A MULTICENTER OPEN-LABEL STUDY OF ETANERCEPT WITHDRAWAL AND RETREATMENT IN SUBJECTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS WHO ACHIEVED ADEQUATE 24 WEEK RESPONSE

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PROTOCOL SUMMARY

Background and Rationale

Axial Spondyloarthritis (ax SpA) is a chronic disease whose most devastating clinical manifestation is the loss of mobility. The Assessment of SpondyloArthritis international Society (ASAS) recently created a classification system for ax SpA based on whether patients meet clinical criteria or imaging criteria. Patients meeting the ASAS criteria for ax SpA without evidence of sacroiliitis on x-ray are classified as having non-radiographic axial spondyloarthritis (nr-ax SpA). In several recent studies, anti-tumor necrosis factor (TNF) agents, including etanercept (ETN), demonstrated efficacy in patients with nr-ax SpA. However, additional long-term data are needed, and little is known about the effects of etanercept withdrawal in subjects who have achieved a significant clinical response.

In a small trial (ESTHER)[3] of etanercept-treated patients who had achieved an ASAS partial remission after 48 weeks of etanercept treatment, 13 with nr-ax SpAwere withdrawn from therapy. The flare rate in year 2 was 69%, and the mean time to flare was 24.4 weeks**.** Retreatment with etanercept showed an improvement in all clinical (Bath Ankylosiong Spondylitis Disease Activity Index [BASDAI], Ankylosing spondylitis Disease Activity Score [ASDAS], C-reactive protein [CRP]) and imaging (magnetic resonance imaging [MRI] sacroiliac joint [SIJ], MRI spine, MRI enthesitis) variables. Only a portion of the subjects re-established remission status (56% ASAS remission; 44% MRI remission; 33% MRI plus ASAS remission).

The proposed study is a followup of this small pilot study that will further our understanding of the benefits and risks of ETN withdrawal in patients who have achieved a significant clinical response. Much is known already from B1801031 about relapse rates of those achieving remission and continuing on ETN, therefore an open-label study estimating the relapse rates in such patients withdrawn from ETN is planned.

Objectives and Endpoints

- The primary objective of this study is to estimate the proportion of subjects who flare within 40 weeks following withdrawal of ETN in subjects who have achieved inactive disease (defined as ASDAS less than 1.3). The key secondary objective is to measure time to flare after withdrawal of ETN.

- The primary endpoint for this study is occurrence of flare within 40 weeks (defined as an ASDAS greater than or equal to 2.1) following withdrawal of ETN. The key secondary endpoint is the time to flare after withdrawal of ETN.

Study Design

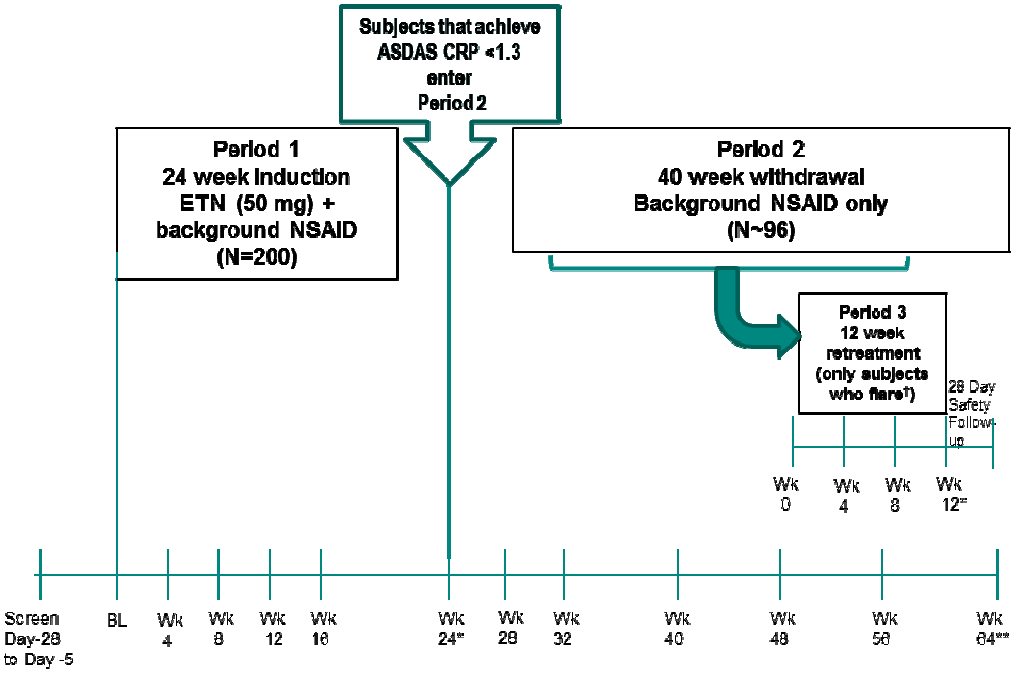
This multicenter, open-label, three period study will evaluate withdrawal and retreatment of ETN in subjects with nr-ax SpA who achieved an adequate response, as measured by Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (ASDAS CRP) less than 1.3 (inactive disease) following 24 weeks of treatment. The study is expected to randomize

approximately 200 subjects in Period 1, in order to have approximately 96 subjects qualify for Period 2.

Period 1 is an open-label, 24-week period in which all eligible subjects will be enrolled and treated with ETN 50 mg once weekly plus a stable background non-steroidal anti-inflammatory drug (NSAID) at the optimal tolerated anti-inflammatory dosage. The target for this period is therapeutic response defined as achieving ASDAS CRP less than 1.3 at Week 24. Subjects who do not achieve ASDAS CRP less than 1.3 will not enter Period 2 and will complete the study at the Week 28 day follow-up phone call/visit.

Period 2 is a 40-week withdrawal period where subjects will discontinue ETN following the Week 24 dose, yet maintain the background NSAID. If the subject has not flared by the Week 64 visit, their participation in the study is complete. Subjects who flare (defined as an Ankylosing Spondylitis Disease Activity Score Erythrocyte Sedimentation Rate [ASDAS ESR] greater than or equal to 2.1) during Period 2 will enter a retreatment period (Period 3) and receive approximately 12 weekly doses of open-label ETN.

Study Schematic



†Flare is defined as ASDAS ESR ≥2.1
*The follow-up visit is only required 28 days following the last dose of IP. This will occur either at the end of Period 1 (for subjects that don't qualify for Period 2) or at the end of Period 3 (for subjects who flare and require retreatment).
**Subjects who flare at Week 64 will receive 12 weeks of OL ETN and will have their final study visit at Week 76 and their follow-up visit 28 days later.

Study Treatments

For the purposes of this study, investigational product will be defined as ETN. The sponsor will supply ETN. Investigational product will be administered only to subjects who have provided informed consent. Once a subject's participation in the study has ended, ETN will no longer be supplied to the subject by the investigative site and/or sponsor.

Statistical Method

The primary endpoint, the proportion of subjects who flare (ASDAS ESR greater than or equal to 2.1) in Period 2 will be summarized descriptively as the percent with flare with 95% confidence intervals. This estimate will include all subjects who qualify for the retreatment interval and have at least one evaluation after treatment is withdrawn.

For the key secondary endpoint of time to flare, descriptive statistics will include median time to flare and 95% confidence intervals using the Kaplan-Meier approach.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Study Interval	**Screen**	**Period 1 Induction**						**Period 2 Withdrawal**						**Period 3 Retreatment** *(If subject flares during Period 2)*				**Follow-up**[d]	**Early DC**
Study Week	**Screen**[b]	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 24**	**Wk 28**[c]	**Wk 32**	**Wk 40**	**Wk 48**	**Wk 56**	**Wk 64**	**Wk R0**[e]	**Wk R4**	**Wk R8**	**Wk R12**	**28 Days After Last Dose**	**Early DC**[f]
Visit Window[a] **(Days)**	**-28 to -5**		**±4**	**±4**	**±4**	**±4**	**±7**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±4**	**±4**	**±4**	**±4**		
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**R1**	**R2**	**R3**	**R4**	**14**	
Informed Consent	X																		
Review Eligibility Criteria	X	X						X[g]											
Demographics	X																		
Medical History[h]	X																		
Chest Radiograph /TB Testing[i]	X																		
Contraception Check[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Safety Assessments																			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Height/Weight	X						X						X				X		X
Physical Exam	X						X						X				X		X
IBD, Psoriasis, Uveitis Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Events[k]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Laboratory																			
Hematology/Blood Chemistry[l]	X	X			X		X						X	X			X		X
Urinalysis[l]	X												X						
Pregnancy Test[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Study Interval	Screen	Period 1 Induction						Period 2 Withdrawal						Period 3 Retreatment *(If subject flares during Period 2)*				Follow-up[d]	Early DC
Study Week	**Screen[b]**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 24**	**Wk 28[c]**	**Wk 32**	**Wk 40**	**Wk 48**	**Wk 56**	**Wk 64**	**Wk R0[e]**	**Wk R4**	**Wk R8**	**Wk R12**	**28 Days After Last Dose**	**Early DC[f]**
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Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**R1**	**R2**	**R3**	**R4**	**14**	
HLA B27	X																		
hsCRP[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ESR[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Banked Specimen Prep D1		X																	
Banked Specimen Prep B1 and Prep R1		X			X		X												X[n]
Hepatitis B, Hepatitis C Testing	X																		
Imaging																			
SIJ X-ray[o]	X																		
MRI Spine & SIJ[p]	X						X				X		X	X[q]			X		X
Investigational Product																			
Open-Label Treatment Assignment (First dose administered by study personnel)		X																	
Dispense Investigational Product (IP)		X	X	X	X	X								X	X	X			
Collect IP & Accountability[r]			X	X	X	X	X								X	X	X		X
Dispense IP Diary Card		X	X	X	X	X								X	X	X			
Collect & Review IP Diary Card			X	X	X	X	X								X	X	X		X
Prior/Concomitant Treatments	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→[s]	→[s]
Efficacy Assessments																			
Joint Assessment[t,u]		X			X		X		X		X		X	X			X		X
Physician Global Assessment[u] (PGA)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Study Interval	Screen	Period 1 Induction						Period 2 Withdrawal						Period 3 Retreatment *(If subject flares during Period 2)*				Follow-up[d]	Early DC
Study Week	**Screen[b]**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 24**	**Wk 28[c]**	**Wk 32**	**Wk 40**	**Wk 48**	**Wk 56**	**Wk 64**	**Wk R0[e]**	**Wk R4**	**Wk R8**	**Wk R12**	**28 Days After Last Dose**	**Early DC[f]**
Visit Window[a] (Days)	**-28 to -5**		**±4**	**±4**	**±4**	**±4**	**±7**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±4**	**±4**	**±4**	**±4**		
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**R1**	**R2**	**R3**	**R4**	**14**	
Health Outcome Assessments																			
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
BASFI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Subject Assessment of Disease Activity (SADA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Subject Nocturnal and Total Back Pain VAS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
BAS-G		X			X		X		X		X		X	X			X		X
EQ-5D		X			X		X		X		X		X	X			X		X
SF-36		X			X		X		X		X		X	X			X		X
WPAI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Abbreviations: BL=baseline; IBD = inflammatory bowel disease, IP = investigational product; TB=tuberculosis; → = ongoing/continuous event; HLA-B27 = human leucocyte antigen B27; hsCRP = high sensitivity c-reactive protein; SIJ = sacroiliac joint; MRI = magnetic resonance imaging; BASDAI = Bath Ankylosing Spondylitis Disease Activity Score; BASFI = Bath Ankylosing Spondylitis Functional Index; BAS-G = Bath Ankylosing Spondylitis Patient Global Assessment Score; EQ-5D = EuroQol EG-5D Health State Profile; SF-36 = 36-Item Short-Form Health Survey; WPAI = Work Productivity and Activity Impairment Questionnaire .

