8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the Clinical Trial Serious Adverse Event (CT SAE) Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to

Including the Screening visit, subjects will return to the clinic site at above noted intervals for a total of 12 visits. If the subject completes the Follow-up visit, the minimum duration of participation will be approximately 56 weeks (Screening: 30 days, 16 week double blind treatment period, 32 week open-label treatment period, Follow-up visit: 28 days ±7 days) without inclusion of any alterations in the visit schedule according to the protocol.

Selected assessments during the study will need to be completed by a qualified blinded assessor. This blinded assessor should be blinded to subject's baseline treatment assignment, all previously completed efficacy assessments (including patient's global assessment) and all safety data (eg, laboratory results, adverse events) in order that the current assessments are completed in an objective manner throughout the study.

Amendment 3

All subjects in the study will be evaluated for risk factors for VTE[50].

The study investigator or designee will need to review each subject's medical history and study records, including their concomitant medications, to determine whether he/she is at high risk for developing VTE.

A subject may be at high risk for VTE if he/she:

- has heart failure or prior myocardial infarction within past 3 months;
- has inherited coagulation disorders;
- has had VTE, either deep venous thrombosis or pulmonary embolism;
- is taking combined hormonal contraceptives or hormone replacement therapy;
- has a malignancy (association is strongest with cancers other than non-melanoma skin cancers);
- is undergoing major surgery or is immobilized.

Additional risk factors for VTE, such as age, diabetes, obesity (BMI≥30 kg/m^2), smoking status, hypertension, and first degree family history of VTE should also be taken into consideration by the investigator and the sponsor medical monitor when evaluating the benefit:risk for each individual subject whether to discontinue from open-label 5 mg BID dose of tofacitinib.

See Risk Factor Check for VTE in Section 7.1.14 for tofacitinib dosing guidance when a risk factor is identified.

If a subject has one or more of the risk factors for VTE listed above under Amendment 3 and is receiving tofacitinib 5 mg BID, they may remain on tofacitinib 5 mg BID after careful investigator assessment of benefit: risk. For subjects who do not have any of the risk factors

	• ASAS 5/6 response at all time points. • ASAS partial remission criteria at all time points. • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at all time points. • BASDAI50 response at all time points. • ASDAS clinically important improvement, ASDAS major improvement and ASDAS inactive disease at all time points. • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at all time points collected. • Change from baseline in extra-articular Involvement (Specific Medical History and peripheral articular involvement [as assessed by change from baseline in swollen joint count]) at all time points collected. • Change from baseline in spinal mobility at all time points collected. • Change from baseline in EuroQol EQ-5D Health State Profile 3 level (EQ-5D-3L) and Your own health state today (EQ-VAS), at all time points collected. • Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire: Spondyloarthritis at all time points collected.
Tertiary/Exploratory Objectives:	**Tertiary/Exploratory Endpoints:**
• [redacted] • To evaluate the effect of tofacitinib 5 mg BID on lymphocyte subsets using FACS analysis. • To measure the effect of tofacitinib 5 mg BID on healthcare resource utilization at all collected time points.	• [redacted]. • Fluorescence Activated Cell Sorting (FACS) analysis of lymphocyte subsets. • AS HealthCare Resource Utilization Questionnaire (AS-HCRU) at all time points collected.

