AN OPEN-LABEL EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY AND CLINICAL BENEFIT OF ETANERCEPT IN CHILDREN AND ADOLESCENTS WITH EXTENDED OLIGOARTICULAR JUVENILE IDIOPATHIC ARTHRITIS, ENTHESITIS-RELATED ARTHRITIS, OR PSORIATIC ARTHRITIS WHO WERE PREVIOUSLY ENROLLED IN PROTOCOL 0881A1-3338-WW(B1801014)

Compound:	PF-05208752
Compound Name (if applicable):	Etanercept
US IND Number (if applicable):	N/A
European Clinical Trial Database (EudraCT) Number (if applicable):	2010-023802-10
Protocol Number:	B1801023
Phase:	3b

Document History

Document	Version Date	Summary of Changes
Amendment 2	09 March 2015	**Updated 1.2 Background and Rationale** **Added 4.4 Sponsor's Qualified Medical Personnel** **5.3.2.1 Medication Error** • Modified medication error language **6.1.2.2 Withdrawal Period** • "Re-treatment" has been removed given that it is not applicable in this section. **6.1.6 Observational Period Follow-up Visits for Subjects Who Participated in the Active Treatment Period and/or Withdrawal/Re-treatment Period** • Added "active treatment" for clarity **8.0 AE Reporting** • Modified Adverse Event Reporting section **15.1 Communication of Results by Pfizer** • Modified United States Basic Results information • Added European Clinical Trials Database information
Amendment 1	20 July 2012	**Title** • Added 'Clinical Benefit' to study title. **Schedule of Activities – Active Treatment Period** Added the following assessments throughout: • Temperature, pain assessment, duration of morning stiffness, joint assessment, overall back pain and nocturnal pain (ERA only),

		BASMI (ERA only), BSA (PsA only), and PGA of Psoriasis (PsA only). • Added review of inclusion and exclusion criteria for the withdrawal/re-treatment. • Added Informed consent/assent for the Withdrawal/Re-treatment period or Observational Period, as appropriate. **Schedule of Activities – Withdrawal/Re-Treatment Period** • Added a separate withdrawal period and re-treatment period schedule of activities for the new withdrawal/re-treatment period. **Introduction** • Changed age 4 to 2 given that etanercept is approved to treat pediatric patients with polyarticular JIA aged 2 years and above. • Added information & rationale for amending the protocol to include a withdrawal/re-treatment period. **Study Objectives** • Added a secondary objective regarding the evaluation of clinical benefit and physical function. [redacted] **Endpoints** • Clarified primary and secondary endpoints for all subjects. • Added additional endpoints for subjects in the

		active treatment period. • Added endpoints for subjects in the withdrawal/re-treatment period. • Added additional endpoints for subject with ERA & PsA**.** [redacted] **Study Design** • Added a withdrawal/re-treatment period. • Clarified and added additional information to the observational period study design to allow for subjects who participate in the withdrawal/re-treatment period. **Subject Selection** • Added the wording "withdrawal/re-treatment period". **Inclusion and Exclusion Criteria** • Clarified inclusion & exclusion criteria for subjects in the active treatment period. • Added inclusion & exclusion criteria for subjects entering in the withdrawal/re-treatment period. **Life Style Guidelines and Pregnancy Testing** • Added specific information regarding the withdrawal/re-treatment period. • Added language regarding subjects may need to continue using highly effective method of contraception beyond 30 days after last dose of IP for subjects entering into the observational period.

		Study Treatment • Added wording for re-treatment period. • Clarified if more than 4 missed doses of IP are missed and added wording that tapering of IP is not allowed. **Administration** • Added/clarified administration of IP throughout this section. **Medication Errors** • Added wording to state that medication errors are reportable events and must be documented accordingly in the CRF. • Added examples of medication errors. **Compliance** • Clarified if more than 4 missed doses of IP are missed and added wording that tapering of IP is not allowed. **Drug Storage and Drug Accountability** • Clarified section throughout on when to return IP. **Concomitant Medications** • Add permitted and prohibited medications for withdrawal/re-treatment period. • Added more instructions/clarification for receipt of live vaccines. • Added information regarding planned surgical procedures. • Changed permitted medication/dosing information allowed in the active treatment period and withdrawal/re-treatment period for corticosteroids (Oral, IM or IV injections).

		Study Procedures • Add study procedures and assessments for the active treatment period, withdrawal/re-treatment period, including the withdrawal visits. **Subject Withdrawal** • Added withdrawal/re-treatment language. • Added guidance for contacting the Clinical team if a subject is planning to undergo or has undergone any surgical procedure. • Clarified if more than 4 missed doses of IP are missed and added wording that tapering of IP is not allowed. • Added language around lack of compliance with protocol. • Added language regarding infection meeting seriousness criteria other than hospitalization. **Assessments** • Added wording for withdrawal/re-treatment period throughout section. • Added efficacy assessments in the active treatment period and withdrawal/re-treatment period. **Adverse Event Reporting** • Clarified adverse event information around ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. • Added withdrawal/re-treatment wording throughout section.

		Reporting Period • Added adverse event reporting period for the withdrawal/re-treatment period. **Definition of Adverse Event** • Added examples of drug abuse and drug dependency. • Added medication error to signs and symptoms of an adverse event. **Serious Adverse Event** • Expanded the bullet 'Results in persistent or significant disability/incapacity'. **Potential Cases of Drug-Induced Liver Injury** • Clarified the criteria for laboratory abnormalities that require further evaluation n the context of potential cases of drug-induced liver injury. **Causality Assessment** • Clarified that generally the facts (evidence) or arguments to suggest a causal relationship should be provided by the investigator. **Exposure During Pregnancy** • Added to this section to improve clarity. **Data Analysis/Statistical Methods** **Efficacy** • Added an analysis for additional efficacy assessments. • [redacted]

		Safety • Clarified safety analysis for all subjects. • Added safety analysis for subjects in the withdrawal/re-treatment period. **Interim Analysis** • Clarified language around interim analysis. **Data Monitoring Committee** • Clarified internal review committee language. **Subject Information and Consent** • Clarified informed consent process language. **Communication of Results by Pfizer** • Clarified the communication of results.
Original protocol	25 February 2011	N/A

This amendment incorporates all revisions to date including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

SCHEDULE OF ACTIVITIES – ACTIVE TREATMENT PERIOD

For subjects who enter into the active treatment period and receive investigational product in study B1801023

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

	Day 1[a] Baseline	Months 3, 15, 27, 39, 51, 63, 75, 87[b]	Months 6, 18, 30, 42, 54, 66, 78, 90[b]	Months 9, 21, 33, 45, 57, 69, 81, 93[b]	Months 12, 24, 36, 48, 60, 72, 84[b]	Month 96[b]	Active Treatment Early Withdrawal[c]	Follow-up[d]	Observational Period[e]		
Protocol Activity	**Active Treatment Period**								**1st Visit[f]**	**Subsequent Visits[g]**	**Final Visit (Month 96)[h]**
Informed Consent/Assent for the Active Treatment Period	X[a]										
Review Inclusion and Exclusion Criteria for the Active Treatment Period	X[a]										
Collect/update contact information	X[a]	X	X	X	X	X	X		X	X	
Prior and concomitant medications/non-drug treatments	X[a]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[j]	X[j]	X[j]
Height (cm)	X[a]				X	X	X				
Weight (kg)[k]	X[a]	X	X	X	X	X	X				
Blood Pressure (mmHg), Pulse (Beats/min), Temperature	X[a]	X	X	X	X	X	X				
Physical examination	X[a]				X	X	X				
Tanner Stage Assessment[l]	X[a]				X	X	X				
Hematology, Blood chemistry, C-reactive protein[m]	X[a]		X		X	X	X				
Evaluate childbearing potential (females)[n]	X	X	X	X	X	X	X				
Urine pregnancy test[o]	X	X	X	X	X	X	X				
Discuss sexual activity and use of contraception, as appropriate[p]	X	X	X	X	X	X	X				
PGA of Disease Activity	X[a]		X		X	X	X				
Parent/Patient Global Assessment[q]	X[a]		X		X	X	X				