a. Day relative to start of study treatment (Day 1).

b. Screening visit should occur within 4 weeks (28 days) of BL visit but no less than 5 days before BL visit. The screening period may be extended up to 42 days if repeat imaging is required or when tuberculosis prophylactic therapy is started during the screening period.

c. ASDAS CRP will be calculated at the Week 24 visit, which will determine if subjects are eligible to enter Period 2. If the ASDAS CRP is <1.3 at Week 24, subjects will return to the site at Week 28 to continue with the Period 2 procedures. If the Week 24 ASDAS CRP is ≥1.3, the subject should be notified by phone that their participation in the study is complete. A follow-up call will be conducted in place of the Week 28 visit to assess new and ongoing adverse events and medication taken to treat them since the last dose of investigational product.

d. Follow-up: For subjects who discontinue the study during Period 1, or enter Period 2 and discontinue from the study ***before*** the Week 28 visit, or subjects who enter Period 3, there will be a follow-up telephone call to assess new and ongoing adverse events and the medications taken to treat them. This call will be approximately 28 days after the last dose of IP. No follow-up is needed if subjects enter Period 2 and do not experience a flare. If required by local regulations, the follow-up visit may be conducted at the study site.

e. The first visit of the Retreatment period (Period 3) may occur at the same time as a regularly scheduled visit during Period 2 or it may occur as an unscheduled visit.
f. Early discontinuation: If a subject discontinues from the study prior to the last visit of any period every effort should be made during the early discontinuation visit to perform all procedures, laboratory assessments (including biomarker samples), questionnaires and obtain the MRI.
g. Subjects must complete Period 1 and achieve ASDAS CRP <1.3 at the Week 24 visit in order to be eligible to enter Period 2.
h. Medical history evaluation includes: general medical history, disease specific medical history, evaluation of background medication and family medical history.
i. Chest x-ray and TB testing: local country guidelines should be followed for appropriate screening and prophylaxis in the setting of anti-TNF therapy, including a chest radiograph and objective TB testing, such as purified protein derivative (PPD) or Quantiferon. If the subject is known to be PPD positive, the test need not be repeated if documentation is available to show the subject meets local criteria for anti-TNF therapy and has not had active TB in the last 2 years. If the subject has a documented negative PPD or Quantiferon test within 3 months prior to the screening visit, the test need not be repeated.
j. Ensure that the subject is using the appropriate contraception as detailed in Section 4.5 of the protocol and document in the source notes.
k. Adverse Events both serious and non-serious should be recorded on the case report form (CRF) from the first dose of IP through the subject's last visit. In addition, serious adverse events (SAE) must be reported to Pfizer from the time that the subject provides informed consent.
l. Hematology/Blood chemistry/Urinalysis/hsCRP/ESR: These laboratory tests do not need to be repeated at the baseline visit (Visit 2) if they were completed at the screening visit ≤14 days before baseline. Should the laboratory results subsequently show that the subject does not meet the inclusion/exclusion criteria and this is confirmed upon retest, the subject must be withdrawn from the study at that time.
m. Pregnancy Testing: Women of child-bearing potential must have a negative serum pregnancy test at the screening and baseline visit. Additionally they must have a confirmed negative urine pregnancy test prior to the first dose of investigational product at the baseline visit. The pregnancy test(s) may be repeated at the discretion of the investigator if the subject misses a menses, or if the potential of pregnancy is otherwise suspected. Women of this group must be willing to use a highly effective contraceptive method. Pregnancy test may also be repeated as per request of institutional review board (IRB)/ethics committees (ECs) or if required by local regulations.
n. Collection of the Prep B1 and Prep R1 banked specimens are only completed at this time point if the subject discontinues early during Period 1.
o. Screening SIJ x-ray is the first imaging procedure that is performed. The reading to assess eligibility is performed by a central imaging vendor. If the SIJ x-ray must be repeated, the screening period may be extended to 6 weeks. Results of historical x-rays of the SIJ that have been obtained within 4 months prior (12 months in Germany only) to the screening visit could be used in lieu of performing screening x-rays. If historical x-rays are used, the original films, or a copy, must be on site and a copy should be sent to the central reader. If the results are considered unevaluable by the central reader, the x-ray must be performed during screening. The central reader must be able to determine the presence of and/or the degree of sacroiliitis. If the results are considered unevaluable by the central reader and the subject is unable to have a repeat x-ray due to the regulations issued by the German Federation of Radiation Council, the subject will be considered a screen failure.
p. MRI should only be done after eligibility is determined by SIJ x-ray. The MRI is performed during the screening period. If the MRI must be repeated, the screening period may be extended to 6 weeks.
q. If a subject experiences a flare in <8 weeks since their previous MRI, there is no need to conduct the MRI at the first retreatment visit.
r. Drug accountability is done at each clinical visit during Period 1 and Period 3 to assess compliance with the protocol dosing regimen.
s. Record medications taken to treat any new or ongoing adverse events/serious adverse events that occurred since the last study visit.
t. Joint Assessment includes: Tender and swollen joint count, dactylitis and enthesitis (Maastricht Anklyosing Spondylitis Enthesitis Score [MASES]) evaluation.
u. It is recommended that the same qualified personnel complete these assessments at each visit.

1. INTRODUCTION

Spondyloarthritis (SpA) is a chronic, inflammatory disease characterized by joint inflammation, enthesitis and certain extra-articular manifestations in organs such as the eyes, skin, and cardiovascular system. It involves preferentially either the axial skeleton (axial SpA) or peripheral joints (peripheral SpA). The etiology of SpA is unknown but may involve the interaction of genetic and environmental factors. It is currently believed that axial SpA begins in the absence of the classic radiographic features which define ankylosing spondylitis (AS). This beginning disease state is referred to as non-radiographic axSpA. Ankylosing Spondylitis can cause permanent structural changes leading to progressive disability impacting the quality of life. It is unknown if treatment of nr-ax SpA will prevent progression to AS, but SpA at all stages represents significant health and socioeconomic burdens for the individual patient and society.[1]

The use of MRI and improved radiographic technology has generated new interest in initiating early intervention and treatment of axial SpA before significant, irreversible damage has occurred. Early diagnosis could potentially lead to earlier intervention with the goal of disease activity control, maintenance of physical function, and optimization of quality of life.

The name, title, address and telephone number(s) of the sponsor's medical expert for the trial document are provided in the study reference manual.

1.1. Mechanism of Action/Indication

Etanercept (ETN) is a recombinant human necrosis factor alpha (TNFα) soluble receptor that blocks TNFα binding to cell surface receptors and initiation of intracellular signaling. ETN is approved for the treatment of AS and nr-ax SpA.

1.2. Background and Rationale

Axial Spondyloarthritis (ax SpA) is a chronic disease whose most devastating clinical manifestation is the loss of mobility. Commonly ax SpA progresses from sacral inflammation to progressive spine ankylosis over time. Since patients with early disease may not show x-ray abnormalities related to SpA, new technologies such as MRI are increasingly being utilized. The Assessment of SpondyloArthritis international Society (ASAS) recently created a classification system for ax SpA based on whether patients meet clinical criteria or imaging criteria. Patients meeting the ASAS criteria for ax SpA without evidence of sacroiliitis on x-ray are classified as having nr-ax SpA. With the advent of new consensus based criteria that allow earlier identification of patients with ax SpA, before significant x-ray abnormalities develop,[3] earlier therapeutic intervention may potentially impact the natural history of the disease by shutting down early inflammation, as this may be the forerunner of irreversible bony ankylosis.[4] In several recent studies, anti-tumor necrosis factor (TNF) agents, including ETN, demonstrated efficacy in patients with nr-ax SpA. However, additional long-term data are needed, and little is known about the effects of ETN withdrawal in subjects who have achieved a significant clinical response.

In a small trial (ESTHER)[3] of etanercept-treated patients who had achieved an ASAS partial remission after 48 weeks of etanercept treatment, 13 with nr-ax SpAwere withdrawn from therapy. The flare rate in year 2 was 69%, and the mean time to flare was 24.4 weeks **.** Retreatment with etanercept showed an improvement in all clinical (BASDAI, ASDAS, CRP) and imaging (MRI SIJ, MRI spine, MRI enthesitis) variables. Only a portion of the subjects re-established remission status (56% ASAS remission; 44% MRI remission; 33% MRI plus ASAS remission).

In study B1801031, patients with nr-ax SpA given a 12 week course of ETN had significantly reduced clinical signs and symptoms as well as SIJ and spinal inflammation on MRI as compared to patients receiving placebo.[2] An open-label extension is currently underway to examine long-term efficacy and safety.

Little is known about the effects of ETN withdrawal in subjects who have achieved a significant clinical response. A small study with a mixture of AS and nr-ax SpA patients having achieved a significant clinical response showed that approximately 75-80% of subjects had relapses after 2 years. After retreatment, only about a third recovered the level of clinical response they had achieved at the time of withdrawal.[3] However, firm conclusions regarding the effects of withdrawal and retreatment could not be drawn due to the low numbers of patients in the study.

The proposed study is a followup of this small pilot study that will further our understanding of the benefits and risks of ETN withdrawal in patients who have achieved a significant clinical response. Much is known already from B1801031 about relapse rates of those achieving remission and continuing on ETN, therefore an open-label study estimating the relapse rates in such patients withdrawn from ETN is planned.

Overall, the benefits of ETN administration in patients with nr-ax SpA are expected to include reduced disease activity, including less pain, reduced inflammation of the SIJ, and improved physical function. Based on the safety experience from the B1801031 study combined with the long-term safety data and post-marketing safety experience in AS, an acceptable safety profile is expected in nr-ax SpA patients treated with ETN. Consequently, the risk-benefit balance of ETN for the treatment of nr-ax SpA is considered to be positive in patients who have high disease activity despite treatment with NSAIDs. Furthermore, the risk benefit may be more favorable in patients with objective evidence of inflammation, ie, those who have high CRP and/or MRI inflammation. The proposed study will further our understanding of the benefits and risks of ETN withdrawal in patients who have achieved a significant clinical response.