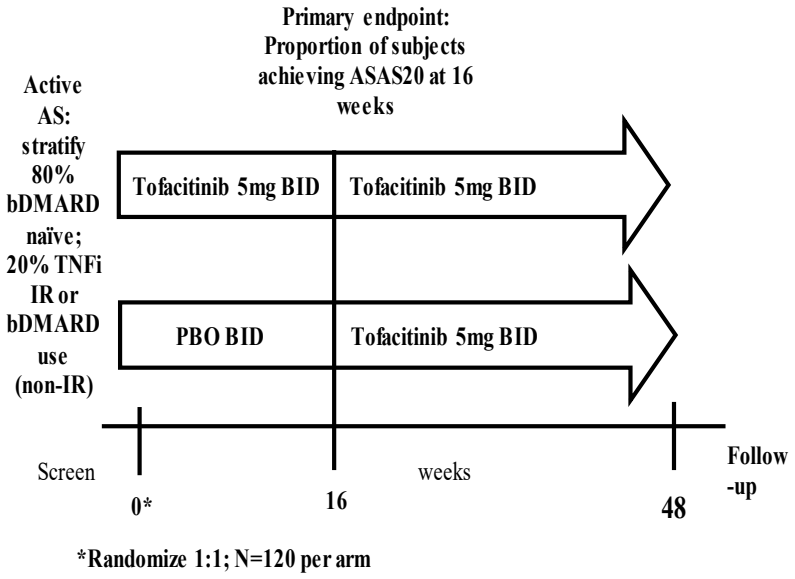
3. STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of tofacitinib in subjects with active AS. Approximately 480 AS subjects will be screened globally in order that approximately 240 eligible subjects (120 per arm) will be randomized in a 1:1 ratio to tofacitinib 5 mg BID or matching placebo BID for a total of 16 weeks of blinded treatment. During the 16-week treatment period subjects will visit the clinic every two weeks (±3 days) until the Week 4 visit and then every 4 weeks (±7 days) until the completion of Week 16. At the Week 16 visit all subjects will be assigned to open-label tofacitinib and will visit the clinic every two months (±7 days) until Week 48. Subjects will then return to the clinic for a Follow-up visit approximately 28 days after the Week 48 visit. There will be a total of 2 planned analyses conducted when all applicable subjects have completed their Week 16 and Week 48 (including follow-up) visits, respectively. CCI [redacted] The first analysis will be conducted when all applicable subjects

have completed their Week 16 visit (see Section 9.2). The investigators, subjects and sponsor study team will remain blinded to the first 16 weeks of treatment assignment through the entire duration of the trial until database release.

Randomization will be stratified by prior treatment history: (1) bDMARD-naive and (2) Tumor Necrosis Factor inhibitor-inadequate responder (TNFi-IR) or bDMARD use (non-IR). Approximately 80% of the subjects will be bDMARD-naïve and have an inadequate response to at least 2 NSAIDs (designed as Stratum bDMARD-naïve), and the other approximately 20% of subjects who had an inadequate response to at least one but not more than 2 TNFi and have an inadequate response to at least 2 NSAIDs or bDMARD use (non-IR) [designed as Stratum TNFi-IR or bDMARD use (non-IR)]. Subjects who had prior bDMARD use (non-IR) will be eligible to participate in the study and will be included in the TNFi-IR or bDMARD use (non-IR) stratum. An inadequate response to NSAID or TNFi treatment is defined as having a treatment related adverse event or lack of response to NSAID or TNFi treatment that was administered in accordance with its labeling recommendations. The sponsor may limit enrollment of subjects with baseline hsCRP below 0.287 mg/dl to match their estimated prevalence in AS. See Figure 1.

Figure 1. Study Design Schematic



Active disease is required for entry into this study and is defined as: Modified New York Criteria for Ankylosing Spondylitis (1984), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 and back pain score (BASDAI Question 2) of ≥4. If subjects have fulfilled entry criteria, they will be randomized to receive either tofacitinib 5 mg BID or placebo.

Laboratory Testing Profile	Tests Included
Urinalysis	Specific gravity, pH, protein, glucose, ketones, blood, leukocyte esterase. Microscopy and/or culture to be performed if clinically indicated or if urinalysis results positive (blood, protein or leukocyte esterase/WBC). Urine HCG pregnancy testing for women of childbearing potential; may be repeated more frequently than indicated if required by local regulation/practices, if a menstrual cycle is missed, or if potential pregnancy is suspected.
Samples at Baseline Only	HLA-B27.
Acute Phase Reactants	High sensitivity C-reactive protein (hsCRP, tested centrally and results blinded except at Screening visit).
FACS Analysis of Lymphocyte Markers	CD3+(%, abs), CD3+CD4+ (%, abs), CD3+CD8+ (%, abs), CD19+ (%, abs), CD56+/CD16+ (%, abs).

a. All subjects will be screened for normal prothrombin time (PT/INR). PT should also be evaluated to rule out acute hepatic injury in cases of hepatic enzyme elevations (see Section 8.3.2).