Protocol Activity	Day 1[a] Baseline	Months 3, 15, 27, 39, 51, 63, 75, 87[b]	Months 6, 18, 30, 42, 54, 66, 78, 90[b]	Months 9, 21, 33, 45, 57, 69, 81, 93[b]	Months 12, 24, 36, 48, 60, 72, 84[b]	Month 96[b]	Active Treatment Early Withdrawal[c]	Follow-up[d]	Observational Period[e]		
	Active Treatment Period								1st Visit[f]	Subsequent Visits[g]	Final Visit (Month 96)[h]
CHAQ/HAQ[r]	X[a]		X		X	X	X				
Pain Assessment[q]	X[a]		X		X	X	X				
Duration of Morning Stiffness[q]	X[a]		X		X	X	X				
Joint Assessment	X[a]		X		X	X	X				
Overall Back Pain and Nocturnal Pain (ERA only)[q]	X[a]		X		X	X	X				
BASMI (ERA only)	X[a]		X		X	X	X				
BSA (PsA only)	X[a]		X		X	X	X				
PGA of Psoriasis (PsA only)	X[a]		X		X	X	X				
Adverse events[s]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[u]	X[u]	X[u]
Dispense visit reminder card	X	X	X	X	X	X	X		X	X	
Dispense IP, and subject diary	X	X	X	X	X						
Collect returned IP and subject diary		X	X	X	X	X	X				
Registration/ Randomization	X										
Review inclusion and exclusion criteria for the Withdrawal/ Re-treatment Period							X				
Informed consent/assent for the Withdrawal/Re-treatment period or Observational Period, as appropriate							X				
End of Treatment Subject Summary						X	X				
End of Study Subject Summary								X			X

a. Every attempt should be made to complete the study B1801023 baseline visit on the same day as the study 0881A1-3338 week 96 visit. For subjects planning to continue investigational product, the baseline visit (day 1) of study B1801023 must occur within 6 weeks of the last dose of investigational product received in study 0881A1-3338. For subjects with ≤14 days between the study 0881A1-3338 week 96 visit and the study B1801023 baseline visit, the indicated procedures do not need to be repeated.

b. All visits during the active treatment period (month 3 to month 96) must occur at the study site within a window of ±14 days of the projected visit date based on the baseline visit date.

[c.] Subjects in the active treatment period of study B1801023 who withdraw from investigational product before completion of the month 96 visit are required to complete the early withdrawal visit at the study site. Subjects in the active treatment period who meet Wallace definition for clinically inactive disease for at least 6 months on investigational product or who, in the investigators judgment, have had a good clinical response and would benefit from withdrawal from investigational product and are otherwise eligible will be asked to participate in the withdrawal/re-treatment period. Subjects in the active treatment period who are ineligible for the withdrawal/re-treatment period will be asked to participate in the observational period.

[d.] The follow-up visit will only be completed for those subjects who are receiving investigational product in either the active treatment period or re-treatment period approximately 96 months after the baseline visit in study B1801023 and will occur 30 days (±7 days) after the Month 96 visit.

[e.] Subjects who receive at least 1 dose of investigational product in the active treatment period of study B1801023 and withdraw from the active treatment period before completion of the month 96 visit and do not participate in the withdrawal/re-treatment period will be asked to participate in the observational period.

[f.] For subjects who consent to participate in the observational period, the first observational visit will occur at the study site and will be scheduled 30 days (±7 days) after the early active treatment withdrawal visit.

[g.] Subsequent observational visits will occur by telephone every 6 months (±4 weeks) after the first observational visit. For subjects <18 years of age, telephone contacts will be conducted with the subject's parent or legal representative/guardian. For subjects aged ≥18 years, telephone contacts will be conducted with the subject or the subject's parent or legal representative/guardian. The number of telephone contacts will be adjusted based on when the subject enters the observational period.

[h.] The final observational visit will occur by telephone contact 96 months (±4 weeks) after the baseline visit of study B1801023.

[i.] For subjects in the active treatment period, the following concomitant medications will be collected: DMARDs, corticosteroids, NSAIDs, and anti-infective agents. Only non-drug treatments received due to an adverse event will be collected.

[j.] For subjects in the observational period, the following concomitant medications will be collected: DMARDs, including any immunosuppressives or anti-TNFs and/or other immunosuppressive biologic agents; corticosteroids; and anti-infective agents taken for medically important infections. Only non-drug treatments received due to an adverse event will be collected.

[k.] Weight will be measured at every visit for subjects who are <18 years of age and who weigh ≤62 kg. For those subjects who are ≥18 years of age or weigh >62 kg, weight will be measured annually as part of the physical examination.

[l.] Tanner Stage Assessment will be performed annually for subjects <18 years of age or who have a score of <5 on 1 or more applicable domain(s). The Tanner Stage Assessment does not need to be repeated at the early withdrawal visit if it was performed within 2 months before the visit.

[m.] Additional laboratory testing may be performed according to local guidelines or standard of care and for follow-up of abnormal laboratory test results.

[n.] The evaluation of childbearing potential in female subjects must be documented in the subject's source documents.

[o.] Urine pregnancy tests will be performed at each of the visits in the active treatment period for all female subjects who, in the opinion of the investigator, are of childbearing potential; this includes subjects who are menstruating at the time of the visit. The baseline pregnancy test must be performed within 7 days before the baseline visit. Pregnancy tests will also be done whenever a menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

[p.] Discussion of sexual activity and use of contraception must be documented in the subject's source documents.

[q.] Assessment will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years, or directly by subjects aged ≥18 years at the time of the assessment.

[r.] Childhood Health Assessment Questionnaire (CHAQ) will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years at the time of the assessment; Health Assessment Questionnaire (HAQ) will be completed directly by subjects aged ≥18 years at the time of the assessment.

[s.] Adverse events will be collected from the signing of the informed consent document through 96 months after the baseline visit of study B1801023. For subjects who complete the Month 96 visit in either the active treatment period or the re-treatment period of study B1801023, adverse events will be collected until 30 days after the last

dose of investigational product. Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and the baseline visit of study B1801023 must be recorded on the appropriate eCRF.

t. For subjects in the active treatment period, all adverse events, malignancies, serious adverse events, infections, medically important infections (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization), and injection site reactions, will be collected.

u. For subjects in the observational period, only serious adverse events, malignancies and medically important infections (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization), will be collected.

Abbreviations: CHAQ=Childhood Health Assessment Questionnaire; DMARD=Disease-Modifying Antirheumatic Drug; eCRF=electronic Case Report Form; HAQ=Health Assessment Questionnaire; IRB=Internal Review Board; IWR/IVR=interactive web response/interactive voice response; NSAID= Nonsteroidal Anti-inflammatory Drug; PGA=physician's global assessment; TNF=tumor necrosis factor

SCHEDULE OF ACTIVITIES – WITHDRAWAL PERIOD

For subjects who enter into the withdrawal period in study B1801023

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Protocol Activity	Withdrawal Period						Observational Period[e]		
	Day 1[a] Baseline	Months 1[b],3,6,9	Months 12, 24, 36, 48, 60, 72, 84[c]	Months 18, 30, 42, 54, 66, 78, 90[c]	Month 96[c]	Re-Treatment Assessment[d]	1st Visit[f]	Subsequent Visits[g]	Final Visit (Month 96)[h]
Informed Consent/Assent for Withdrawal/Re-treatment Period	X					X			
Review Inclusion and Exclusion Criteria for Withdrawal/Re-treatment Period	X								
Collect/update contact information	X	X	X	X	X		X	X	
Prior and concomitant medications/non-drug treatments	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[j]	X[j]	X[j]
Height (cm)	X[a]		X		X	X			
Weight (kg)	X[a]	X[k]	X[k]	X[k]	X	X			
Temperature, Blood Pressure (mmHg), Pulse (Beats/min)	X[a]	X	X	X	X	X			
Physical examination	X[a]		X		X	X			
Tanner Stage Assessment[l]	X[a]		X		X	X			
Hematology, Blood chemistry, C-reactive protein[m]	X[a]	X	X	X	X	X			
Evaluate childbearing potential (females)[n]	X	X	X	X	X	X			
Urine pregnancy test[o]	X	X	X	X	X	X			

Protocol Activity	Withdrawal Period						Observational Period[e]		
	Day 1[a] Baseline	Months 1[b],3,6,9	Months 12, 24, 36, 48, 60, 72, 84[c]	Months 18, 30, 42, 54, 66, 78, 90[c]	Month 96[c]	Re-Treatment Assessment[d]	1st Visit[f]	Subsequent Visits[g]	Final Visit (Month 96)[h]
Discuss sexual activity and use of contraception, as appropriate[p]	X	X	X	X	X	X			
PGA of Disease Activity	X[a]	X	X	X	X	X			
Parent/Patient Global Assessment[q]	X[a]	X	X	X	X	X			
CHAQ/HAQ[r]	X[a]	X	X	X	X	X			
Pain Assessment[q]	X[a]	X	X	X	X	X			
Duration of Morning Stiffness[q]	X[a]	X	X	X	X	X			
Joint Assessment	X[a]	X	X	X	X	X			
Overall Back Pain and Nocturnal Pain (ERA only)[q]	X[a]	X	X	X	X	X			
BASMI (ERA only)	X	X	X	X	X	X			
BSA (PsA only)	X[a]	X	X	X	X	X			
PGA of Psoriasis (PsA only)	X[a]	X	X	X	X	X			
Adverse events[s]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[u]	X[u]	X[u]
Dispense visit reminder card	X	X	X	X		X	X	X	
Dispense IP and subject diary						X			
Registration/ Randomization	X								
Review inclusion and exclusion criteria for the Re-treatment Period						X			
Informed consent/assent for the Observational Period, if appropriate						X			
End of Phase Subject Summary					X	X			
End of Study Subject Summary					X				X

a. The baseline visit is only for subjects who enter directly into the withdrawal/re-treatment period. Every attempt should be made to complete the study B1801023 baseline visit on the same day as the study 0881A1-3338 week 96 visit. The baseline (Day 1) visit must occur within 14 days of the last dose of investigational product received in study 0881A-3338. For subjects with ≤14 days between the study 0881A1-3338 week 96 visit and the study B1801023 baseline visit, the indicated procedures do not need to be repeated.