The dosing regimen chosen for this study is in agreement with the recommended dosage for AS in adults ages 18 or older.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To estimate the proportion of subjects who flare within 40 weeks following withdrawal of ETN in subjects who have achieved ASDAS CRP less than 1.3 (inactive disease).

2.1.2. Secondary Objectives

- To estimate time to flare after withdrawal of ETN, and to compare it to that in subjects from B1801031 who continued ETN therapy.
- To estimate the efficacy of 12 weeks of retreatment in subjects who experience a flare after withdrawal of ETN.
- To estimate the efficacy of ETN over 24 weeks of initial treatment.
- To estimate the safety and tolerability of ETN in this population.

2.2. Endpoints

This study will not use an Endpoint Adjudication Committee.

2.2.1. Primary Endpoint

- The primary endpoint is the occurrence of flare (defined as an ASDAS ESR greater than or equal to 2.1) within 40 weeks following withdrawal of ETN.

2.2.2. Secondary Endpoints and Outcome Measures

The following key secondary endpoint will be estimated:

- The time to flare following withdrawal of ETN (as measured from treatment withdrawal until ASDAS ESR greater than or equal to 2.1).

The following secondary endpoints and outcome measures will be estimated within 40 weeks following withdrawal of ETN and during the 12 week re-treatment period (if applicable):

- Occurrence of ASDAS CRP less than 1.3 (inactive disease);
- Occurrence of ASAS 20 and ASAS 40;
- Occurrence of ASAS partial remission;
- ASDAS;
- Occurrence of ASDAS major improvement and clinically important improvement;

- Nocturnal and total back pain;
- Bath Ankylosing Spondylitis Functional Index (BASFI) and its components;
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and its components;
- Occurrence of BASDAI 50;
- High sensitivity C Reactive Protein (hsCRP);
- Health Outcomes Assessments using the following instruments: EuroQoL-5D Health Questionnaire (EQ-5D), SF-36 and Work Productivity and Activity Impairment (WPAI);
- MRI SIJ/spine as measured by Spondyloarthritis Research Consortium of Canada (SPARCC).

The following secondary endpoint will be estimated over 12 weeks following re-treatment of subjects who flare:

- Time to ASDAS inactive disease after re-treatment.

Other endpoints:

- Subject Assessment of Disease Activity (SADA);
- Physician Global Assessment (PGA);
- Bath Ankylosing Spondylitis Patient Global Assessment Score (BAS-G);
- Tender and swollen joint counts (44 count);
- Dactylitis and enthesitis score (Maastricht Anklyosing Spondylitis Enthesitis Score [MASES]).

2.2.3. Safety Endpoints

Safety will be assessed throughout the study. The following variables will be assessed: physical examination, vital signs, hematology, chemistry, urinalysis, premature withdrawal, inflammatory bowel disease (IBD), psoriasis, and uveitis evaluations, adverse events and serious adverse events during the study.

3. STUDY DESIGN

This multicenter, open-label, three period study will evaluate withdrawal and retreatment of ETN in subjects with nr-ax SpA who achieved an adequate response, as measured by ASDAS CRP less than 1.3 (inactive disease) following 24 weeks of treatment. The study is expected to randomize approximately 200 subjects in Period 1, in order to have approximately 96 subjects qualify for Period 2.

3.1. Period 1

This is an open-label, 24-week period in which all eligible subjects with nr-ax SpA will be enrolled and treated with ETN 50 mg once weekly plus a stable background NSAID at the optimal tolerated anti-inflammatory dosage as determined by the investigator. The target for this period is therapeutic response defined as achieving Ankylosing Spondylitis Disease Activity Scale C-reactive protein (ASDAS CRP) less than 1.3 at Week 24. Subjects who qualify at Week 24 will enter Period 2 after all Period 1 procedures are completed. Subjects who do not achieve ASDAS CRP less than 1.3 will not enter Period 2 and will complete the study following the Week 28 day follow-up phone call/visit.

3.2. Period 2

The Week 24 visit ends Period 1 and marks the beginning of Period 2. This is a 40-week withdrawal period where subjects will discontinue ETN following the Week 24 dose, yet maintain the background NSAID. If the subject has not flared by the Week 64 visit, their participation in the study is complete.

3.3. Period 3

Subjects who flare (defined as an ASDAS ESR greater than or equal to 2.1) during Period 2 will enter a retreatment period and receive approximately 12 weekly doses of open-label ETN. Subjects experiencing increased disease activity can come into the office any time for an evaluation; if flare criteria are met, open-label ETN is started at this unscheduled visit. If the subject has experienced increased disease activity during Period 2, but does not meet the protocol defined criteria for flare, it is the investigator's judgment to determine if the subject should remain in the study or discontinue the study to pursue alternative treatment.

3.4. Follow-up

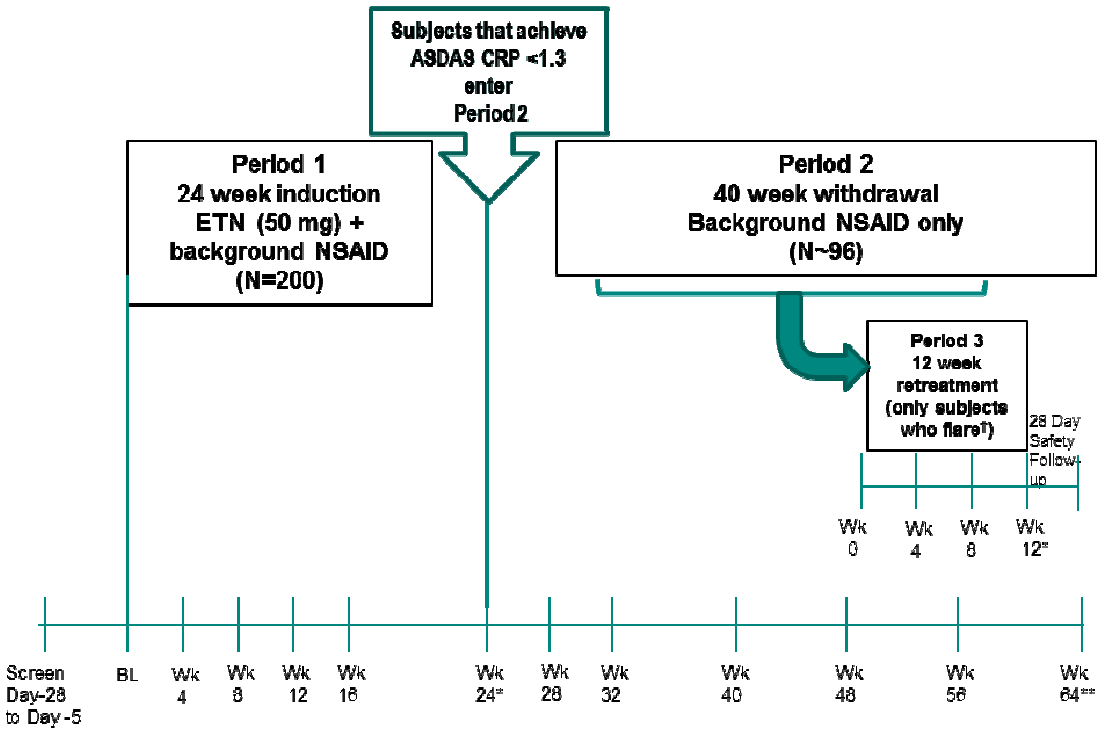
A safety follow-up phone call/visit will only be completed for subjects who:

- Receive investigational product (IP) in Period 1, but who do not enter Period 2, or,
- Enter Period 2 and discontinue from the study ***before*** the Week 28 visit or,
- Enter Period 3 (Retreatment period).

The purpose of this visit is to assess any new and/or ongoing adverse events and will be performed approximately 28 days after the last dose of IP. This follow-up visit will be done by telephone, unless local regulations require a visit to the study site.

A safety follow-up visit does not need to be completed for subjects who discontinue from the study after the Week 28 visit and who do not enter Period 3 for retreatment.

Figure 1. Study Schematic



†Flare is defined as ASDAS ESR ≥2.1
*The follow-up visit is only required 28 days following the last dose of IP. This will occur either at the end of Period 1 (for subjects that don't qualify for Period 2) or at the end of Period 3 (for subjects who flare and require retreatment).
**Subjects who flare at Week 64 will receive 12 weeks of OL ETN and will have their final study visit at Week 76 and their follow-up visit 28 days later.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria – Period 1

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study. An eligibility worksheet will be provided to document the review of the inclusion and exclusion criteria.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the entire study and for 28 days after the last study visit.

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   - Have medically confirmed ovarian failure; or

   Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state

4. Duration of symptoms of ≥3 months and <5 years at the time of consent.

5. Diagnosis of ax SpA as defined by the ASAS criteria (Appendix 2).

   The ASAS criteria state that subjects have to have ≥3 months of back pain and age of onset <45 years, and:

   - Sacroiliitis on imaging plus 1 SpA feature

   OR

   - Positive Human Leucocyte Antigen B27 (HLA-B27) plus 2 SpA features.

   Sacroiliitis on imaging is defined as either:

   - Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA

   OR

   - Defined radiographic sacroiliitis according to the Modified NY criteria**

   Subjects in this study cannot meet the criteria based on the second bullet (since defined radiographic sacroiliitis is an exclusion criterion). In order to meet the imaging criteria for ASAS, subjects must have positive sacroiliitis on MRI based on readings performed by the central imaging vendor. This criterion **cannot be based on local MRI evaluation or historical MRIs.

If a subject has negative sacroiliitis on MRI, then they must have positive HLA-B27 plus 2 SpA features. Conversely, if a subject is HLA-B27 negative, then they must have positive sacroiliitis on MRI and at least 1 SpA feature. (See flowchart in Appendix 6).

The SpA features are listed below and defined in Appendix 4.

- Inflammatory back pain;
- Arthritis;
- Enthesitis (heel);
- Uveitis;
- Dactylitis;
- Psoriasis;
- Crohn's/ Colitis;
- Good response to NSAIDs;
- Family history of SpA;
- HLA-B27;
- Elevated hsCRP.

6. Subjects must have positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as hsCRP >3 mg/l).

7. Active symptoms defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit.

8. Back pain with a less than favorable response to current intake of an NSAID at the optimal tolerated dose as determined by the investigator. Subjects must have experienced less than favorable response to at least 2 NSAIDs (including the current one) taken separately at the optimal tolerated dose with a total combined duration of >4 weeks.

9. Subject must be taking a stable dose of an NSAID for at least 14 days before the first dose.

10. Female or male 18 years or older (20 or older if required by local regulations) but less than 50 at the time of consent.