7.1.1. Hepatitis B and C Virus Testing

Subjects will be excluded with a known hepatitis B infection. All subjects will be tested for HBsAg and HBcAb at the Screening visit. Any subject who is HBsAg+ is excluded from study participation. Subjects who are HBsAg- but HBcAb+ must undergo further testing for HBsAb by the central laboratory to be considered for enrollment. Subjects who are HBsAg-/HBcAb+/HBsAb+ may be eligible for enrollment. Subjects who are HBsAg-/HBcAb+/HBsAb- are excluded from study participation.

Subjects will be excluded with a known hepatitis C infection. At the Screening visit all subjects will be tested for HCV Ab. Subjects that are HCV Ab+ must undergo further testing for HCV RNA by the central laboratory to be considered for enrollment. HCV RNA must be negative per the central laboratory to allow entry into the study.

7.1.2. Pregnancy Testing

A woman of childbearing potential must have a negative highly sensitive pregnancy test (urine, serum) as required by local regulations within 24 hours before the first dose of investigational product. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Pregnancy tests will also be repeated at all visits and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed; during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and all the necessary follow up will be conducted.

classified as ≥40% and ≥2 units in at least 3 domains on a scale of 0-10 and no worsening at all in the remaining domain.

ASAS 5/6 assesses 6 domains: the domains as noted in the ASAS20 and 40, CRP and Spinal mobility, specifically lateral spinal flexion (from the BASMI). Improvement is defined as ≥20% in at least 5 domains.

ASAS partial remission is based on the same 4 ASAS domains noted above. Partial remission is defined as a response if a score of 2 or less (on a scale of 0-10) for each of the 4 domains.

7.2.2. Ankylosing Spondylitis Disease Activity Score ($ASDAS_{CRP}$)

The ASDASCRP endpoint is derived from several patient reported outcomes and CRP which will be calculated by the sponsor. In order for this calculation to be completed, the investigator is responsible to ensure completeness of the PROs and appropriately conduct the assessments that comprise this endpoint. Following is the formula used for calculating the ASDASCRP.[53]

$ASDAS_{CRP}$ = 0.121 × Back Pain + 0.058 × Duration of Morning Stiffness + 0.110 × Patient Global + 0.073 × Peripheral Pain/Swelling + 0.579×Ln(CRP mg/L+1).[52]

Question 2 of the BASDAI provides the data for Back Pain, Question 6 of the BASDAI provides the data for Duration of Morning Stiffness, the score from the Patient Global Assessment of Disease is utilized for the Patient Global and Question 3 of the BASDAI contributes the data for Peripheral Pain/Swelling.

The ASDAS clinically important improvement, major improvement and inactive disease will be calculated from the ASDAS data.[53]

7.2.3. High Sensitivity C-Reactive Protein (hsCRP)

Blood samples will be collected at each visit for analysis of hsCRP using an assay analyzed by the central laboratory. The investigator, study site personnel and Sponsor study team will be kept blinded to the results of this test at all visits except the Screening visit.

7.2.4. Specific Medical History and Peripheral Articular Involvement

Subjects will be assessed at Screening, Baseline/Day 1, Week 8, Week 16, Week 32, Week 48, and at Follow-up to determine if they have experienced an adverse event of IBD, psoriasis or uveitis as well as any complaints suggestive of peripheral articular involvement (as assessed by swollen joint count) since the last visit.