b. The month 1 visit will occur at the study site 1 month (±7 days) after the baseline visit or active treatment early withdrawal visit.

c. The month 3 to month 96 visits must occur at the study site within ±14 days of the projected visit date based on the actual date of the baseline or active treatment early withdrawal visit. Subjects who do not experience disease relapse will continue in the withdrawal period for a total of 96 months (±14 days) after the baseline visit of study B1801023.

d. Subjects in the withdrawal period who experience disease relapse or discontinue from the withdrawal period for any reason (eg, for adverse events) will be seen for a re-treatment assessment visit. For subjects experiencing disease relapse, the re-treatment assessment visit should occur as soon as possible after disease relapse. Those subjects requiring re-treatment per the investigator's clinical judgment and who are otherwise eligible will be offered the option to re-start treatment with investigational product. Subjects who participate in the withdrawal period and are ineligible for the re-treatment period will be asked to participate in the observational period.

e. Subjects who participate in the withdrawal period, and discontinue from the withdrawal period before completion of the month 96 visit, and do not participate in the re-treatment period will be asked to be followed in the observational period for a total of 96 months from the time of the baseline visit in study B1801023. Once the subject is in the observational period, he or she cannot resume investigational product for the remaining time in the study.

f. For subjects who agree to participate in the observational period, the first observational visit will occur at the study site 30 days (±7 days) after the re-treatment assessment visit. This visit may be waived if the subject had already been seen at the study site ≥30 days after the most recent dose of investigational product in either study 0881A1-3338 or B1801023.

g. Subsequent observational visits will occur by telephone every 6 months (±4 weeks) after the first observational visit (if conducted) or after the re-treatment assessment visit. For subjects <18 years of age, telephone contacts will be conducted with the subject's parent or legal representative/guardian. For subjects aged ≥18 years, telephone contacts will be conducted with the subject or the subject's parent or legal representative/guardian. The number of telephone contacts will be adjusted based on when the subject enters the observational period.

h. The final observational visit will occur by telephone contact 96 months (±4 weeks) after the baseline visit of study B1801023.

i. For subjects in the withdrawal period, the following concomitant medications will be collected: DMARDs, corticosteroids, NSAIDs, and anti-infective agents. Only non-drug treatments received due to an adverse event will be collected.

j. For subjects in the observational period, the following concomitant medications will be collected: DMARDs, including any immunosuppressives or anti-TNFs and/or other immunosuppressive biologic agents; corticosteroids; and anti-infective agents taken for medically important infections. Only non-drug treatments received due to an adverse event will be collected.

k. Weight will be measured at every visit for subjects who are <18 years of age and who weigh ≤62 kg. For those subjects who are ≥18 years of age or weigh >62 kg, weight will be measured annually as part of the physical examination.

l. Tanner Stage Assessment will be performed annually for subjects <18 years of age or who have a score of <5 on 1 or more applicable domain(s). The Tanner Stage Assessment does not need to be repeated at the re-treatment assessment visit if it was performed within 2 months before the visit.

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

n. The evaluation of childbearing potential in female subjects must be documented in the subject's source documents.

o. Urine pregnancy tests will be performed at each of the visits in the withdrawal period for all female subjects who, in the opinion of the investigator, are of childbearing potential; this includes subjects who are menstruating at the time of the visit. For subjects entering directly into the withdrawal/re-treatment period, the baseline pregnancy test must be performed within 7 days before the baseline visit. Pregnancy tests will also be done whenever a menstrual cycle is missed during the withdrawal/re-treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

p. Discussion of sexual activity and use of contraception must be documented in the subject's source documents.

q. Assessment will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years, or directly by subjects aged ≥18 years at the time of the assessment.

r. Childhood Health Assessment Questionnaire (CHAQ) will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years at the time of the assessment; Health Assessment Questionnaire (HAQ) will be completed directly by subjects aged ≥18 years at the time of the assessment.

s. Adverse events will be collected from the signing of the informed consent document through 96 months after the baseline visit of study B1801023. For subjects who complete the Month 96 visit in either the active treatment period or the re-treatment period of study B1801023, adverse events will be collected until 30 days after the last dose of investigational product. Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and the baseline visit of study B1801023 must be recorded on the appropriate eCRF.

t. For subjects in the withdrawal period, all adverse events including malignancies, serious adverse events, infections, medically important infections (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization), and injection site reactions will be collected.

u. For subjects in the observational period, only serious adverse events, malignancies and medically important infections (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization), will be collected.

Abbreviations: CHAQ=Childhood Health Assessment Questionnaire; DMARD=Disease-Modifying Antirheumatic Drug; eCRF=electronic Case Report Form; HAQ=Health Assessment Questionnaire; IRB=Internal Review Board; IWR/IVR=interactive web response/interactive voice response; NSAID= Nonsteroidal Anti-inflammatory Drug; PGA=physician's global assessment; TNF=tumor necrosis factor

SCHEDULE OF ACTIVITIES – RE-TREATMENT PERIOD

For subjects who enter into the re-treatment period and receive investigational product in study B1801023

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Protocol Activity		Re-Treatment Period							Observational Period[e]		
	Months 3,6, 9[a]	Months 12, 24, 36, 48, 60, 72, 84[a]	Months 15, 27, 39, 51, 63, 75, 87[a]	Months 18, 30, 42, 54, 66,78, 90[a]	Months 21, 33, 45, 57, 69, 81, 93[a]	Month 96[b]	Re-treatment Early Withdrawal[c]	Follow-up[d]	1st Visit[f]	Subsequent Visits[g]	Final Visit (Month 96)[h]
Ensure the most recent version(s) of the informed consent/assent for withdrawal/re-treatment period has been signed and dated	X[i]										
Ensure that the subject meets the inclusion/exclusion criteria that apply to the re-treatment period	X[i]										
Collect/update contact information	X	X[i]	X	X	X		X		X	X	
Prior and concomitant medications/non-drug treatments	X[j]	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[k]	X[k]	X[k]
Height (cm)	X	X									
Weight (kg)[l]	X	X	X	X	X	X	X				
Temperature, Blood Pressure (mmHg), Pulse (Beats/min)	X	X	X	X	X	X	X				
Physical examination		X				X	X				
Tanner Stage Assessment[m]		X				X	X				
Hematology, Blood chemistry, C-reactive protein[n]	X	X		X		X	X				
Evaluate childbearing potential (females)[o]	X	X	X	X	X	X	X				
Urine pregnancy test[p]	X	X	X	X	X	X	X				
Discuss sexual activity and use of contraception, as appropriate[q]	X	X	X	X	X	X	X				
PGA of Disease Activity	X	X		X		X	X				
Parent/Patient Global Assessment[r]	X	X		X		X	X				
CHAQ/HAQ[s]	X	X		X		X	X				
Pain Assessment[r]	X	X		X		X	X				
Duration of Morning Stiffness[r]	X	X		X		X	X				

Protocol Activity		Re-Treatment Period							Observational Period[e]		
	Months 3,6, 9[a]	Months 12, 24, 36, 48, 60, 72, 84[a]	Months 15, 27, 39, 51, 63, 75, 87[a]	Months 18, 30, 42, 54, 66,78, 90[a]	Months 21, 33, 45, 57, 69, 81, 93[a]	Month 96[b]	Re-treatment Early Withdrawal[c]	Follow-up[d]	1st Visit[f]	Subsequent Visits[g]	Final Visit (Month 96)[h]
Joint Assessment	X	X		X		X	X				
Overall Back Pain and Nocturnal Pain (ERA only)[r]	X	X		X		X	X				
BASMI (ERA only)	X	X		X		X	X				
BSA (PsA only)	X	X		X		X	X				
PGA of Psoriasis (PsA only)	X	X		X		X	X				
Adverse events[t]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[v]	X[v]	X[v]	X[v]
Dispense visit reminder card	X	X	X	X	X	X	X		X	X	
Dispense IP and subject diary	X	X	X	X	X						
Collect returned IP and subject diary	X	X	X	X	X	X	X				
End of Treatment Subject Summary						X	X				
End of Study Subject Summary								X			X

a. The Month 3 to Month 96 visits must occur at the study site within ±14 days of the projected visit date based on the actual date of the re-treatment assessment visit.

b. Subjects who remain eligible for re-treatment will continue in the re-treatment period for a total of 96 months (±14 days) from the time of the baseline visit in study B1801023.