11. In the opinion of the investigator, subject is reasonable candidate for treatment with ETN.

12. No contraindication to MRI examination (metal implants or inability to lie flat for 30-60 minutes for example).

13. Negative serum pregnancy test performed at screening, negative urine pregnancy test performed prior to the first dose and negative serum pregnancy test collected for analysis prior to the first dose.

14. Ability to self-inject investigational product or have a designee who can do so.

15. Ability to store injectable investigational product under refrigerated conditions.

16. Demonstrated an adequate screening for tuberculosis (TB) in accordance with local country guidelines.

17. Subject is able to complete health outcomes assessments and investigational product diary.

18. In Germany only: Subjects who are not eligible to get new spine and/or pelvic x-rays, due to local regulations must have had these x-rays taken within 12 months prior to the screening visit. The central reader must consider the x-rays to be acceptable for evaluation of sacroiliitis.

4.2. Inclusion Criteria – Period 2

1. Completion of Period 1.

2. Subjects must achieve ASDAS CRP (inactive disease) less than 1.3 at the Week 24 visit in order to be eligible to enter Period 2.

4.3. Inclusion Criteria – Period 3

Subjects must meet the criteria for flare in order to be eligible to enter Period 3. Flare is defined as ASDAS ESR greater than or equal to 2.1.

4.4. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

2. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before the current study begins and/or during study participation. Participation in studies involving investigational drug greater than 4 weeks to one year before the current study begins will be permitted on a case-by-case basis.

3. Radiological sacroiliitis Grades 3-4 unilaterally or Grade ≥2 bilaterally as defined by the NY criteria (Appendix 3). Only results from the central imaging reader will determine eligibility. In all countries except Germany: Historical x-rays (obtained within 4 months of screening) may be utilized, however these subjects must exhibit radiological sacroiliitis Grade 0-1 unilaterally or Grade 0 bilaterally.

4. Any previous treatment with a tumor necrosis factor-alpha (TNF-α) inhibitor, B/T cell inhibitor or other biologic or immunosuppressive agent for a condition other than IBD.

5. Subject is currently being treated or had previous treatment within 6 months for IBD with any tumor necrosis factor-alpha (TNF-α) inhibitor or any other immunosuppressant.

6. Evidence of IBD flare within 6 months of first dose.

7. Evidence of active uveitis within 6 months of first dose.

8. Any current or past orthopedic or medical condition that in the opinion of the investigator could cause chronic back pain.

9. Subject has known or suspected allergy, hypersensitivity, or contraindication to ETN, its excipients, or other compounds, related to this class of medication.

10. Subject has concurrent treatment with more than 1 NSAID within 14 days at first dose. Aspirin use, at daily doses up to 325 mg if indicated for cardiovascular protection is permissible and will not be counted as an additional NSAID.

11. Disease modifying anti-rheumatic drugs (DMARDs) other than methotrexate (MTX), sulfasalazine and hydroxychloroquine taken within 4 weeks of first dose. Subjects may be taking only one allowable DMARD at a time.

12. Subject has had an oral dose of prednisone >10 mg/day (or equivalent) or has had a dose change within 4 weeks of first dose.

13. Subject has received an intra-articular, intravenous, intramuscular, or subcutaneous (SC) corticosteroid within 4 weeks of first dose.

14. Subject has current or recent (within 2 years of screening) active TB infection.

- Subjects with remote history (more than 2 years before screening) of active TB are allowed if clear documentation of completion of adequate treatment (as defined by local guidelines) exists.

- Local country guidelines should be observed for appropriate TB screening in the setting of anti-TNF therapy, including a minimum of a chest radiograph and objective TB testing such as a purified protein derivative (PPD) or Quantiferon depending on what is acceptable per local guidelines.

15. Subject has untreated latent TB. (Subjects with known latent TB may be allowed only if local guidelines are followed for therapy and if treatment for latent TB has been adequately completed or initiated at least 4 weeks prior to screening.)

16. Subject has received treatment for latent TB during screening and has had alanine aminotranferase (ALT) and/or aspartate aminotranferase (AST) ≥2 times the upper limit of normal (ULN) during this period.

    - For subjects that have been diagnosed with latent TB and started treatment during the screening period, additional blood samples for ALT and AST must be drawn between 3-4 weeks after initiating treatment. The results need to be reviewed prior to first dose.

17. Subjects with a chronic infection, or a serious infection (infection associated with hospitalization and/or intravenous antibiotics) within 4 weeks prior to investigational product administration.

18. Subjects with active infection at the time of the screening visit and or the first dose visit. Certain minor active infections (ie, vaginitis, tinea, etc) could be allowed on a case-by-case basis only after approval from the Pfizer Physician Clinician.

19. Subject has planned elective surgery during the active dosing period (ie, Period 1).

20. Subject has received any live vaccines (attenuated vaccine) within 4 weeks prior to first dose.

21. Investigational drugs half-lives of greater than 5 weeks taken less than 6 months prior to first dose.

22. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product or longer based upon the compound's half-life characteristics.

23. Subject has an abnormal hematology or blood chemistry profile during the screening period. Refer to Section 6.8 for management of exclusionary lab values at baseline.

    - White blood cell (WBC) count <3.5 x 10^9/L;
    - Hemoglobin level <8.5 g/L or <5.3 mmol/L;
    - Hematocrit <27%;
    - Platelet count <125 x 10^9/L;
    - Serum creatinine level >175 μmol/L (>1.98 mg/dL);
    - AST or ALT level >2 times the laboratory's ULN.

24. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. Subject has any clinically relevant concurrent medical conditions, including;

    - Known history or presence of acute or chronic hepatitis B or hepatitis C or human immunodeficiency virus (HIV) infection; (If required by Health Authorities, an HIV test must be performed at a local lab during screening. Results of this test will be used to determine eligibility).
    - Uncompensated congestive heart failure, or class III or IV heart failure defined by the New York Heart Association classification;
    - Uncontrolled hypertension (defined as screening systolic blood pressure >160 mm Hg or screening diastolic blood pressure >100 mm Hg;
    - Myocardial infarction within 12 months before the screening visit;
    - Coronary artery by-pass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within 12 months before the first dose visit;
    - Unstable angina pectoris within 6 months before the screening visit;
    - Severe pulmonary disease requiring recurrent hospitalization or supplemental oxygen;
    - Presence or history of confirmed blood dyscrasias;
    - Diagnosis of multiple sclerosis or other central or peripheral nervous system demyelinating diseases;

- Presence or history of cancer (or carcinoma in situ) other than resected cutaneous basal cell or squamous cell carcinoma;
- Uncontrolled diabetes mellitus;
- Diagnosis of rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or polymyositis;
- Open cutaneous ulcers;
- Liver cirrhosis or fibrosis.

4.5. Lifestyle Guidelines

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the study and for 28 days after the last study visit. According to investigator judgment, subjects may need to continue using a highly effective method of contraception beyond 28 days after the last study visit based on concomitant medications (eg, MTX) or local guidelines. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for non-childbearing potential, as described below:

   Female subjects of non-childbearing potential must meet at least one of the following criteria:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

   All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For the purposes of this study, investigational product will be defined as ETN. The sponsor will supply ETN. Investigational product will be administered only to subjects who have provided informed consent. Once a subject's participation in the study has ended, ETN will no longer be supplied to the subject by the investigative site and/or sponsor.

5.1. Allocation to Treatment

This is an open-label study; however, subjects must also receive a treatment assignment number. Enrollment will be accomplished using interactive response technology (IRT), an automated web/telephone system. At the screening visit, the investigative site will contact the IRT (online or by telephone call). The site will enroll the subject into the IRT by indicating minimal information sufficient to distinguish one subject from another and receive the unique Subject identification (ID) number. A subject who discontinues or is withdrawn from the study before receiving a treatment assignment code and who re-enrolls at a later time must be assigned a new unique Subject ID number. A Subject ID number must never be reassigned or reused for any reason. At the baseline visit, enrollment will be accomplished by the IRT system, which will allocate a drug package to the subject.

All subjects will have the option of discontinuing the study at any time (eg, for flare or if the subject and/or treating physician feels that it is in the best interest of the subject to do so). Subjects who are screen failures or discontinue must have their statuses changed in the IRT system.

5.2. Subject Compliance

Reasonable efforts should be made to ensure that administration of investigational product occurs on the day that it is scheduled. However, if unavoidable, the investigational product may be given ±3 days from the scheduled day (ie, 4 to 10 days from the previous dose). The next dose will then return to the normal schedule. If more than 10 days have elapsed since the last dose then the next dose should be taken as soon as possible and the subsequent dose will be given 7 days later, with a new dosing schedule established.

Compliance with IP administration will be reviewed at each study visit during Period 1 and Period 3. At each visit, subjects will return any empty containers and provide information to the study personnel regarding their compliance with the IP. Subjects will also be required to complete a subject diary card to capture weekly IP administration. Compliance is monitored by study personnel at the site by using the subject diary card source documents and is recorded on the case report form (CRF). If any subject misses more than 2 consecutive doses of investigational product, they must be discontinued from the study. Temporary suspension

of the injectable IP for up to 2 consecutive injections is allowed following the occurrence of an adverse event (AE)/serious adverse event (SAE). Reasons for missed doses will be recorded in the subject diary and CRF.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

ETN will be supplied by the sponsor as 1 ml (50 mg/ml) pre-filled syringes for the duration of the trial. This dose of IP is in alignment with the approved dose for this indication. At each dispensing visit, subjects will receive sufficient quantity of IP to last until their next scheduled visit. The pre-filled syringes are open-label and will be labeled to allow for identification of the contents.

5.3.2. Preparation and Dispensing

Refer to separate instructions for complete details regarding the preparation and administration of the investigational product. Each subject will receive IP at scheduled visits; baseline (BL), Weeks 4, 8, 12 and 16 during Period 1, and if necessary, Weeks 0, 4 and 8 during Period 3. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.4. Administration

Pfizer Pharmaceuticals will supply IP for the duration of the study. Investigational product will be administered only to subjects who have provided informed consent. Once a subject's participation in the study has ended, IP will no longer be supplied to the subject by the sponsor. Subjects will record all IP dosing in a dosing diary which should be reviewed during each clinical visit. Site personnel will instruct the subject or designated person on the proper sterile technique to administer a subcutaneous (SC) injection when using the pre-filled syringe at home. During the baseline visit, the initial dose of investigational product must be administered in the office by study personnel, while the subject (or designee) observes. The subject will be provided with an ethics committee (EC)/institutional review board (IRB)-approved administration guide to use at home.

5.5. Investigational Product Storage

ETN prefilled syringes must be stored under refrigerated conditions (2°C to 8°C) and must not be frozen. The subject or designated person will be given instruction regarding the storage and transportation of ETN.