7.2.5. Bath Ankylosing Spondylitis Metrology Index (BASMI)

The Bath Ankylosing Spondylitis Metrology Index (BASMI)[54] is used to assess the axial status and mobility (cervical, dorsal and lumbar spine, hips and pelvic soft tissue). Five clinical measures comprise this scale and in this clinical study the linear function method[55] will be used; these measures will be obtained by the qualified blinded assessor. It is

The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 0-10 numerical rating scale is used to answer the questions with 0 being "Easy" and 10 being "Impossible." The score will be derived from the mean of the 10 items by the sponsor and is indicative of the subject's level of ability.

7.2.9.3. Patient Global Assessment of Disease

Subjects will assess their overall disease activity over the last week using a numerical rating scale between 0 (Not Active) and 10 (Very Active) to the question, "How active was your spondylitis on average during the last week?" Results of this assessment will be used to calculate the ASAS improvement criteria.

7.2.9.4. Patient Assessment of Spinal Pain

Two NRS scales will be used to assess the subject's spinal pain: level of nocturnal pain and total back pain on average during the last week. For each of these scales, subjects will mark their level of pain on a 0-10 NRS anchored by 0 for "No Pain" to 10 "Most Severe Pain." Results of total back pain will be used to calculate the ASAS improvement criteria.

7.2.9.5. Ankylosing Spondylitis Quality of Life

The Ankylosing Spondylitis Quality of Life (ASQoL) is an 18-item questionnaire assessing the amount of restriction the subject is experiencing in daily activities, level of pain and fatigue, and the impact on the subject's emotional state.[59] Each item is scored as 0 (no impact) or 1 (yes - impact). A total score is calculated by summing the items. The total score ranges from 0 to 18, with higher values indicating more impaired health-related quality of life.

7.2.9.6. SF-36v2 Health Survey)

The SF-36 v.2 (Acute) is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.[60] These domains can also be summarized as physical and mental component summary scores. This questionnaire should be completed by the subject prior to any procedures being performed at the visit. The form should be checked for completeness by the site staff.

7.2.9.7. EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) Health State Profile

The EuroQol 3 Levels EQ-5D-3L Health State Profile (3 levels) is a subject completed instrument designed to assess impact on health related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[61] Additionally, scores from the five domains may be used to calculate a single index value, also known as a utility score. The validity and reliability of the EuroQol 3 Levels EQ-5D-3L has been established in a number of disease states, including rheumatoid arthritis. In addition, "Your own health state today" (EQ-VAS) records the subject's self-rated health, a score ranging from 0 to 100 mm will be recorded, with higher scores representing better health state today.

7.4. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. It is a strong preference that the same rater perform all assessments for a subject throughout the study. However, if a situation arises where this is not feasible and a back-up rater must conduct the assessments this will not be considered a protocol deviation. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the study Rater Experience Questionnaire for Blinded Assessors provided to each participating site. The level of experience with the target population (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not they are qualified to perform the assessments. Documentation that the rater is certified to perform selected study assessments before he or she can participate in the conduct of the study is required. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

The following procedures require a health care professional who is competent to perform the assessments: swollen joint count; Bath Ankylosing Spondylitis Metrology Index (BASMI); Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); spinal mobility.

[redacted]

the event, such as concomitant medications and 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 Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious 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.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal due to Adverse Events (see also the Subjects Discontinuation from the Investigational Product section)

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

When a subject withdraws from the investigational product because of an SAE, the SAE must be recorded on the eCRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

Subjects that are withdrawn due to an AE 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. In this case, no further evaluation 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.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any

study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, 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. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 (outside of any protocol-specified dose adjustments) or discontinuation from the investigational product, 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 recording as an AE.

8.2.3. 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.

Or that is considered to be:

- An important medical event.

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.

8.2.4. Infections

Some infections may be classified as serious infections, as defined below.