c. Subjects in the re-treatment period who withdraw from investigational product for any reason before completion of the Month 96 visit are required to complete the retreatment early withdrawal visit at the study site. At that time, the subject will be asked to participate in the observational period. Subjects may not enter the withdrawal/re-treatment period more than once during the study.

d. The follow-up visit will only completed for subjects who are receiving investigational product in either the active treatment period or the re-treatment period approximately 96 months after the baseline visit in study B1801023 and will occur at the study site 30 days (±7 days) after the Month 96 visit.

e. Subjects who receive at least 1 dose of investigational product in the re-treatment period of study B1801023 and withdraw from the re-treatment period before completion of the month 96 visit will be asked to be followed in the observational period for a total of 96 months from the time of the baseline visit in study B1801023. Once the subject is in the observational period, he or she cannot resume investigational product for the remaining time in the study.

f. For subjects who agree to participate in the observational period, the first observational visit will occur at the study site and will be scheduled 30 days (±7 days) after the retreatment early withdrawal visit.

g. Subsequent observational visits will occur by telephone every 6 months (±4 weeks) after the first observational visit. For subjects <18 years of age, telephone contacts will be conducted with the subject's parent or legal representative/guardian. For subjects aged ≥18 years, telephone contacts will be conducted with the subject or the subject's parent or legal representative/guardian. The number of telephone contacts will be adjusted based on when the subject enters the observational period.

h. The final observational visit will occur by telephone contact 96 months (±4 weeks) after the baseline visit of study B1801023.

i. Applies to the Month 3 visit.

j. For subjects in the re-treatment period, the following concomitant medications will be collected: DMARDs, corticosteroids, NSAIDs, and anti-infective agents. Only non-drug treatments received due to an adverse event will be collected.

k. For subjects in the observational period, the following concomitant medications will be collected: DMARDs, including any immunosuppressives or anti-TNFs and/or other immunosuppressive biologic agents; corticosteroids; and anti-infective agents taken for medically important infections. Only non-drug treatments received due to an adverse event will be collected.

l. Weight will be measured at every visit for subjects who are <18 years of age and who weigh ≤62 kg. For those subjects who are ≥18 years of age or weigh >62 kg, weight will be measured annually as part of the physical examination.

m. Tanner Stage Assessment will be performed annually for subjects <18 years of age or who have a score of <5 on 1 or more applicable domain(s). The Tanner Stage Assessment does not need to be repeated at the re-treatment assessment visit if it was performed within 2 months before the visit.

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

o. The evaluation of childbearing potential in female subjects must be documented in the subject's source documents.

p. Urine pregnancy tests will be performed at each of the visits in the re-treatment period for all female subjects who, in the opinion of the investigator, are of childbearing potential; this includes subjects who are menstruating at the time of the visit. Pregnancy tests will also be done whenever a menstrual cycle is missed during the re-treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

q. Discussion of sexual activity and use of contraception must be documented in the subject's source documents.

r. Assessment will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years, or directly by subjects aged ≥18 years at the time of the assessment.

s. Childhood Health Assessment Questionnaire (CHAQ) will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years at the time of the assessment; Health Assessment Questionnaire (HAQ) will be completed directly by subjects aged ≥18 years at the time of the assessment.

t. Adverse events will be collected from the signing of the informed consent document through 96 months after the baseline visit of study B1801023. For subjects who complete the Month 96 visit in either the active treatment period or the re-treatment period of study B1801023, adverse events will be collected until 30 days after the last dose of investigational product. Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and the baseline visit of study B1801023 must be recorded on the appropriate eCRF.

u. For subjects in the withdrawal period, all adverse events including malignancies, serious adverse events, infections, medically important infections(ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization), and injection site reactions will be collected.

v. For subjects in the observational period, only serious adverse events, malignancies and medically important infections (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization), will be collected.

Abbreviations: CHAQ=Childhood Health Assessment Questionnaire; DMARD=Disease-Modifying Antirheumatic Drug; eCRF=electronic Case Report Form; HAQ=Health Assessment Questionnaire; IRB=Internal Review Board; IWR/IVR=interactive web response/interactive voice response; NSAID= Nonsteroidal Anti-inflammatory Drug; PGA=physician's global assessment; TNF=tumor necrosis factor

SCHEDULE OF ACTIVITIES – OBSERVATIONAL PERIOD

For subjects who enter directly into the observational period and do not receive investigational product in study B1801023

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Protocol Activity	Day 1 (Baseline)	Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90[a]	Month 96[a]
	Observational Period		
Informed Consent/Assent	X		
Review inclusion and exclusion criteria	X		
Collect/update contact information	X	X	
Prior and concomitant medications/non-drug treatments[b]	X	X	X
Serious adverse events, malignancies, and medically important infections[c]	X	X	X
Dispense visit reminder card	X	X	
End of Study Subject Summary			X

a. The Month 6 to Month 96 visits will occur every 6 months (±4 weeks) after the baseline visit. For subjects <18 years of age, telephone contact will be conducted with the subject's parent or legal representative/guardian. For subjects aged ≥18 years, telephone contact will be conducted with the subject or the subject's parent or legal representative/guardian.

b. Prior and concomitant medications (DMARDs, including any immunosuppressives or anti-TNFs and other immunosuppressive biologic agents; corticosteroids; and anti-infective agents taken for medically important infections) and non-drug treatments received due to an adverse event.

c. Serious adverse events, malignancies, and medically important infections (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization) will be collected from the signing of the informed consent document through 96 months after the baseline visit of study B1801023. Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and the baseline visit of study B1801023 must be recorded on the appropriate eCRF.

Abbreviations: DMARD=Disease-Modifying Antirheumatic Drug; eCRF=electronic Case Report Form; TNF= tumor necrosis factor

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APPENDICES

1. INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common autoimmune-autoinflammatory disease in childhood and affects approximately 1 in 1,000 children. Despite advances in diagnosis and treatment options, JIA remains a chronic condition for most affected children. Etanercept is approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat pediatric patients with polyarticular JIA aged 2 years and above, who have had an inadequate response to, or who have proved intolerant of, methotrexate. In addition, etanercept is approved by the EMA for use in pediatric patients with severe plaque psoriasis from the ages of 6 to 17 years.

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular JIA, and the resulting joint pathology. Elevated levels of TNF are found in the synovial fluid of RA patients and in both the synovium and psoriatic plaques of patients with psoriatic arthritis.[1]

1.1. Indication

Etanercept is a TNF inhibitor that is being developed for the treatment of extended oligoarticular JIA, enthesitis related arthritis (ERA) or psoriatic arthritis (PsA) in pediatric patients.

1.2. Background and Rationale

JIA is a clinically heterogeneous group of several disease types that are characterized by arthritis beginning before the age of 16 years with symptoms persisting for more than 6 weeks. The International League Associations for Rheumatology (ILAR) classification defines 7 distinct subtypes of JIA: systemic arthritis, oligoarthritis (persistent oligoarthritis, extended polyarticular), polyarthritis rheumatoid factor (RF) positive, polyarthritis RF negative, PsA, ERA, and undifferentiated arthritis.

Protocol 0881A1-3338 (B1801014) was designed to assess the clinical benefit and the long-term safety of etanercept for 2 years in pediatric subjects with extended oligoarticular JIA, ERA or PsA. Protocol B1801023 is an 8-year extension study designed to further characterize the long-term safety profile, including malignancy and other serious adverse events, and clinical benefit for those pediatric subjects who received at least one dose of etanercept and completed 96 weeks of investigational product and/or follow-up in study 0881A1-3338.

At the time of the original approved B1801023 protocol, the product label allowed for the use of etanercept in polyarticular JIA, regardless of JIA onset type (refer to the current version of the Summary of Product Characteristics of etanercept for the latest approved indications).[2] The approval of etanercept in this indication was based on a controlled study which mainly enrolled subjects with polyarticular-onset JIA. Because of the relative paucity of data in other JIA subtypes, this study is being conducted to assess the long-term safety and clinical benefit of etanercept in subjects with extended oligoarticular JIA, ERA, or PsA. In

August 2012, the sponsor was granted approval to extend the indication for JIA to include three new subtypes of the disease and to include long-term safety information for the JIA population, together with reclassification of the licensed indication of polyarticular JIA into the International League of Associations for Rheumatology (ILAR) classification of polyarthritis (rheumatoid factor positive) and polyarthritis (rheumatoid factor negative).