The investigator, or an approved representative (eg, pharmacist) will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. Storage conditions stated in the single reference safety document (SRSD) (ie, investigator's brochure [IB]) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (eg, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (eg, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product, prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions. More specific details will be provided to the sites separately.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All unused investigative product must be returned to the investigator by the subject.

5.7. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

1. Only one NSAID is allowed to be used chronically at a time (an additional NSAID may be given as needed for acute conditions [ie, not to exceed 4 days in duration], and provided it is not given within 24 hours before any visit). During Period 1, the dose and type of NSAID should remain stable. If there is an AE/SAE related to the NSAID the dose may be stopped or lowered temporarily up to two weeks. If after reinstitution of the previous dose of NSAID the adverse event(s) recurs, a lower dose could be used for the remainder of Period 1. If the subject cannot remain on an NSAID during Period 1, they must be discontinued.

2. The intent during Period 2 and Period 3 is to maintain the NSAID at the optimal dose as determined by the investigator.

    a. The NSAID dose may not be increased during these periods.

    b. If the subject develops an AE/SAE related to the NSAID, the dose may be lowered temporarily for up to two weeks. If after reinstitution of the previous dose of NSAID the AE/SAE recurs, a lower dose could be used for the remainder of the study. If the lower dose is not tolerated, the subject can remain in the study during these periods.

3. During all periods of the study, short acting analgesics with no anti-inflammatory action (such as paracetamol, or short acting narcotics) may be used at the discretion of the investigator. However, on the day of the study visit, analgesics must not be taken until after all clinical evaluations have been performed and all blood samples collected.

4. Aspirin use, at daily doses up to 325 mg if indicated for cardiovascular protection is permissible and will not be counted as an additional NSAID. Any regular administration of a dose higher than 325 mg will be considered as a second NSAID use, which is not permitted during this study.

5. If needed, oral corticosteroids are allowed during all periods of the study if they were used in stable doses for at least 4 weeks before first dose. The dose of oral corticosteroids should be <10 mg/day of prednisone or equivalent. The dose of corticosteroids must be kept constant.

6. Treatment with only one of the following 3 DMARDs: sulfasalazine, hydroxychloroquine, and methotrexate, are allowed during the study, but the dose must be stable for at least 4 weeks before first dose and for the duration of the study. If the subject develops an AE/SAE related to the DMARD, the dose may be lowered temporarily for up to two weeks. If after reinstitution of the previous dose of DMARD the AE recurs, a lower dose could be used for the remainder of the study. Route of administration of DMARD must remain constant during the study.

7. Medications for acute or chronic conditions that are not listed under exclusion criteria are permitted.

5.8.1. Non Pharmacologic Interventions

Subjects participating in this trial may continue all non-pharmacologic therapies such as physical therapy, herbal therapy or homeopathic therapy, if they were begun before screening. These therapies should remain on a stable regimen for the duration of the study.

5.8.2. Prohibited Medications

The following list of medications is prohibited during the entire course of the study.

1. Any live (attenuated) vaccine. Vaccinations with live components are prohibited within 4 weeks prior to the first dose of IP, during the study and for 6 weeks after the last study visit.

2. Treatment with other TNF antagonists, B cell depleters, T cell depleters, immunosuppressants (including biologic agents), and tofacitnib.

3. Multiple NSAIDs.

4. DMARDs other than sulfasalazine, hydroxychloroquine and methotrexate.

5. Dose of oral prednisone ≥10 mg/day (or equivalent) and used as described in exclusion criteria.

6. Intra-articular, intravenous, subcutaneous and intramuscular corticosteroid injections.

7. Long-acting analgesics and long-acting narcotics.

8. Investigational or experimental drugs.

6. STUDY PROCEDURES

6.1. Screening

Screening tests and procedures should not commence until after the informed consent form has been signed for this study. The results of the tests and procedures should be reviewed with the subject at the BL visit. Subject screening should be conducted within 4 weeks and no less than 5 days prior to the BL visit. The screening period may be extended up to 42 days if repeat imaging is required or when tuberculosis prophylactic therapy is started during the screening period. No re-screening is permitted in this study. However, if screening laboratory test results exclude the subject and the investigator is reasonably certain that the results(s) were due to laboratory error; or in the opinion of the investigator the result(s) were flawed by a transient condition, that laboratory test(s) may be repeated once during the screening period for confirmation.

This change in process must be accurately recorded and documented in the subjects file and the test should be repeated in a very timely manner (within 4 days of obtaining the result). The re-test is done under the same subject number (this will not be considered a re-screening).

6.1.1. Screening Procedures

- Informed consent must be read, signed and dated by subject and witnessed by the investigator or designee.
- Record subject demography and medical history. Medical history evaluation includes; general medical history, disease specific medical history, evaluation of background medication and family medical history.
- Review all inclusion/exclusion criteria.
- Record all prior medications including DMARDs, corticosteroids, and NSAID use. All medications taken within 30 days prior to screening should be recorded.
- Physical examination (performed by a physician) evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, abdomen, lower extremities, neurological, back/spinal, and lymph nodes. Results must be recorded in the subject's source documents and any significant findings must be recoded on the Medical History CRF and/or appropriate AE CRF.
- Measure height in centimeters (cm) and weight in kilograms (kg).
- Vital sign measurements, including pulse rate (after sitting 5 minutes) and blood pressure. A sitting blood pressure (BP) will be obtained by qualified site personnel. If possible, a different arm should be used for the collection of blood samples.
- BASDAI evaluation.
- SADA.
- Chest radiograph and TB testing:
    - Local country guidelines should be followed for appropriate TB screening in the setting of anti-TNF therapy, including a minimum of:
        - A chest radiograph, to be performed at the screening visit and read locally by a qualified reader unless a chest radiograph has been done within 12 weeks before the screening visit and the report is available and included in the subject's source documents. If required by local regulations, a chest x-ray taken within 6 months of the screening visit may be used as long as the report is available and included in the subject's source documents;

- Objective TB testing, such as Quantiferon or PPD depending on what is available and acceptable per local guidelines.

  - Quantiferon must be used unless not available or not accepted per local guidelines;

  - If the PPD tuberculin skin test is performed, the subject must return 48-72 hours post-test for evaluation. A PPD of >5 mm should be considered positive for TB unless local guidelines for testing of immunocompromised subjects are available and different;

  - TB testing with Quantiferon or PPD need not be done during screening if there is documentation of either test being negative within 12 weeks before the screening visit and if this approach is not prohibited by local guidelines;

  - If the subject is known to be Quantiferon positive or PPD positive, the Quantiferon or PPD tuberculin skin test need not be repeated at the screening visit.

- Collect samples for the following laboratory evaluations:

  - Hematology, blood chemistry, HLA-B27, hsCRP and ESR;

  - Routine urinalysis;

  - Hepatitis B and Hepatitis C testing.

- Serum pregnancy test for women of childbearing potential:

  For female subjects and male subjects whose partners are of childbearing potential, evaluate childbearing potential and sexual activity. This discussion should include highly effective methods of contraception (see Section 4.5 Life Style Guidelines). This evaluation and discussion must be documented in the subject's source documents.

  - Female subjects who, in the opinion of the investigator, are of childbearing potential will be required to have a serum pregnancy test; this includes subjects who are menstruating at the time of the visit and/or who are not sexually active;

  - Urine pregnancy test will also be done whenever one menstrual cycle is missed during the study period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations.

- X-ray of SIJ - Results of historical x-rays that have been obtained within 4 months (12 months in Germany only) prior to screening could be used in lieu of performing screening x-rays. If historical x-rays are used, the original films, or a copy, must be on site and a copy should be sent to the central imaging vendor. Then central reader must be able to determine the presence of and/or degree of sacroiliitis. If the results are considered unevaluable by the central reader, the x-ray must be repeated. If the subject is unable to have a repeat x-ray due to the regulations issued by the German Federation of Radiation Council, the subject would be considered a screen failure.

- MRI Spine and SIJ - MRI evaluation must occur after SIJ x-rays have been obtained and the report from the central imaging vendor has been reviewed by the investigator. MRI should only occur after the subject is found to meet eligibility criteria by evaluation of the SIJ x-ray.

- Adverse Event reporting - serious adverse events must be reported to Pfizer from the time that the subject provides informed consent.

6.2. Baseline (Day 1)

The baseline visit (Day 1) will occur no later than 4 weeks after the screening visit unless treatment for latent TB or repeat imaging is necessary; for which it may be extended to 6 weeks only. It is intended that all procedures for the baseline visit will occur on the same day. All results from the screening visit (including any repeat laboratory tests) must be available and reviewed before the baseline visit. Baseline tests and procedures must be performed before administration of the first dose of IP. However, results of the baseline laboratory tests (with the exception of urine pregnancy test) are not required in advance of dispensing IP. Should the laboratory results subsequently show that the subject does not meet the inclusion/exclusion criteria and this is confirmed upon retest, the subject must be withdrawn from the study at that time.

For women of childbearing potential, both a serum and urine pregnancy test should be performed at the baseline visit, prior to the first injection of the IP. If the serum pregnancy test at baseline subsequently is resulted as positive, the subject MUST be withdrawn from the study.

The following tests and procedures will be performed at the Baseline visit.

- Review all inclusion/exclusion criteria.

- Record prior medications including DMARDs, corticosteroids, and NSAID use.

- Urine and serum pregnancy test.

- Vital signs including sitting BP and pulse.

- Record any AEs that occur following the first dose of investigational product.

- Blood chemistry, hematology, hsCRP and ESR (these parameters do not need to be repeated at the baseline visit if they were completed at the screening visit ≤14 days before baseline).
- Collect blood samples for banked biospecimens Prep D1, Prep R1 and Prep B1.
- Confirm and document that subject is using highly effective method of birth control.
- Joint assessment 44 count, including MASES (enthesitis) and dactylitis evaluation.
- Assessment of IBD, psoriasis and uveitis.
- BASDAI, BASFI, BAS-G.
- PGA.
- SADA.
- Subject Nocturnal and Total Back Pain Assessment.
- Health Outcomes: EQ-5D, SF-36 and WPAI.
- Open label treatment assignment (first dose).
- Dispense IP and IP diary card if randomized. **The first dose of IP must be administered in the investigational site office by study personnel after all baseline evaluations are completed.**

6.3. Induction Period (Period 1)

The following information/assessments will be collected at the study visits for Weeks 4, 8, 12, and 16 (within ±4 days of the projected visit date based on the actual baseline visit date); and Week 24 (±7 days of the projected visit date based on the actual baseline visit date). It is intended that all procedures for a visit will occur on the same day. If the Week 24 ASDAS CRP is ≥1.3, the subject should be notified by phone that their participation in the study is complete. A follow-up call will be conducted in place of the Week 28 visit to assess new and ongoing adverse events and medication taken to treat them since the last dose of investigational product.