8.2.5. Serious Infections

A serious infection is any infection (viral, bacterial, and fungal) that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A subject who experiences a serious infection should be discontinued from the investigational product and the serious adverse event should be listed as the reason for discontinuation in the CRF. Appropriate laboratory investigations, including but not limited to cultures should be performed to establish the etiology of any serious infection. All adverse events, including serious adverse events, should be reported as described in Section 8 on Adverse Event Reporting.

8.2.6. 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 is 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 a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);

are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

All statistical tests will be conducted at the 2-sided 5% (or equivalently 1-sided 2.5%) significance level for comparing tofacitinib 5 mg BID to placebo. Type I error will be controlled at 2-sided 5% or equivalently 1-sided 2.5%.

For the primary endpoint of ASAS20 at Week 16, if the 2-sided p value is ≤5%, the superiority of tofacitinib 5 mg BID to placebo will be declared for this primary endpoint and the primary objective of this study is met.Hypothesis testing will continue to the global family of select set of secondary endpoints stated below (*Global Type I Error Control (for the primary endpoint and a select set of secondary endpoints))*. For each of the endpoints within this family, superiority of tofacitinib 5 mg BID to placebo will be declared if statistical significance is achieved under the step-down testing procedure. In addition, three other families of hypotheses, ASAS family endpoints (*Type I Error Control for Endpoints in the ASAS Family*), ASAS20's earlier time points (*Type I Error Control for ASAS20 at Earlier Time Points*) and ASAS40's earlier time points (*Type I Error Control for ASAS40 at Earlier Time Points*) will also be tested. For each of the endpoints or time points of ASAS20/ASAS40, superiority of tofacitinib 5 mg BID to placebo will be declared if statistical significance is achieved under its respective step-down testing procedure.

Global Type I Error Control (for the primary endpoint and a select set of secondary endpoints): The family-wise Type I error rate will be controlled at the 2-sided 5% (or equivalently 1-sided 2.5%) significance level using a step-down testing procedure for the primary endpoint of ASAS20, the key secondary endpoint of ASAS40 and a select set of secondary endpoints at Week 16 tested in the sequence below: ASAS20, ASAS40, change from baseline in $ASDAS_{CRP}$, change from baseline in hsCRP, change from baseline in ASQoL, change from baseline in SF-36v2 Physical Component Summary (PCS), change from baseline in BASMI, and change from baseline in the FACIT-F Total score. When an endpoint fails to declare statistical significance, this endpoint and the remaining endpoints lower in the hierarchy will be considered non-significant. The rationale for the selection and ordering of the select set of secondary endpoints are clinical importance, precedence and likelihood of statistical success based on the results of the A3921119 study.

Type I Error Control for Endpoints in the ASAS Family: Δ in Patient Global Assessment (PGA) of disease, change from baseline in total back pain, ΔBASFI, and change from baseline in in inflammation (average of questions 5 and 6 of BASDAI) are the 4 ASAS components used in deriving ASAS20, thus they are considered belonging to the ASAS family of endpoints. A step-down testing procedure will be applied to them and tested in the sequence below: ASAS20, change from baseline in PGA, change from baseline in total back pain, change from baseline in BASFI, and change from baseline in inflammation (average of questions 5 and 6 of BASDAI) at Week 16. When an endpoint fails to declare statistical significance, this endpoint and the remaining endpoints lower in the hierarchy will be considered non-significant. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of ASAS endpoints.

Type I Error Control for ASAS20 at Earlier Time Points: In order to be more rigorous about establishing the onset of efficacy as measured by ASAS20 at the earliest time point at which

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 investigator 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 investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. 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.