Although the risk-benefit profile of etanercept in JIA has been well characterized, little is known about when or how to discontinue etanercept treatment in patients with JIA after a good clinical response has been achieved, nor are there guidelines from recognized bodies to define criteria for discontinuing treatment of etanercept.[3] Thus, the decision to temporarily hold or completely stop therapy is currently a clinical one made between the health care provider and the patient, and is not based on clinical practice guidelines. The criteria for clinically inactive disease in oligoarticular (persistent and extended), polyarticular (RF positive and negative), and systemic JIA have recently been revised by Wallace. Clinically inactive disease is defined as 1) no joints with active arthritis; 2) fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; 3) erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level within normal limits; 4) Physician Global Assessment (PGA) of disease activity score of best possible on scale used; 5) duration of morning stiffness of ≤ 15 minutes; and 6) no active uveitis.[4]

There are some limited data from retrospective studies in the literature regarding discontinuation of etanercept during disease remission. These data provide some support for the concept that etanercept can be withdrawn during remission, and in the event of relapse, restarted with a good clinical response. Remesal et al analyzed the progress of patients with JIA after discontinuation of etanercept and the clinical response to re-introduction of the drug in those who relapsed.[5] This retrospective chart review of patients between 2004 to 2009 revealed that therapy with etanercept had been discontinued in 26 patients with JIA who had achieved inactive disease using the original definition from Wallace et al for clinically inactive disease.[6] They note that the majority of patients (69%) relapsed after discontinuation of etanercept, the probability of remaining symptom-free at 6 months was 50%, and the response to re-introduction of treatment was satisfactory. They concluded that etanercept can be discontinued after an "as-yet undetermined period of disease inactivity," given that even if there is a relapse of disease patients will respond to re-introduction of etanercept. Prince et al found similar results in 9 patients with JIA who experienced relapse after withdrawal of etanercept.[7] Unlike Remesal et al, they found the period of remission after discontinuation of etanercept was not associated with the duration of inactive disease before the withdrawal of treatment nor the method of withdrawal used (i.e., tapering of treatment versus abrupt cessation), and all 8 patients re-treated with etanercept achieved subsequent remission of disease activity "promptly". Finally, a retrospective chart review of 171 JIA patients receiving anti-TNF agents, between 1998 and 2009 has recently been reported by Baszis et al.[8] Of the 171 patients included in the review, 75% received etanercept. Similar to the findings of Prince et al, no correlation between the risk of flare and the length of anti-TNF therapy after inactive disease was achieved was observed in this study. The median time to withdrawal of anti-TNF therapy after inactive disease was achieved was 6.1 months. Of the 136 patients with inactive disease at the time of cessation of TNF treatment, 25% experienced a disease flare within 3 months of the withdrawal of

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Etanercept 0.8 mg/kg once weekly (QW, up to a maximum dose of 50 mg QW) will be studied in this clinical trial. Based on a previous pediatric plaque psoriasis study, which used etanercept 0.8 mg/kg QW (up to a maximum dose of 50 mg QW), this dose was found to have similar pharmacokinetic and safety profiles to etanercept 0.4 mg/kg twice-weekly (BIW, up to a maximum dose of 25 mg BIW), which was used in the pediatric JIA studies. In the pediatric plaque psoriasis study using etanercept 0.8 mg/kg QW (up to a maximum dose of 50 mg QW) and in adult RA studies using etanercept 50 mg QW, etanercept was well tolerated and efficacious. In addition, the etanercept 0.8 mg/kg QW dose is generally more convenient for pediatric patients and their caregivers. In August 2012, the sponsor was granted approval of etanercept dosage regimen of 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for the treatment of JIA.

Complete information for etanercept may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure (IB).

The names, title, address and telephone number(s) of the sponsor's medical expert (Physician Clinician) for the trial is documented in the study contact list in the Study Reference Manual.

1.2.1. Disease Information

1.2.1.1. Extended Oligoarticular JIA

This subtype presents in children as young as 2 to 4 years of age and affects female patients more often than male patients.[9] The most commonly affected joints are the ankles and knees, with the knees being most affected. Children with this disease generally have a poorer prognosis than children with persistent oligoarthritis and 50% have active arthritis or disability as adults.[10]

In order to be diagnosed with extended oligoarticular JIA per the ILAR criteria, a patient must have arthritis affecting 1 to 4 joints during the first 6 months of the disease that progresses to affect more than 4 joints after the first 6 months of disease.

Given the positive effect of etanercept on both polyarticular-onset JIA as well as oligoarticular-onset JIA with polyarticular course, it is expected that etanercept will also be effective in extended oligoarticular JIA. This is further supported by sparse reports in the literature of extended oligoarticular JIA patients successfully treated with anti-TNF agents.[11]

1.2.1.2. Enthesitis-Related Arthritis

Ankylosing spondylitis (AS) in adults and ERA in children share a number of important features, including a key role for TNF-α in disease pathogenesis. These conditions in both adults and children appear to be immune mediated and unfold at the interface where articular cartilage and ligaments attach to bone.[13] ERA mainly affects male patients after the age of 6 years and is characterized by the association of enthesitis and arthritis. In some patients, arthritis may progress to affect the spine and the sacroiliac joint, as in adult AS.[14] ERA may be present with oligo or polyarthritis, affecting large or small joints as well as enthesitis. Compared with adult AS, ERA involves more peripheral joint involvement and less axial disease at disease onset.[10]

In order to be diagnosed with ERA per the ILAR criteria, a patient must have arthritis and enthesitis, or arthritis or enthesitis plus 2 of the following: 1) presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain; 2) the presence of human leukocyte antigen, subtype B, number 27 antigen (HLA-B27); 3) onset of arthritis in a male over 6 years of age; 4) acute (symptomatic) anterior uveitis; 5) a history of AS, ERA, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative.

Based upon the pathophysiology of the disease and the mechanism of action for etanercept, it is expected that etanercept will be effective in children with ERA. This is supported by sparse reports in the literature of juvenile subjects with ERA successfully treated with anti-TNF agents.[11, 15]

1.2.1.3. Psoriatic Arthritis

PsA in adults and children share a number of important features, including an immune-mediated mechanism and a key role for TNF-α in disease pathogenesis.[16] PsA mainly affects children over the age of 9, with males and females equally affected.[17] This disease is rare in children but the long-term outcome may be unfavorable and reports suggest that the need for disease-modifying anti-rheumatic drug (DMARD)/anti-TNF agents is frequent in this JIA subcategory.[18]

In order to be diagnosed with PsA per the ILAR criteria, a patient must have arthritis and psoriasis, or arthritis plus at least 2 of the following: 1) dactylitis; 2) nail pitting or onycholysis; 3) psoriasis in a first-degree relative.

Based upon the pathophysiology of the disease and the mechanism of action for etanercept, it is expected that etanercept will be effective in children with PsA. One (1) literature report of a small number of subjects with juvenile PsA successfully treated with etanercept was identified.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary

- To monitor the occurrence of malignancy in pediatric subjects with extended oligoarticular JIA, ERA, or PsA.

Secondary

- To assess the long-term safety profile of etanercept;
- To evaluate the long-term effect of etanercept on clinical benefit and physical function.

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2.2. Endpoints

- Multiple endpoints will be evaluated in the overall population and in each of the JIA subpopulations during the study to meet the stated objectives.

2.2.1. Primary Endpoint for All Subjects

- Occurrence of malignancy over the course of the study.

2.2.2. Secondary Endpoints for Subjects in the Observational Period

- Occurrence of serious adverse events, including serious infections;
- Occurrence of medically important infections (ie, an infection requiring hospitalization and /or parenteral [intravenous (IV), intra-muscular (IM)] anti-infective agents).

2.2.3. Secondary Endpoints for Subjects in the Active Treatment Period, and Withdrawal/Re-treatment Period

- Occurrence of serious adverse events, including serious infections;
- Occurrence of medically important infections (ie, an infection requiring hospitalization and /or parenteral [intravenous (IV), intra-muscular (IM)] anti-infective agents);

- Occurrence of all adverse events, including infections, infections considered preventable by vaccination, and injection site reactions;
- Occurrence of withdrawals from investigational product due to adverse events;
- Laboratory evaluations;
- Growth parameters;
- Tanner Stage Assessment for selected subjects;
- ACR Pediatric 30, 50, 70, 90, and 100, defined as ≥ 30% (and 50%, 70%, 90%, 100%, respectively) improvement from baseline in at least 3 of the 6 following variables, with no more than 1 of the remaining variables worsening by > 30 %:
    - Physician's Global Assessment (PGA) of Disease Activity on a 21-circle visual analogue scale (VAS);
    - Patient/Parent Global Assessment on a 21-circle VAS;
    - Childhood Health Assessment Questionnaire (CHAQ)/Health Assessment Questionnaire (HAQ);
    - Number of joints with active arthritis, defined as joints that are swollen or, in the absence of swelling, joints with limited range of motion accompanied by pain and/or tenderness;
    - Number of joints with limited range of motion;
    - Laboratory measure of inflammation, c-reactive protein (CRP);
- Individual components of the ACR Pediatric Assessments;
- Pain Assessment on a 21-circle VAS;
- Duration of morning stiffness in minutes;
- Clinically inactive disease defined as follows per Wallace Criteria:[12]
    - No joints with active arthritis (defined as joints that are swollen or, in the absence of swelling, joints with limited range of motion accompanied by pain and/or tenderness);
    - No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA;
    - No active uveitis;

- CRP level within normal limits in the laboratory where tested or, if elevated, not attributable to JIA;
- PGA of disease activity score of best possible on the scale used;
- Duration of morning stiffness of ≤ 15 minutes;

- The Juvenile Arthritis Disease Activity Score (JADAS), using 4 components (PGA of Disease Activity, Patient/Parent Global Assessment, number of joints with active arthritis and CRP).[20]

2.2.3.1. Additional Secondary Endpoints for ERA Subjects

- Overall Back Pain and Nocturnal Back Pain on a 100 mm VAS;
- Bath Ankylosing Spondylitis Metrology Index (BASMI) and its components (Intermalleolar Distance, Cervical Rotation, Modified Schober's Test, Lateral Flexion, and Tragus to Wall Distance).

