of observation will be about 30%. To minimize this limitation, the study will enroll 39 patients to ensure that the number of subjects entering the analysis *Per Protocol* will be enough (27 subjects). In addition, secondary analyses will evaluate data on completers vs patients dropping out before completion separately.

The potential issue of missing data is limitation of the study. To minimize this limitation, patients with missing data are planned to enter the analysis of LOCF. Data recorded on the last visits of patients or the visit after the missing one will contribute to the analysis.

8.3 Sample Size and Power Calculations

Sample size calculation is based on data from GO-RAISE registrational study in which golimumab was evaluated in patients with AS [18-21]. The baseline BASFI was 5.0 which changed by mean (± SD, standard deviation) −2.5 (± 2.12) at week 52 (approximately 12 months) [19].

Sample size formula evaluation is $n = f(\alpha, \beta/2) \times 2 \times \sigma^2/d^2$ where:

n is sample size;

α is type 1 error = 5%;

β is type 2 error = 10%;

σ is standard deviation;

d is equivalents limit;

$f(\alpha, \beta) = [\Phi\text{-}1(\alpha) + \Phi\text{-}1(\beta)]^2$ where Φ is cumulative distribution function for the normal distribution.

Power of the study is 90% with formula evaluation P = 1-β where:

P is power;

β is type 2 error = 10%.

Thus, the analysis of the data shows that the minimum necessary sample size should be at least 18 patients to show a statistically significant change of BASFI from baseline to 12 months.

On this basis and considering that the dropout rate over the two years of the study is expected to be about 30% (ranging from 21% in a randomized controlled study [19] to 37% in real clinical practice [25]), it is decided that the necessary number of patients to be included into the study should be 39 individuals. It is expected that at least 27 patients will be included in the patient set completing the study.

9 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Confidentiality

9.1.1 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 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 study 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.

9.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or Institutional Review Board/Independent Ethics Committee (IRB/IEC), may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study 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 study in accordance with all applicable privacy laws, rules and regulations.

9.1.3 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 study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;

- curriculum vitae or other summary of qualifications and credentials; and
- 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 agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

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

9.2 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.

9.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-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 study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable local laws, rules and regulations;

and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. 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 study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. 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. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study 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 study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study 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 sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. 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 study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

9.4 Compliance with Study 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 study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, www.clinicaltrials.gov. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and 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 study or its results to the Clinical Trials Data Bank.

9.5 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 studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

9.6 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.

For an outsourced study the institutional policies of the vendor should be followed for development of data management plans. However, the vendor should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study

10 List of abbreviations

AE	*Adverse event*
AR	*Adverse reaction*
AS	*Ankylosing Spondylitis*
ASDAS	*Ankylosing Spondylitis Disease Activity Score*
BASDAI	*Bath Ankylosing Spondylitis Activity Index*
BASFI	*Bath Ankylosing Spondylitis Functionality Index*
BASMI	*Bath Ankylosing Metrological Index*
BASRI	*Bath Ankylosing Radiology Index*
CRF	*Clinical Registration Form*
CRP	*C-reactive protein*

CSR	*Clinical Study Report*
DMARD	*Disease Modifying Anti-Rheumatic Drugs*
DSUR	*Development Safety Update Report*
ERC	*Ethic Review Committee*
FDAAA	*Food and Drug Administration Amendments Act*
FDAMA	*Food and Drug Administration Modernization Act*
HLA B27	*Human Leukocyte Antigen B27*
HOI	*Health Outcomes of Interest*
ICF	*Informed Consent Form*
IEC	*Independent Ethics Committee*
IRB	*Independent Review Board*
LOCF	*Last Observation Carried Forward*
MAH	*Market Authorization Holder*
MRI	*Magnetic Resonance Imaging*
NIS	*Non-Interventional Study*
NSAR	*Non-Serious Adverse Reaction*
Protocol CI	*National Principal Coordinator*
PSUR	*Periodic Safety Update Report*
SAE	*Serious Adverse Event*
STIR	*Short Tau Inversion Recovery*
TNF	*Tumor Necrosis Factor*
US	*Ultrasound*

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12 SIGNATURES

Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

Investigator

I agree to conduct this study 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); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology 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 experiences as defined in Section 7 – Safety Reporting and Related Procedures. 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 study 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	SIGNATURE	DATE
_____	_____	_____