- Review concomitant medications including NSAIDs, DMARDs, and corticosteroids at every visit.
- Vital signs including sitting BP and pulse at every visit.
- Physical examination (performed by a physician) at Week 24.
- Measure height (cm) and weight (kg) at Week 24.

- Review of any AEs at every visit that occurred since the previous visit.
- Collect samples for the following laboratory evaluations:
  - Hematology and blood chemistry at Week 12 and Week 24;
  - hsCRP and ESR at every visit;
  - Urine pregnancy test at every visit;
  - Banked biospecimens Prep B1 and R1 at Week 12 and Week 24.
- Confirm and document at every visit the subject is using a highly effective method of birth control.
- MRI of spine and SIJ at Week 24.
- Joint assessment including MASES (enthesitis) and dactylitis evaluation at Week 12 and Week 24.
- Assessment of IBD, psoriasis and uveitis at every visit.
- BASDAI, BASFI, PGA, SADA, Subject Nocturnal and Total Back Pain Assessment and WPAI at every visit.
- BAS-G, EQ-5D and SF-36 at Weeks 12 and 24.
- Dispense IP and IP diary card at Weeks 4, 8, 12 and 16.
- Collect and review IP diary card at every visit.
- Collect IP and complete IP return and accountability document at every visit.

6.4. Withdrawal Period (Period 2)

Subjects who are eligible to enter the withdrawal period will have the following assessments performed at all visits during the withdrawal period unless otherwise indicated:

- Review Period 2 eligibility criteria at Week 28.
- Review concomitant medications including NSAIDs, DMARDs, and corticosteroids at every visit.
- Vital signs including sitting BP and pulse at every visit.
- Physical examination (performed by a physician) at Week 64.
- Measure height (cm) and weight (kg) at Week 64.

- Review of any AEs at every visit that occurred since the previous visit.
- Collect samples for the following laboratory evaluations:
  - Hematology, blood chemistry and urinalysis at Week 64;
  - hsCRP and ESR at every visit;
  - Urine pregnancy test at every visit.
- Confirm and document at every visit the subject is using a highly effective method of birth control.
- MRI of spine and SIJ at Weeks 48 and 64.
- Joint assessment including MASES (enthesitis) and dactylitis evaluation at Weeks 32, 48 and 64.
- Assessment of IBD, psoriasis and uveitis at every visit.
- BASDAI, BASFI, PGA, SA DA, Subject Nocturnal and Total Back Pain Assessment and WPAI at every visit.
- BAS-G, EQ-5D and SF-36 at Weeks 32, 48 and 64.

6.5. Re-Treatment Period for Subjects in the Withdrawal Phase (Period 3)

Subjects in the withdrawal period (Period 2) who experience disease flare will be seen for a re-treatment assessment visit at the study site, which should occur as soon as possible after disease flare. The first visit of the Retreatment period (Period 3) may occur at the same time as a regularly scheduled visit during Period 2 or it may occur as an unscheduled visit. Subjects requiring re-treatment (based on a protocol-defined flare of ASDAS ESR greater than or equal to 2.1) will be offered the option to enter re-treatment (Period 3) and receive 12 weekly doses of open-label ETN (50 mg).

Subjects who discontinue (eg, for an adverse event) at any time are ineligible to enter the re-treatment phase.

Subjects who are eligible to enter the re-treatment period will have the following assessments performed at all visits during the re-treatment period unless otherwise indicated:

- Review concomitant medications including NSAIDs, DMARDs, and corticosteroids at every visit.
- Vital signs including sitting BP and pulse at every visit.
- Physical examination (performed by a physician) at Week R12.

- Measure height (cm) and weight (kg) at Week R12.
- Review of any AEs at every visit that occurred since the previous visit.
- Collect samples for the following laboratory evaluations:
  - Hematology and blood chemistry at Weeks R0 and R12;
  - hsCRP and ESR at every visit;
  - Urine pregnancy test at every visit.
- Confirm and document at every visit the subject is using a highly effective method of birth control.
- MRI of spine and SIJ at Weeks R0 and R12.
- Joint assessment including MASES (enthesitis) and dactylitis evaluation at Weeks R0 and R12.
- Assessment of IBD, psoriasis and uveitis at every visit.
- BASDAI, BASFI, PGA, SA DA, Subject Nocturnal and Total Back Pain Assessment and WPAI at every visit.
- BAS-G, EQ-5D and SF-36 at Weeks R0 and R12.
- Dispense IP and IP diary card at Weeks R0, R4, and R8.
- Collect and review IP diary at Weeks R4, R8, R12.
- Collect IP and complete IP return and accountability document at Weeks R4, R8 and R12.

6.6. Follow-up Call

A safety follow-up telephone call approximately 28 days after the last dose of investigational product will only be completed for subjects who:

- Receive IP in Period 1, but who do not enter Period 2, or,
- Enter Period 2 and discontinue from the study ***before*** the Week 28 visit or,
- Enter Period 3 (Retreatment period).

No follow-up is needed if subjects enter Period 2 and do not experience a flare. If required by local regulations, the follow-up visit may be conducted at the study site. It is intended

that all procedures for the follow-up visit will occur on the same day. The following information will be collected:

- Record AEs that were ongoing at the time of the last visit as well as those starting between the last visit and the follow-up call.
- Record medications taken to treat any new or ongoing AEs/SAEs that occurred since the last visit.

6.7. Early Discontinuation Visit

For all subjects who withdraw from the study prior to completing the last visit of any period, the following information/assessments will be collected at the early discontinuation visit. The early withdrawal visit should be completed as soon as possible after the last dose of investigational product. It is intended that all procedures for the early discontinuation visit will occur on the same day.

- Review concomitant medications including NSAIDs, DMARDs, and corticosteroids.
- Vital signs including sitting BP and pulse.
- Physical examination (performed by a physician).
- Measure height (cm) and weight (kg).
- Review of any AEs that occurred since the previous visit.
- Collect samples for the following laboratory evaluations:
    - Hematology and blood chemistry;
    - hsCRP and ESR;
    - Urine pregnancy test;
    - Banked biospecimens Prep B1 and R1 only if subject discontinues during Period 1.
- Confirm and document the subject is using a highly effective method of birth control.
- MRI of spine and SIJ.
- Joint assessment including MASES (enthesitis) and dactylitis evaluation.
- Assessment of IBD, psoriasis and uveitis.

- BASDAI, BASFI, BAS-G, PGA, SADA, Subject Nocturnal and Total Back Pain Assessment, EQ-5D, SF-36 and WPAI.

- Collect and review IP diary card.

- Collect IP and complete IP return and accountability document.

6.8. Subject Withdrawal

The sponsor's Clinical team must be consulted as soon as possible if any of the following occur during the active treatment period (Period 1 or Period 3) to determine whether the subject should continue taking the investigational product:

- Any infection requiring parenteral (IV, IM) anti-infective agents but not meeting criteria for serious infection (see below).

- The sponsor's Clinical team must be notified as soon as possible if a subject is planning to undergo or has undergone any surgical procedure. It is recommended that investigational product be withheld surrounding most surgical procedures.

    - For most planned surgeries, investigational product should be withheld for a period of time prior to the procedure; the specific duration should be determined by the clinical judgment of the investigator;

    - Investigational product should be withheld following most surgeries. The investigational product can be reintroduced once the investigator judges the risk for post-operative infection to be low;

    - If it is clinically judged that more than two consecutive weekly does of investigational product should be withheld, then the subject must be withdrawn from the study.

- Lack of compliance with the protocol, including protocol required schedule of study visits and/or lack of procedures.

Subjects MUST be withdrawn from investigational product if any of the following occurs:

- If baseline lab value is confirmed to meet Exclusion criteria, the subject must be discontinued. Confirmation of the value should be performed prior to the Week 4 visit.

- Pregnancy.

- Grade 3 or 4 systemic toxicity or a SAE thought to be related to investigational product and not alleviated by symptomatic treatment after cessation of investigational product use of up to two doses or Grade 3 or 4 systemic toxicity that recurs after resumption of investigational product use (see Appendix 5).

- Receipt of any live (attenuated) vaccines.

- Subjects with clinical signs and symptoms suggestive of active tuberculosis should have investigational product withheld until a diagnosis can be confirmed. If diagnosis or tuberculosis is confirmed, investigational product must be discontinued.

- Suspected sepsis.

- Any serious infection (defined as an infection meeting any SAE criteria).

- Confirmed blood dyscrasia or a demyelinating disorder (such as multiple sclerosis or optic neuritis).

- Confirmed malignancy other than squamous cell, basal cell carcinoma or cervical carcinoma in situ.

- If more than 2 consecutive doses of investigational product are missed.

- Joint surgical procedures (open or arthroscopic) and synoviorthesis in Period 1 or Period 3.

- Withdrawal of consent: Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

- Lost to follow-up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data

necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

- Principal investigator decision [ie the investigator or the family doctor considers treatment indicated using a medication that is not permitted (within the scope of the trial).
- Sponsor decision.
- The study is stopped by the IRB or EC, or by a regulatory agency.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The number and types of attempts to reach the subject must be documented in the subject's source documents. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all used/unused investigational product(s) and packages, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Pregnancy Testing

For female subjects of childbearing potential, a serum and/or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, before investigational product administration at the baseline visit, and at the end of treatment visit. A negative

pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at every visit and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRBs/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of IP and from the study.

7.2. Banked Biospecimens

7.2.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will

they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4-mL blood biospecimen **Prep D1 (K_2 edetic acid [ethylenediaminetetraacetic acid] [EDTA] whole blood collection optimized for DNA analysis)** will be collected at the baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

Additional biospecimens to be retained for exploratory analyses in this study include the following:

- **Prep B1 (K_2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis)**: A 10-mL blood biospecimen will be collected at Baseline, Week 12, Week 24, and Early Discontinuation visit during Period 1.

- **Prep R1 (PAXGene whole blood collection optimized for RNA analysis)**: A 2.5-mL blood biospecimen will be collected at Baseline, Week 12, Week 24, and Early Discontinuation visit during Period 1.

The banked biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

7.2.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions.

- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation among people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimen specified in the Markers of Drug Response section will be used. Subjects may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.3. Efficacy Assessments

It is recommended that the same qualified site personnel complete these assessments for a subject at every visit throughout the study.

Refer to the Schedule of Activities for specific time points at which the following efficacy assessments will be completed.

7.3.1. Physician's Global Assessment (PGA)

The investigator will estimate the subject's overall disease activity over the previous 48 hours (this should be independent of the Subject's Assessment of Disease Activity) using a scale between 0 millimeters (mm) [none] and 100 mm (severe).