2.2.3.2. Additional Secondary Endpoints for PsA Subjects

- Body Surface Area (BSA);
- PGA of Psoriasis.

2.2.4. Health Outcomes Assessment for Subjects in the Active Treatment Period, and Withdrawal/Re-treatment Period

- Childhood Health Assessment Questionnaire (CHAQ): for subjects aged <18 years at the time of assessment;
- Health Assessment Questionnaire (HAQ): for subjects aged ≥18 years at the time of assessment.

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3. STUDY DESIGN

This is an open-label, single treatment, multi-center, 8-year extension study in pediatric subjects who have been diagnosed with one of 3 subtypes of JIA (extended oligoarticular JIA, ERA, or PsA), have received at least one dose of etanercept and completed approximately 96 weeks of participation in study 0881A1-3338. These subjects will be asked to participate in study B1801023.

It is anticipated that approximately 100 subjects will be enrolled in study B1801023. This 96-month study contains 3 periods: an active treatment period, a withdrawal/re-treatment period, and an observational period.

Active treatment period:

- Subjects who completed approximately 96 weeks of active treatment with investigational product (etanercept) in study 0881A1-3338 and are eligible to continue investigational product in study B1801023 will enter directly into the active treatment period. These subjects may continue to receive investigational product for up to 8 additional years (96 months).

Withdrawal/Re-treatment period:

- **Withdrawal:** Subjects who have either completed approximately 96 weeks of treatment in study 0881A-3338 or were enrolled in the active treatment period of study B1801023 and who have either met the Wallace definition for clinically inactive disease for at least 6 months on investigational product (etanercept) or who, in the investigators judgment, have had a good clinical response and would benefit from withdrawal from investigational product and are otherwise eligible can enter the withdrawal/re-treatment period. However, the withdrawal/re-treatment period is optional and it is ultimately up to the investigator and subject to determine when the subject should be withdrawn from treatment.

- **Re-treatment:** Subjects requiring re-treatment per the investigator's clinical judgment and who are otherwise eligible will be offered the option to re-start treatment with investigational product.

Subjects may not enter the withdrawal/re-treatment period more than once during the study.

Observational period:

All subjects will be followed for a total of 8 years from the time of initial entry into the study as follows:

- Subjects who discontinued investigational product prior to completing 96 weeks of active treatment in study 0881A1-3338 for any reason or who are not eligible to continue investigational product in study B1801023 will not be permitted to re-start investigational product in study B1801023 and will be asked to enter the observational period.

- Subjects who participate in the active treatment period of study B1801023 and subsequently discontinue use of investigational product at any time before completion of the study and do not participate in the withdrawal/re-treatment period for any reason (i.e., ineligible or subject declined participation) will be asked to participate in the observational period.

- Subjects who participate in the withdrawal period and are ineligible for re-treatment with investigational product for any reason will be asked to participate in the observational period.

- Subjects who participate in the re-treatment period and subsequently discontinue investigational product prior to the completion of the study will be asked to participate in the observational period.

Once a subject enters into the observational period, he or she cannot resume investigational product for the remaining time in the study. Subjects participating in the observational period of study B1801023 may receive standard of care including any anti-TNF agents (eg, commercial etanercept) and/or other immunosuppressive biologic agents for treatment of their disease at the discretion of the investigator.

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 surveillance in the observational period or receipt of investigational product in the active treatment period and/or withdrawal/re-treatment period is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

4.1.1. Inclusion Criteria for All Subjects at Baseline

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. 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 (and assent document, as applicable) indicating that the subject (and/or a legal representative/guardian(s) as applicable according to subject age and local guidelines) has been informed of all pertinent aspects of the period of the study in which participation is being considered.

2. Subjects who are willing and able to comply with all applicable aspects of the period of the study in which participation is being considered, including scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Receipt of at least 1 dose of investigational product and participation for approximately 96 weeks in study 0881A1-3338.

4. The subject and/or the parent or legal representative/guardian of the subject must be able to provide contact information, including primary care physician or other treating physician.

4.1.2. Additional Inclusion Criteria for Subjects Planning to Continue Investigational Product in the Active Treatment Period

Subjects must meet the following additional inclusion criteria at the baseline visit to be eligible to continue investigational product in study B1801023:

1. Have completed approximately 96 weeks of investigational product in study 0881A1-3338 and, in the investigator's judgment, is appropriate to continue treatment with etanercept.

2. Either the subject or an available adult must be capable (according to the investigator's judgment) of reconstituting and administering injections of subcutaneous (SC) etanercept.

3. The subject, parent, or legal representative/guardian of the subject must be able to read and complete the protocol-specified efficacy assessments.

4. The first dose of investigational product in study B1801023 must be administered within 6 weeks of receiving the last dose of investigational product in the study 0881A1-3338.

4.1.3. Additional Inclusion Criteria for Subjects Planning to Enter in the Withdrawal/Re-treatment Period

1. Evidence of a personally signed and dated informed consent document (and assent document, as applicable) indicating that the subject (and/or a legal representative/guardian(s) as applicable according to subject age and local guidelines) has been informed of all aspects of the withdrawal/re-treatment period of the study. Only one informed consent document/assent will be signed and dated for the withdrawal/re-treatment period.

2. The subject is willing and able to comply with all applicable aspects of the withdrawal/re-treatment period of the study, including scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. The subject and/or the parent or legal representative/guardian of the subject must be able to provide contact information, including primary care physician or other treating physician.

4. For subjects entering directly into the withdrawal/re-treatment period, have completed approximately 96 weeks of investigational product in study 0881A1-3338.

5. For subjects entering directly into the withdrawal/re-treatment period, the baseline visit in study B1801023 must be completed within 14 days of the last dose of investigational product in study 0881A1-3338.

6. The subject has met the Wallace definition for clinically inactive disease for at least 6 months on investigational product (etanercept) or, in the investigator's judgment,

has had a good clinical response and would benefit from withdrawal from investigational product.

7. The subject, parent, or legal representative/guardian of the subject must be able to read and complete the protocol-specified efficacy assessments.

4.1.3.1. Additional Inclusion Criteria for Subjects Planning to Restart Investigational Product in the Re-treatment Period

1. Re-treatment with investigational product should be based on the investigator's clinical judgment as long as all other inclusion/exclusion criteria for re-treatment period are met.

2. Either the subject or an available adult must be capable (according to the investigator's judgment) of reconstituting and administering injections of subcutaneous (SC) etanercept.

4.2. Exclusion Criteria

4.2.1. Exclusion Criteria for All Subjects at Baseline

Subjects presenting with any of the following will not be included in the study:

1. Subjects who are investigational site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

4.2.2. Additional Exclusion Criteria for Subjects Planning to Continue Investigational Product in the Active Treatment Period

Subjects who completed approximately 96 weeks of investigational product in study 0881A1-3338 and present with any of the following will not be allowed to continue investigational product in study B1801023:

1. Withdrawal from investigational product in study 0881A1-3338 for any reason.

2. History of malignancy other than squamous cell, basal cell carcinoma or cervical carcinoma in situ.

3. Participation in other clinical studies of investigational drugs or investigational combinations of approved drugs between the week 96 visit in study 0881A1-3338 and the baseline visit in study B1801023 or during participation in the active treatment period of study B1801023.

4. Pregnant or breastfeeding female subjects.

5. Receipt of any of the following between the week 96 visit in study 0881A1-3338 and the baseline visit in study B1801023:

- Any immunosuppressive biologic drugs, including but not limited to TNF inhibitors (other than etanercept), abatacept, rituximab, anakinra and tocilizumab;

- Immunosuppressive drugs (excluding corticosteroids) (eg, cyclophosphamide, cyclosporine, azathioprine);

- Leflunomide;

- Use of more than 1 of the non-biologic DMARDs permitted in study 0881A1-3338 (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine) in subjects <18 years of age;

- Use of more than 2 of the non-biologic DMARDs permitted in study 0881A1-3338 (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine) or hydroxychloroquine and chloroquine taken at the same time in subjects ≥18 years of age;

- Non-biologic DMARDs other than those permitted in study 0881A1-3338 (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine), or those not listed under other exclusion criteria;

- Any live (attenuated) vaccines.

6. 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.