Abbreviation	Term
CYP2C19	Cytochrome P450 enzyme 2C19
CYP450	Cytochrome P450
CV	Cardiovascular
CV EAC	Cardiovascular Endpoint Adjudication Committee
DAS	Disease Activity Score
DILI	Drug-induced liver injury
DMARD	Disease-Modifying Anti-Rheumatic Drug
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
EBV-LPD	Epstein-Barr Virus induced lymphoproliferative disease
eCRF	Electronic case report form
ECG	Electrocardiogram
EDP	Exposure During Pregnancy
EMA	European Medicines Agency
Emax	Maximal effect
EIU	Exposure in Utero
EQ-5D-3L	The EuroQol 5 Dimensions 3 Level Health State Profile
EQ-VAS	Your Own Health State Today Questionnaire
ER	Exposure Response
ESRD	End stage renal disease
EC	Ethics committees
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EULAR	The European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GIPRC	Gastrointestinal Perforation Review Committee
gm	gram
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HCVAb+	Hepatitis C Virus Antibody Postitive
HDL	High Density Lipoprotein
HEENT	Head, eyes, ears, nose, throat
HERC	Hepatic Event Review Committee
HDL-c	High Density Lipoprotein cholesterol

Appendix 8. France Appendix

This appendix applies to study sites located in France.

1. GCP Training.

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product.

No subjects or third-party payers will be charged for investigational product.

for VTE listed above under Amendment 3, he/she will remain on their open-label tofacitinib dose of 5 mg BID.

4. SUBJECT ELIGIBILITY CRITERIA

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 non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

4.1. Inclusion 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 and is capable of comprehending all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Subject is at least 18 years old (*or* the minimum country-specific age of consent if >18) at the screening visit.

4. The subject has a diagnosis of AS based on the Modified New York Criteria for Ankylosing Spondylitis (1984). See Appendix 2.

5. The subject must have a radiograph of the SI joints (AP Pelvis) documenting diagnosis of AS. Previous radiographs (up to 2 years old) can be used if they are accepted by the central reader. Otherwise, a new radiograph will be obtained during the screening period.

6. Subject has active AS Screening and Baseline (Day 1) visits defined as:

   - BASDAI score of ≥4; and

   - Back pain score (BASDAI Question 2) of ≥4.

7. Subject has active disease despite nonsteroidal anti-inflammatory drug (NSAID) therapy or is intolerant to NSAIDs as defined by:

   Subject must have had at least a total of 2 occurrences of an inadequate clinical response (minimum of 4 week trial) or intolerance to at least 2 different oral NSAIDs. An inadequate response to a previous NSAID or TNFi is defined as a lack of sufficient clinical response based on a clinical judgment or based on a related adverse

7.1.3. Cardiovascular (CV) Risk Factor Assessment

CV risk factor assessment will be obtained at the Screening Visit. The assessment includes:

- Smoking status;
- Average weekly alcohol consumption: units/week, where a unit contains 14 g of pure alcohol, an amount equivalent to that contained in 5 oz (a glass) of wine at 12% alcohol, 8-9 oz of malt liquor at 7% alcohol, 12 oz of beer at 5 % alcohol, or 1.5 oz of drinks containing 40% alcohol;
- Family history of premature coronary heart disease (CHD): CHD in a male first degree relative <55 years of age, CHD in a female first degree relative <65 years of age.

7.1.4. Complete Physical Examination

A standard complete physical examination will be performed at Screening, Baseline/Day 1, Week 16, and Week 48. The following parameters and body systems will be examined and any abnormalities described: general appearance, skin (presence of rash), HEENT (head, ears, eyes, nose, throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremity exam (for peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Any clinically significant change(s) from Baseline/Day 1 should be recorded as an adverse event(s).

7.1.4.1. Targeted Physical Examination

At all other visits, an abbreviated physical examination will be performed assessing the following: lungs, heart, abdomen, lower extremities (for peripheral edema), skin (presence of rash) and lymph nodes. Any clinically significant change(s) from Baseline (Day 1) should be recorded as an adverse event(s).

7.1.5. Weight, Height and Waist Circumference

Weight will be measured at each study visit. It is preferred that weight be measured in kilograms (kg) with shoes removed. Weight should be measured to the nearest 0.1 kg.

Height will be measured at the Screening visit. It is preferred that height be measured in centimeters (cm) with shoes removed.