7.3.2. Tender/Painful Joint Count (44)

Forty-four joints will be assessed by the qualified assessor to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial joints). The 44 joints to be assessed are:

- Upper Body: sternoclavicular, acromioclavicular.
- Upper extremity: shoulder, elbow, wrist (includes radiocarpal, carpal and carpometacarpal considered as one unit), metacarpophalangeals (MCP I, II, III, IV, V), thumb interphalangeal (IP), proximal interphalangeals (PIP II, III, IV, V).
- Lower Extremity: knee, ankle, metatarsophalangeals (MTP I, II, III, IV, V).

7.3.3. Swollen Joint Count (44)

The qualified assessor will also assess joints for swelling using the following scale: Present/Absent/Not done/Not applicable (to be used for artificial joints). Forty-four joints will be assessed for swelling, the same as those listed above for tenderness/pain. Artificial joints will not be assessed.

7.3.4. Dactylitis

Each of the 10 fingers and 10 toes is evaluated by a qualified assessor for dactylitis. A score of 0, 1, 2 or 3 (where 0 = none, 1= mild, 2 = moderate, 3 = severe) is assigned to each.

7.3.5. Maastricht Anklyosing Spondylitis Enthesitis Score (MASES)

There are 13 sites evaluated by a qualified assessor for enthesitis: 1st costochondral joint (left/right), 7th costochondral joint (l/r), posterior superior iliac spine (l/r), posterior anterior iliac spine (l/r), iliac crest (l/r), proximal insertion of Achilles tendon (l/r) and 5th lumbar spinous process. Each site is scored as 0 or 1 depending on whether enthesis is present or absent.

7.4. Health Outcomes Assessments

7.4.1. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI consists of a 0 through 100 mm scale (zero being no problem and 100 being very severe) which is used to answer 6 questions pertaining to the 5 major symptoms of AS: fatigue; spinal pain; joint swelling and pain; morning stiffness duration; morning stiffness severity.

7.4.2. Bath Ankylosing Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those with AS. The ten questions were chosen with a major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions asses the subjects' ability to cope with everyday life. A 100 mm visual analog scale ranging from 0 (Easy) to 100 (Impossible) is used to answer the questions.

7.4.3. Subject's Assessment of Disease Activity (SADA)

Subjects will assess the overall disease activity over the last 48 hours using a pain scale between 0 mm (none) and 100 mm (severe).

7.4.4. Subject Nocturnal and Total Back Pain

Two VAS items will be used to assess the level of nocturnal pain and total back pain during the past 48 hours. For each of these assessments, subjects will mark their level of pain on a 100 mm VAS anchored by 0 for "no pain" to 100 mm "most severe pain".

7.4.5. Bath Ankylosing Spondylitis Patient Global Assessment Score (BAS-G)

The BAS-G is a two question assessment evaluating the effect of AS on the subject's well-being over the last week and the last 6 months. Responses are made on a 100 mm VAS using an anchor of "very good" to "very bad" at the ends.

7.4.6. EuroQoL-5D Health Questionnaire (EQ-5D)

The EQ-5D instrument is designed to assess impact on health-related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores from the five domains calculate a single index value, known as a utility score. In addition, the EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

7.4.6.1. Short Form-36 (SF-36)

The SF-36 is a widely used generic quality of life instrument that assesses the subject's general health and functional status. It consists of 36 questions that are grouped into 8 domains (physical functioning, vitality, social functioning, mental health, role-physical, bodily pain, role-emotional and general health). Domain scores range from 0-100, with greater scores reflecting better health status. In addition, SF-36 has 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

7.4.7. Work Productivity and Activity Impairment (WPAI)

The WPAI assesses work productivity and impairment. It is a 6-item questionnaire regarding current employment, hours missed and actually worked, and degree to which a specified health problem affected work productivity and regular activities over the past 7 days. Subscale scores include percent work time missed with to the health problem; percent impairment while working due to problem; percent overall work impairment due to problem; and percent activity impairment due to problem. Each subscale score is expressed as an impairment percentage (0-100) where higher numbers indicate greater impairment and less productivity.

7.5. Safety Assessments

Safety will be assessed in all subjects who receive at least one dose of investigational product using the following measures. Refer to the Schedule of Activities for specific time points at which the following safety assessments will be completed. Safety assessments include the following:

7.5.1. Physical Examinations

Physical examinations will be performed by a physician and evaluate any clinically significant abnormalities within the following body systems: general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose, throat), heart (auscultation for presence of murmurs, gallops, rubs), lungs (auscultation), abdomen (palpation and auscultation), lower extremities (peripheral edema), neurological (mental status, gait, reflexes, motor and sensory function, coordination), back/spinal and lymph nodes.

- At the screening visit, the results of the physical examination will be recorded in the subject's source documents and any significant findings will be recorded on the Medical History CRF and/or the appropriate AE CRF.

- At the subsequent study visits, the results of the physical examination will be recorded in the subject's source documents and any clinically significant changes from the physical performed at the screening visit will be recorded on the appropriate AE CRF.

7.5.2. Vital Signs/Height/Weight

Vital signs consist of sitting blood pressure and pulse rate. Blood pressure and pulse will be measured at every visit. The blood pressure and pulse rate should be obtained while the subject is sitting. Blood pressure will be measured in the subject's arm and recorded to the nearest mm Hg. It is preferable to take the blood pressure in the same arm at each visit, using an appropriate cuff size. Every effort should be made to take the blood pressure reading after the subject rests for at least 5 minutes. If possible, a different arm should be used for the collection of blood samples

Height and weight will be recorded at the screening visit, Week 24 visit as well as the final study visit (either Week 64, Week R12 or early discontinuation).

7.5.3. Chest X-ray and TB Testing

Local country guidelines should be followed for appropriate screening and prophylaxis in the setting of anti-TNF therapy, including a chest radiograph and objective TB testing, such as purified protein derivative (PPD) or Quantiferon. If the subject is known to be PPD positive, the test need not be repeated if documentation is available to show the subject meets local criteria for anti-TNF therapy and has not had active TB in the last 2 years. If the subject has a documented negative PPD or Quantiferon test within 3 months prior to the screening visit, the test need not be repeated.

7.5.4. IBD, Psoriasis, Uveitis Assessment

Subjects will be assessed to determine if they have experienced an episode of IBD, psoriasis and uveitis since the last visit.

7.5.5. Adverse Events and Serious Adverse Events

Refer to Section 8 for details.

7.5.6. Clinical Laboratory Evaluations

Clinical laboratory evaluations include hematology, blood chemistry and urinalysis (see Section 7.6 Laboratory Evaluations).

7.6. Laboratory Evaluations

As much as possible, only one central laboratory will be used by each investigator for all determinations. Laboratory certification and laboratory normal ranges must be provided to the sponsor for all laboratories used, excluding the sponsor-designated central laboratory.

All laboratory tests that become abnormal to a clinically significant degree after investigational product administration must be repeated and the investigator must continue to follow up as medically indicated until values have returned to baseline or until the condition stabilizes. If laboratory values do not return to normal or baseline within a reasonable period, the etiology must be identified and the sponsor notified. In the judgment of the investigator, all clinically significant abnormal laboratory tests will be recoded on the

appropriate AE CRF. Additional laboratory testing may be performed according to local guidelines or standard of care and for follow-up of abnormal laboratory test results.

All laboratory tests will be performed by the central laboratory with the exception of the ESR and urine pregnancy testing, which will be performed by the investigative site. The ESR will be performed at the investigative site using an ESR kit supplied by the central laboratory. A locally supplied ESR kit should not be used for this study. The urine pregnancy testing will use a urine pregnancy kit supplied by the central laboratory.

All laboratory samples should be collected at the subject's scheduled visit, however, to accommodate rare instances when a subject is unable to fast (or did not fast), all scheduled lab samples for the visit may be drawn within 4 days of the visit. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Sample collection, storage, and shipping information can be found in the laboratory manual supplied by the sponsor-designated central laboratory. Laboratory evaluations will include the following (see the Schedule of Activities for specific time points):

- Blood Chemistry: sodium, potassium, chloride, carbon dioxide (or bicarbonate), blood urea nitrogen (or urea), creatinine, ALT, AST, alkaline phosphatase, total direct bilirubin, albumin and total protein.

- Hematology: white blood cell count with differential, red blood cell (RBC) with morphology, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red cell distribution width [RDW]), platelets, hemoglobin and hematocrit.

- Urinalysis: glucose, albumin and hemoglobin.

- Other Serum Blood Tests: serum pregnancy test, high sensitivity C-reactive protein, Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody and Human Leukocyte antigen B27 (HLA-B27).

7.7. Imaging

- X-ray SIJ – this x-ray is obtained at the screening visit to determine eligibility. The reading of this x-ray is performed by the central imaging vendor. If it is necessary to repeat the x-ray of the SIJ to determine eligibility, the screening period may be extended to 6 weeks. Results of historical x-rays that have been obtained within 4 months prior to the screening visit could be used in lieu of performing screening x-rays. If historical x-rays are used, the original films, or a copy, must be on site and a copy should be sent to the central reader. If the results are considered unevaluable by the central reader, the x-ray must be repeated. The original films or digital images will be sent to the central imaging vendor for digitization, masking of any personal identifying information and archiving. Copies of the original films and/or digital images may be made and kept at the sites. In Germany only: historical x-rays of pelvis taken within 12 months prior to the screening could be used in lieu of the

screening x-ray. This can only occur if the x-rays are deemed to be evaluable by the central reader for the presence of and/or degree of sacroiliitis.

- MRI – the initial MRI takes place at the screening visit, but should not be performed until the SIJ x-ray has been read and the results communicated to the investigator as the x-ray results may determine non-eligibility. The first MRI should be performed prior to the initial dosing with the investigational product. This first MRI will evaluate for the presence of inflammation of sacroiliac joints. If it is necessary to repeat the MRI, the screening period may be extended to 6 weeks. MRI evaluation will be repeated at Weeks 24, 48, 64, R0, R12, or early discontinuation. When the subject enters the retreatment period (Period 3), if it has been <8 weeks since their previous MRI, there is no need to conduct the MRI at the first retreatment visit (Visit R0).

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and nonserious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject;
- Administration of a dose other than that specified in the protocol, Note: Missed doses of investigational product are not considered to be a medication error;
- Administration of investigational product in which deviations from the protocol-specified storage and refrigeration requirements have been noted (except those approved by the Pfizer study team);
- Administration of ETN from a commercial supply rather than ETN labeled for investigational use (unless specifically instructed to do so by the Pfizer study team);
- Administration of the investigational product to anyone other than the subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (x ULN) concurrent with a total bilirubin value ≥2 x ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 x ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 x ULN, or ≥8 x ULN (whichever is smaller).