7. Signs and symptoms or suspicion of active tuberculosis.

4.2.3. Additional Exclusion Criteria for Subjects Planning to Enter in the Withdrawal/Re-treatment Period

1. Withdrawal from investigational product in study 0881A1-3338 for any reason.

2. Prior and/or current participation in the observational period of study B1801023.

3. Prior and/or current participation in the withdrawal/re-treatment period of study B1801023.

4.2.3.1. Additional Exclusion Criteria for Subjects Planning to Restart Investigational Product in the Re-treatment Period

1. History of malignancy other than squamous cell, basal cell carcinoma or cervical carcinoma in situ.

2. Participation in other clinical studies of investigational drugs or investigational combinations of approved drugs during participation in study B1801023.

3. Pregnant or breastfeeding female subjects.

4. Receipt of any of the following during participation in study B1801023:

    - Any immunosuppressive biologic drugs, including but not limited to TNF inhibitors (other than etanercept), abatacept, rituximab, anakinra and tocilizumab;

    - Immunosuppressive drugs (excluding corticosteroids) (eg, cyclophosphamide, cyclosporine, azathioprine);

    - Leflunomide;

    - Use of more than 1 of the non-biologic DMARDs permitted in study B1801023 (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine) in subjects <18 years of age;

    - Use of more than 2 of the non-biologic DMARDs permitted in study B1801023 (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine) or hydroxychloroquine and chloroquine taken at the same time in subjects ≥18 years of age;

    - Non-biologic DMARDs other than those permitted in study B1801023 (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine), or those not listed under other exclusion criteria;

5. Receipt of any live (attenuated) vaccine within 4 weeks after the last dose of investigational product in active treatment period and within 8 weeks prior to the first dose of investigational product in the re-treatment period.

6. Any of the following laboratory abnormalities based on the most recent laboratory results:

    - White blood cell (WBC) count <3.50 x 10^3/mm^3 (SI units: <3.50 x 10^9/L) and neutrophils < 1x10^9/L;

    - Hemoglobin < 8.5 g/dL (SI units: <85 g/L);

    - Platelet Count < 125,0000/mm^3 or ≥1,000,000/mm^3 (SI units: <125 x 10^9/L or ≥1,000 x 10^9/L);

    - Aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT) ≥ 2.0 x upper limit of normal (ULN);

- Should the laboratory results drawn at the time of re-treatment shows that the subject has met any of the above laboratory exclusions, the subject may be withdrawn from investigational product at that time (refer to Section 6.1.4).

7. 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 the re-treatment period of this study.

8. Signs and symptoms or suspicion of active tuberculosis.

4.3. Life Style Guidelines

4.3.1. Pregnancy Testing

At the baseline visit and each subsequent visit in the active treatment period, and the withdrawal/re-treatment period, including the early withdrawal visit(s) and the re-treatment assessment visit, childbearing potential must be evaluated in female subjects and the evaluation must be documented in the subject's source documents. Female subjects who, in the opinion of the investigator, are biologically capable of having children (of childbearing potential) must have a urine pregnancy test performed within 7 days prior to the baseline (day 1) visit and at each of the visits while participating in the active treatment period, and the withdrawal/re-treatment period; including the early withdrawal visit(s) and the re-treatment assessment visit; this includes subjects who are menstruating at the time of the visit. A negative urine pregnancy test must be obtained prior to administration and/or dispensing of investigational product at each visit in the active treatment period, and re-treatment period.

Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period and withdrawal/re-treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or if required by local regulations.

4.3.2. Sexually Active Female Subjects

As appropriate, sexual activity must be discussed with subjects at the baseline visit and each subsequent visit in the active treatment period, and in the withdrawal/re-treatment period, including the early withdrawal visit(s) and the re-treatment assessment visit. For those subjects who either plan on becoming sexually active or who are sexually active, the requirement for highly effective methods of contraception outlined below must also be discussed. The discussion must be documented in the subject's source documents.

All female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree and commit to the use of a highly effective method of birth control (failure rate less than 1% when used consistently and correctly) for the duration of the active treatment period, and withdrawal/re-treatment period of the study and for 30 days after the last dose of investigational product for those subjects entering into

the observational period. According to investigator judgment, subjects may need to continue using a highly effective method of contraception beyond 30 days after the last dose of investigational product for those subjects entering into the observational period based on concomitant medications (eg, MTX) or local guidelines.

Medically-approved methods of contraception for this study include the following:

- Properly used barrier contraception with spermicide;
- Hormonal contraceptive; either oral, injectable, implanted or patch delivery systems;
- Intrauterine device (IUD);
- Documented surgical sterilization, such as tubal ligation, hysterectomy or bilateral oophorectomy.

4.3.3. Sexually Active Male Subjects

As appropriate, sexual activity must be discussed with subjects at the baseline visit and each subsequent visit in the active treatment period, and in the withdrawal/re-treatment period, including the early withdrawal visit(s) and the re-treatment assessment visit. For those subjects who either plan on becoming sexually active or who are sexually active, the requirement for highly effective methods of contraception outlined below must also be discussed. The discussion must be documented in the subject's source documents.

Sexually active male subjects must agree to use highly effective method contraception (failure rate <1% when used consistently and correctly, such as properly used barrier contraception with spermicide or surgical sterilization and appropriately confirmed absence of sperm in the post vasectomy ejaculate) to protect his partner from becoming pregnant during the active treatment period, and in the withdrawal/re-treatment period of the study and for at least 30 days after the last dose of investigational product for those subjects entering into the observational period. According to investigator judgment, subjects may need to continue using a highly effective method of contraception beyond 30 days after the last dose of investigational product for those subjects entering into the observational period based on concomitant medications (eg, MTX) or local guidelines.

4.4. 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 MyTrials 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. For sites other than a Pfizer Clinical Research Unit, 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 TREATMENT

The following only applies to those subjects who are in the active treatment period, or the re-treatment period in this study:

- Etanercept will be provided as investigational product by the sponsor throughout the course of the subject's participation in this study for up to 8 years (96 months) unless early withdrawal of treatment is warranted.

- Subjects aged <18 years and ≤62 kg will receive etanercept SC at a dose of 0.8 mg/kg QW (up to a maximum dose of 50 mg QW).

- Subjects aged ≥18 years or >62 kg will receive etanercept SC at a dose of 50 mg QW.

- No dose reductions of etanercept are permitted, except those due to changes in the subject's weight (ie, for subjects aged <18 years and weighing ≤62 kg).

    - If more than 4 consecutive doses are missed due to AEs, infections, or surgeries, or if more than 2 consecutive doses are missed due to reasons other than AEs, infections, or surgery (eg, subject forgot to take investigational product or away from home without enough investigational product), the Pfizer Clinical Team must be consulted in order to determine whether the subject should continue taking investigational product.

    - Tapering of the investigational product (ie, prescription or receipt of a dose lower than that described in Section 5 or less than once-weekly on an average basis) is not allowed.

5.1. Allocation to Treatment

Enrollment and assignment to investigational product will be accomplished using interactive web response/interactive voice response (IWR/IVR, an automated web/telephone randomization system provided by the sponsor). At the baseline visit, the investigative site will contact the IWR/IVR (online or by telephone call). The site will enroll the subject into the IWR/IVR by indicating minimal information sufficient to distinguish one subject from another (eg, date of birth) and receive the Subject ID number.

For subjects entering into the active treatment period, or re-treatment period, the IWR/IVR system will allocate investigational product according to the subject's age and weight and assign a randomization number. Sites must access the IWR/IVR system each time investigational product is dispensed.

The use of the IWR/IVR allows for proper drug coverage by monitoring enrollment, inventory and drug shipments.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Investigational product will be provided by the sponsor:

- Subjects aged <18 years and ≤62 kg will be provided with vials containing lyophilized etanercept 25 mg with pre-filled syringes of sterile water for injection.

- Subjects aged ≥18 years or >62 kg will be provided with pre-filled syringes containing etanercept 50 mg diluted in 1.0 ml of sterile water for injection or vials containing lyophilized etanercept 25 mg with pre-filled syringes of sterile water for injection.

5.2.2. Preparation and Dispensing

Refer to separate instructions regarding the preparation, and administration of the investigational product.

At each dispensing visit in the active treatment period and the re-treatment period, subjects will receive sufficient quantities of investigational product to last until the next scheduled visit. Investigational product will not be dispensed at the early withdrawal or month 96 visit.

5.2.3. Administration

The dose of etanercept will be based on the subject's weight and age at the previous visit. Therefore, if the subject's weight or age changes then the dose will be increased or decreased accordingly. The investigational product should be administered QW on the same day of the week throughout the study. 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 regularly scheduled day (eg, 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 may be taken as soon as possible and the subsequent dose must not be given sooner than 4 days later.