Waist circumference will be measured at the Baseline visit. Waist measurement should be taken directly on the skin without clothing, in the standing position, and at the end of normal expiration. Waist circumference should be measured immediately above the iliac crest. Waist measurement should be measured to the nearest 0.1 cm.

recommended that the same qualified personnel be used for each visit. The combined index score will be calculated by the sponsor using the individual scores from the following measures: lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance, and cervical rotation.

Constricting clothing should be removed to ensure the subject can adequately move for the examinations and visualization of anatomical positions where necessary.

7.2.5.1. Lateral Spinal Flexion

The subject should stand upright and the subject's head and back should rest against the wall as close as possible with shoulders level and feet 30 cm apart and feet parallel. There should be no flexion in the knees, no bending forward. Subject's hands should be resting on his/her lateral thighs. At the tip of the middle finger, place a mark on the thigh. This is the neutral position mark. Measure and record the neutral position. Have the subject bend sideways without bending knees or lifting heels while attempting to keep the shoulders in the same position (flexion position). Place a second mark and record the lateral flexion (left or right as appropriate) using a centimeter tape measure. Measure and record two tries for the left and two tries for the right. The results of the two tries are recorded for left and right separately in cm to the nearest 0.1 cm. The difference between the neutral position and the lateral flexion for each side will be calculated by the sponsor and the better of two tries will be used in the analysis of the data.

Alternatively, measure the distance between the subject's middle fingertip and the floor before (this is the neutral position) and after bending sideways. Record the neutral position in cm to the nearest 0.1 cm. Measure and record two tries for the left and two tries for the right. The results of the two tries are recorded for the left and right separately in cm to the nearest 0.1 cm. The difference between the neutral position and the lateral flexion for each site will be calculated by the sponsor and the better of two tries will be used in the analysis. If this technique is used, it must be consistently used for the entire time this subject is participating. If marks are placed on the subject, ensure marks are not visible at the next clinic visit.

7.2.5.2. Tragus-to-Wall Distance

Place the subject standing with his/her back against the wall; knees straight; scapulae, buttocks, and heels against wall; and head in as neutral position as possible. Measure the distance between the tragus and wall in cm (to the nearest 0.1 cm) from both the right side and left side at the maximum effort to touch the head against the wall. Measure two tries on the right side and two tries on the left side. Record both tries on the appropriate eCRF.

7.2.5.3. Lumbar Flexion (Modified Schober)

With the subject standing erect and outer edges of feet 30 cm apart, place a mark in the midpoint of a line that joins the posterior superior iliac spines (baseline mark). Place a second mark (A) 10 cm above the baseline mark and a third mark (B) 5 cm below the baseline mark. Then have the subject maximally bend forward, keeping the knees fully extended. With the subject's spine in full flexion, re-measure the distance between marks

This questionnaire should be completed by the subject prior to any procedures being performed at the visit. The form should then be checked by site staff for completeness.

7.2.9.8. Functional Assessment of Chronic Illness Therapy – Fatigue Scale

The FACIT – Fatigue Scale is a subject completed questionnaire consisting of 13 items that assess fatigue.[62] Instrument scoring yields a range from 0 to 52 for the total score, with higher scores representing better subject status (less fatigue). The FACIT - Fatigue Scale will also be summarized as FACIT-Fatigue experience domain score and FACIT-Fatigue impact domain score. This questionnaire should be completed by the subject prior to any procedures being performed at the visit. The form should then be checked by site staff for completeness.

7.2.9.9. Work Productivity & Activity Impairment Questionnaire: Spondyloarthritis

The Work Productivity & Activity Impairment Questionnaire (WPAI): Spondyloarthritis is a 6-item questionnaire that is specific for spondyloarthritis which yields four types of scores: absenteeism, presenteesism (impairment at work/reduced job effectiveness), work productivity loss and activity impairment.[63] WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity. This questionnaire should be completed by the subject prior to any procedures being performed at the visit, if possible. The form should be checked for completeness by the site staff.