  Concurrent with

  - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 x ULN **or** if the value reaches ≥3 x ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an

expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The focus of this open label study is estimation. The sample size for this study was determined based on both the primary and key secondary endpoints. For the primary endpoint, 70% of subjects are expected to flare following treatment withdrawal. With an enrollment of approximately 200 subjects, approximately 96 subjects are expected to enter the treatment withdrawal period. If 70% of subjects with treatment withdrawn flare, the half width of the 95% confidence interval on flare rate estimate will be approximately 10%. For the key secondary endpoint of retreatment response, it is anticipated that 60% of the subjects who flare and are retreated will recover the initial ASDAS less than 1.3 response. The half-width confidence interval on this estimate will be approximately 12%.

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoint

The primary endpoint, the occurrence of flare (ASDAS ESR greater than or equal to 2.1) in Period 2 will be summarized descriptively as the percent with flare with 95% confidence interval. This estimate will include all subjects who qualify for the retreatment interval and have at least one evaluation after treatment is withdrawn.

ASDAS is calculated from the following parameters[4]:

1. Total back pain (BASDAI question 2);
2. Subject global assessment of disease activity;
3. Peripheral pain/swelling (BASDAI question 3);
4. Duration of morning stiffness (BASDAI question 6);
5. C-reactive protein (CRP) in mg/litre or ESR in mm/h.

The ASDAS score is then calculated as follows:

ASDAS CRP = (0.121 x total back pain) + (0.110 x subject global) + (0.073 x peripheral pain/swelling) + (0.058 x duration of morning stiffness) + (0.579 x Ln(CRP+1)).

ASDAS ESR = (0.08 x total back pain) + (0.11 x subject global) + (0.09 x peripheral pain/swelling) + (0.07 x duration of morning stiffness) + (0.29 x √(ESR).

9.2.2. Analysis of Secondary Endpoints

For the key secondary endpoint of time to flare, descriptive statistics will include median time to flare and 95% confidence interval using the Kaplan-Meier approach. In addition an estimate of the relative flare rates in the current study and that seen in those subjects in protocol B1801031 who met the treatment withdrawal criteria for the current protocol will also be obtained; subjects in B1801031 did not discontinue treatment and will serve as a reference population. For this estimate a Cox Proportional Hazards model will be used. A 99% confidence interval will be calculated for the Hazard Ratio. Additional sensitivity analyses evaluating the impact of covariates may be performed, details will be provided in the statistical analysis plan.

The efficacy upon retreatment will be assessed descriptively as the proportion of subjects who achieve an ASDAS CRP inactive disease less than 1.3; this will be expressed as a percent with 95% confidence interval.

Dichotomous clinical and subject rated endpoints measured during Periods 1 and 2 will be summarized as number evaluated, percent with response of interest and 95% confidence intervals.

For continuous clinical and subject rated endpoints measured during Periods 1 and 2, both raw and change values will be summarized with the following descriptive statistics: n, mean, standard deviation, min and max, median and the 25th and 75th percentiles (quartiles).

9.3. Safety Analysis

The safety data will be summarized in accordance with Pfizer data standards. The safety analysis set will include all randomized subjects who have taken at least one dose of investigational product.

Listings and summary tabulations of AEs and treatment-emergent AEs will be generated. AEs will be classified by body system and preferred term and summaries of the number of subjects with events will be provided for each treatment group.

Listings and summary tables will be produced for vital signs (sitting blood pressure and pulse rate), weight, laboratory evaluations (hematology, blood chemistry, and urinalysis).

9.4. Interim Analysis

Descriptive analyses of Period 1 will be performed when all subject data for Period 1 is complete. No interim analysis with the aim of stopping or modifying the trial in any way is planned.

9.5. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects’ personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of ETN at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and

the hospital pharmacy (if applicable) within one week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product.

However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Kelly's Textbook of Rheumatology. Van Der Linden in Elsevier Saunders, 7th edition 2005, Vol II pg 1133.

2. Symptomatic Efficacy of Etanercept and Its Effects on Objective Signs of Inflammation in Early Nonradiographic Axial Spondyloarthritis. Dougados, M, et al: Arthritis & Rheumatology, 2014; Vol 66, No 8, pp 2091-2102.

3. Frequency and Duration of Drug-free Demission After 1 Year of Treatment with Etanercept versus Sulfasalazine in Early Axial Spondyloarthritis: 2 Year Data of the ESTHER Trial. IH Song et al, Ann Rheum Dis 2012;71:1212-1215.

4. Ankylosing Spondylitis Disease Activity Score (ASDAS): Defining Cut-off Values for Disease Activity States and Improvement Scores. Machado, P, et al: Ann Rheum Dis 2011;7047-53.

Appendix 1. Abbreviations

This is a list of abbreviations that may or may not be used in the protocol.	
Abbreviation	**Term**
AE	adverse event
ALT	alanine aminotransferase
ASAS	Assessment of SpondyloArthritis Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	aspartate aminotransferase
ax SpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BAS-G	Bath Ankylosing Spondylitis Patient Global Assessment Score
BL	baseline
BP	blood pressure
CDS	core data sheet
CM	centimeter
CRF	case report form
CSA	clinical study agreement
CRP	c-reactive protein
CTA	clinical trial application
DAI	dosage and administration instructions
DMARD	disease modifying anti-rheumatic drug
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EQ-5D	EuroQoL-5D Health Questionnaire
ESR	erythrocyte sedimentation rate
ETN	etanercept
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HLA-B27	Human Leucocyte Antigen B27
hsCRP	high sensitivity c-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
IBP	inflammatory back pain
ICH	International Conference on Harmonisation

ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IVR	interactive voice response
IWR	interactive web response
KG	kilogram
LFT	liver function test
LOCF	last observation carried forward
LSLV	last subject last visit
MASES	Maastricht Anklyosing Spondylitis Enthesitis
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCS	mental component summary
MCV	mean corpuscular volume
MM	millimeter
MRI	magnetic resonance imaging
N/A	not applicable
nr-ax SpA	non-radiographic axial spondyloarthritis
NSAID	non-steroidal anti-inflammatory drug
PCD	primary completion date
PCS	physical component summary
PFS	pre-filled syringe
PPD	purified protein derivative
PT	prothrombin time
RDW	red cell distribution width
RNA	ribonucleic acid
SADA	Subject's Assessment of Disease Activity
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	Supply Chain Lead
SF-36	Short-Form 36
SIJ	sacroiliac joint
SOP	standard operating procedure
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SPC	summary of product characteristics
SRSD	single reference safety document
TB	tuberculosis

TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
USPI	United States package insert
UTN	Universal Trial Number
VAS	visual analogue scale
WPAI	Work Productivity and Activity Impairment

Appendix 2. ASAS Classification Criteria for Axial Spondyloarthritis (ax SpA) in Patients with ≥3 Months of Back Pain and Age at Onset <45

Sacroiliitis on imaging* Plus ≥1 SpA Feature #	OR	**Positive HLA-B27 Plus ≥2 other SpA Features #**

# SpA Features	*Sacroiliitis on Imaging
Inflammatory back pain	Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA
Arthritis	Defined radiographic sacroiliitis according to the Modified New York criteria
Enthesitis (heel)	
Uveitis	
Dactylitis	
Psoriasis	
Crohn's or Colitis	
Good response to NSAIDs	
Family history of SpA	
HLA-B27	
Elevated CRP	

Reference: Assessment of SpondyloArthritis International Society (ASAS) handbook: A guide to Assess spondyloarthritis.. J Sieper, M Rudwaleit, X Baraliakos, J Brandt, J Braun, R Burgos-Vargas,et al. Ann Rheum Dis 2009;68(Suppl II):ii1– ii44. doi:10.1136/ard.2008.104018.

Appendix 3. Radiographic Criterion in the Modified New York Criteria for Ankylosing Spondylitis

Radiographic criterion: Sacroiliitis Grade ≥2 bilaterally or Grade 3 4 unilaterally.

Grade 0: normal

Grade 1: suspicious changes

Grade 2: minimal abnormality – small localized areas with erosion or sclerosis, without alteration in the joint width.

Grade 3: unequivocal abnormality – moderate or advanced sacroiliitis with one or more erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis.

Grade 4: severe abnormality – total ankylosis.

Reference:

Assessment of SpondyloArthritis International Society (ASAS) handbook: A guide to Assess spondyloarthritis. J Sieper, M Rudwaleit, X Baraliakos, J Brandt, J Braun, R Burgos-Vargas ,et al. Ann Rheum Dis 2009;68(Suppl II):ii1– ii44. doi:10.1136/ard.2008.104018.

Appendix 4. Definition of Parameters Applied in the Classification Criteria for Ax SpA

Inflammatory back pain	At least 4 out of 5 parameters present: 1. age at onset <40; 2. insidious onset; 3. improvement with exercise; 4. no improvement with rest; 5. pain at night (with improvement upon getting up).
Arthritis	Past or present synovitis diagnosed by a physician.
Enthesitis (heel)	Heel enthesitis: past or present spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus.
Uveitis anterior	Past or present uveitis anterior confirmed by an ophthalmologist.
Dactylitis	Past or present dactylitis, diagnosed by a physician.
Psoriasis	Past or present psoriasis diagnosed by a physician.
Inflammatory bowel disease	Past or present Crohn disease or ulcerative colitis diagnosed by a physician.
Good response to NSAID	24-48 hours after a full dose of NSAID the back pain is not present any more or has improved.
Family History of SpA	Presence in a first degree relative (mother, father, sister , brother or children) or second degree relative (maternal or paternal grandparent, aunt, uncle, niece or nephew) of any of the following : 1. AS; 2. psoriasis; 3. uveitis; 4. reactive arthritis; 5. inflammatory bowel disease
Elevated CRP	CRP above upper normal limits in the presence of backache, after exclusion of other causes for elevated CRP.
HLA-B27	Positive testing according to standard laboratory techniques.
Sacroiliitis by radiographs	Bilateral grade 2-4 or unilateral grade 3-4 sacroiliitis on plain x-ray according to the New York criteria.
Sacroiliitis by MRI	Active inflammatory lesions of sacroiliac joint with defined marrow oedema/osteitis, suggestive of sacroiliitis associated with SpA.

Reference: The Development of Assessment of Spondyloarthritis International Society Classification criteria for Axial Spondyloarthritis (Part II): validation for Final Selection. M Rudwaleit, D. van der Heijde et al. Annual Rheum Dis. 2009 68(6):777-783.

Appendix 5. Grades of Adverse Events

The following scale should be used to grade the event when determining whether a subject should be discontinued from investigational product, as outlined in Section 6.8 Subject Withdrawal:

0 = No adverse event or within normal limits

1 = Mild adverse event

2 = Moderate adverse event

3 = Severe and undesirable adverse event

4 = Life-threatening or disabling adverse event

5 = Death related to adverse event

Reference: National Cancer Institute (NCI) Common Toxicity Manual. Common toxicity Criteria Version 2.0 June 1st, 1999. http://www.rtog.org/members/toxicity/ctcmanual6-1-99.pdf.

Appendix 6. ASAS Eligibility Flowchart