7.2.9.10. Ankylosing Spondylitis Healthcare Resource Utilization Questionnaire

The AS Healthcare Resource Utilization Questionnaire (AS-HCRU) is a seventeen item scale that is designed to assess healthcare usage during the previous three months across a wide number of direct medical cost domains. The scale also assesses indirect costs associated with functional disability and impaired productivity at home and at work. This questionnaire should be completed by the subject prior to any procedures being performed at the visit, if possible. The form should be checked for completeness by the site staff.

7.3. Imaging Assessments (Chest and SI joint radiographs)

Management of incidental findings

An incidental finding is one unknown to the subject that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

Radiograph images will be reviewed by a central review facility. The purpose of this review is to evaluate images for TB screening or diagnosis of AS. Central image review is not a complete medical review of the subject and no incidental findings will be shared with the principal investigator, site staff, or the subject. All safety reviews will be the sole responsibility of site staff.

[redacted]

8.1.6. 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.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

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

- 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 SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

Severity Assessment

If required on the AE page of the CRF, 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.

8.3. Special Situations

8.3.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.3.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt

The subject should return to the investigator 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 and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.3.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.3.1. Exposure During Pregnancy

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

- 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).

there is statistical separation between tofacitinib 5 mg BID and placebo, a step-down approach with the ASAS20 from Week 16 to earlier time points (order of testing: Weeks 16, 12, 8, 4, and 2) will also be used for each time point. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of ASAS20 time points.

Type I Error Control for ASAS40 at Earlier Time Points: In order to be more rigorous about establishing the onset of efficacy as measured by ASAS40 at the earliest time point at which there is statistical separation between tofacitinib 5 mg BID and placebo, a step-down approach with the ASAS40 from Week 16 to earlier time points (order of testing: Weeks 16, 12, 8, 4, and 2) will also be used for each time point. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of ASAS40 time points.

9.3. Safety Analysis

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations:

- Incidence and severity of adverse events;
- Categorical summary of absolute vital signs and vital sign changes compared to baseline by subject;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials, will be summarized;
- Any safety events that trigger withdrawal of a subject;
- Safety laboratory tests will be summarized according to Pfizer standards.

Special attention will be given to the following safety criteria: neutrophil counts, lymphocyte counts, serum creatinine levels, platelet counts, transaminase levels, bilirubin levels (and other measures of liver function), events of anemia.

9.4. Interim Analysis

No formal interim analysis will be conducted for this study. The analysis of the primary, key secondary endpoint and the other Type I error controlled secondary endpoints conducted at Week 16 is the final analysis for these endpoints (see Section 9.2).

9.5. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions,

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 shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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 or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/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/assent 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. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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.

Abbreviation	Term
HIV	Human Immunodeficiency Virus
hsCRP	High Sensitivity C-Reactive Protein
HZ	Herpes Zoster
IB	Investigator brochure
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IND	Investigational New Drug Application
ILDRC	Interstitial Lung Disease Review Committee
IP	Interphalangeal
IRB	Institutional Review Board
IRC	Internal Review Committee
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IWR	Interactive Web-based response
IWRS	Interactive Web-based response system
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
LDL	Low Density Lipoprotein
LFT	Liver function test
LPD	Lymphoproliferative Disease
LTE	Long-term Extension
LTFU	Lost to Follow-Up
MAC	Malignancy Adjudication Committee
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCP	Metacarpophalangeal
mg	Milligrams
MRI	Magnetic Resonance Imaging
MTP	Metatarsophalangeal
MTX	Methotrexate
N/A	Not Applicable
NMSC	Non-melanoma skin cancer
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OIRC	Opportunistic Infection review Committee
Oz	Ounce
PBO	Placebo
PCD	Primary Completion Date
PCS	physical component summary
PD	Pharmacodynamics