All doses will either be self-administered or given by a designated person at the subject's home. Study personnel will provide training to the person designated to administer the investigational product on how to store the investigational product at home and how and when to administer the investigational product. The individual administering the investigational product must demonstrate competency to the site staff regarding their ability to correctly administer the SC dose. The subject or person designated to administer the

investigational product and the site's assessment of this person will be documented in the subject's source documents. If necessary, doses may be given at the study site until the person designated to administer the investigational product feels comfortable administering the dose.

Subjects will also be given a diary card on which their subject number and the date of their next appointment will be written. For subjects in the active treatment period and re-treatment period, the diary will also be used by the person designated to administer the investigational product to record the date of each of the SC injection(s), the volume (mL) delivered from each syringe, the injection site location, and the reason for change from the protocol-specified dose (if applicable).

5.2.3.1. Medication Errors

A medication error is any preventable event that may cause or lead to inappropriate investigational use or subject harm while the investigational product is in control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Medications errors are to be captured on the medication error CRF page irrespective of the presence of an associated adverse event/serious adverse event, including, but not limited to the following:

- 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, including doses that differ from the calculated dose based on the subject's age and weight by >20%.
    - (([administered dose, mg] – [expected dose, mg])/[expected dose]) X 100% is greater than 20% for an overdose or less than -20% for an underdose.
    - Note: missed doses of investigational product are not considered to be a medication error.
- Errors in the reconstitution of the investigational product, including use of the wrong diluents, and deviations from the protocol-specified timeframe in which the investigational product should be used after reconstitution (see Drug Storage and Accountability section).
- 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 as outlined in Section 5.2.5).

- Administration of etanercept from a commercial supply rather than etanercept 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 adverse event, as determined by the investigator, the medication error is captured on the medication error CRF and, if applicable, any associated adverse event(s) is captured on an adverse event CRF page (refer to adverse event reporting section for further details).

In the event of a medication error involving investigational product, a site staff member (ie, Investigator, Study Coordinator) must inform the sponsor's site monitor of the incident.

5.2.4. Compliance

Compliance will be monitored by study personnel at each study visit using diary cards, and verbal information from the parent and/or subject. Reasons for missed doses must be recorded in the subject's source documents and CRF.

Subjects provided with vials will be instructed to return all investigational product packages and vials (including used, empty, and unused vials). Subjects provided with pre-filled syringes will be instructed to return the empty investigational product packages and unused prefilled syringes in order to review drug accountability and subject compliance.

If more than 4 consecutive doses are missed due to AEs, infections, or surgeries, or if more than 2 consecutive doses are missed due reasons other than AEs, infections, or surgery (eg, subject forgot to take investigational product or away from home without enough investigational product), the Pfizer Clinical team must be consulted in order to determine whether the subject should continue taking investigational product.

Tapering of the investigational product (i.e., prescription or receipt of a dose lower than that described in Section 5 or less than once-weekly on an average basis) is not allowed.

5.2.5. Drug Storage and Drug Accountability

The investigational product must be stored under refrigerated conditions (2°C - 8°C). The investigational product must not be frozen. For subjects using lyophilized vials of etanercept, after reconstitution of the investigational product, the solution may be stored upright in a refrigerator (2°C – 8°C) for up to 6 hours. Storage conditions stated in the IB and/or local product package insert will be superseded by the storage conditions stated on the investigational product label.

The investigational product must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor's site monitor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

The subject or the designated person will be given instructions regarding the reconstitution and storage of etanercept.

The investigator, or approved representative (eg, pharmacist) must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. Pfizer may supply drug accountability forms to be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or package numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities dispensed. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.

All unused investigational product must be returned to the study site. Subjects must return all investigational product packages and vials (including used, empty, and unused etanercept vials); subjects provided with pre-filled syringes will be instructed to return the empty investigational product packages and unused pre-filled syringes to the investigative site. Drug accountability will be reviewed by the monitor during routine monitoring visits. Returned and/or used investigational product can be destroyed only after the monitor has verified the accuracy of the dispensing and inventory record. The monitor must verify that site staff follows instructions regarding the return of investigational product to the Supply Chain Organization or vendor for destruction.

Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction 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. Destruction must be adequately documented.

5.3. Concomitant Medication(s)

Any medication that the subject takes other than investigational product specified in the protocol after signing the informed consent document is considered concomitant medication.

Active treatment period: Concomitant DMARDs, corticosteroids (including intra-articular injections), nonsteroidal anti-inflammatory drugs (NSAIDs), and anti-infective agents will be reported on the appropriate eCRF up to the final follow-up visit.

Withdrawal/re-treatment period: Concomitant DMARDs, corticosteroids (including intra-articular injections), NSAIDs, and anti-infective agents will be reported on the appropriate eCRF up to the final follow-up visit.

Observational period: Concomitant DMARDs (including any immunosuppressives or anti-TNFs and other immunosuppressive biologic agents), corticosteroids (including intra-articular injections), and anti-infective agents taken for medically important infections will be reported on the appropriate eCRF up to the month 96 visit.

The start date, stop date (if applicable), dose, unit, frequency, route of administration, and indication for use for concomitant DMARDs, corticosteroids, NSAIDs, and anti-infective agents will be recorded on separate CRFs.

Concomitant medications other than those listed above will not be recorded on the study eCRFs, but must be maintained in the subject's source documents.

The start date and stop date (if applicable) of non-drug treatments received due to an adverse event will be reported on a separate CRF throughout all periods up to the month 96 visit or the final follow-up visit, as applicable.

5.3.1. Prohibited and/or Permitted Medication(s)

Subjects who are participating in the observational period may receive standard of care medications including any anti-TNF agents (eg, commercial etanercept) and other immunosuppressive biologic agents for treatment of their disease at the discretion of the investigator. However, subjects entering the observational period are not permitted to receive any live (attenuated) vaccines within 4 weeks after the last dose of investigational product in the active treatment period or re-treatment period.

The following prohibited and/or permitted medications/treatments will only apply to subjects while they are in the active treatment period and withdrawal/re-treatment period of this study.

Prohibited medications and/or treatments during active treatment period and withdrawal/re-treatment period:

1. Use of more than 1 permitted non-biologic DMARD (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine) in subjects <18 years of age.

2. Use of more than 2 of the permitted non-biologic DMARDs (ie, methotrexate, hydroxychloroquine, chloroquine, sulfasalazine) or hydroxychloroquine and chloroquine taken at the same time in subjects ≥18 years of age.

3. Non-biologic DMARDs (other than methotrexate, hydroxychloroquine, chloroquine, or sulfasalazine), immunosuppressive agents (including azathioprine, cyclosporine, cyclophosphamide), TNF inhibitors (other than investigational product) or other immunosuppressive biologic agents.

4. Chronic use of more than 1 NSAID.

5. Any other investigational drugs or investigational combinations of approved drugs.

6. Plasma exchange therapy.

7. Any live (attenuated) vaccines:

    - At any time while receiving investigational product in the active treatment period or the re-treatment period;

- Within 4 weeks after the last dose of investigational product in active treatment period and within 8 weeks before the last dose of investigational product in the re-treatment period.

8. The 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 (See Withdrawal Section).

Additional prohibited medications and/or treatment for subjects with PsA:

9. Receipt of psoralen + ultraviolet A (PUVA), ultraviolet A (UVA), or ultraviolet B (UVB) therapy, including narrow band UVB and excimer laser.

10. Oral retinoids.

Permitted medications and/or treatments during active treatment period and withdrawal/re-treatment period:

1. Subjects <18 years of age may take no more than 1 of the 4 following permitted non-biologic DMARDs at the same time. Subjects ≥18 years of age may take no more than 2 of the 4 following permitted non-biologic DMARDs at the same time (hydroxychloroquine and chloroquine must not be taken at the same time). Subjects may either start a permitted non-biologic DMARD, continue at same dose, reduce the dose, stop taking the permitted non-biologic DMARD, or switch to a different permitted non-biologic DMARD; subjects ≥18 years may also add 1 of the permitted DMARDs to the existing DMARD.

    - Hydroxychloroquine (≤ maximum recommended dose per local product information);

    - Chloroquine (≤ maximum recommended dose per local product information);

    - Sulphasalazine (≤ maximum recommended dose per local product information);

    - Methotrexate (≤15 mg/m^2/week not to exceed 20 mg/week in subjects aged <18 years or 25 mg/week in subjects aged ≥18 years).

2. The following treatments may be adjusted at the discretion of the investigator using the lowest possible dose:

    a. Oral corticosteroids (≤0.2 mg/kg/day up to a maximum dose of 10 mg/day of prednisone or equivalent).

    b. No more than a total of 3 administrations per calendar year for any of the following corticosteroid regimens:

- Oral corticosteriods: The dose may be increased to no more than 40 mg prednisone/day (or equivalent) for no more than 3 days and then dose tapered over no more than 2 weeks to a stable daily dose that is ≤0.2 mg/kg/day up to a maximum dose of 10 mg/day of prednisone or equivalent.

- IV or IM corticosteroid injections: The dose of corticosteroid injected at each time point should not exceed the anti-inflammatory equivalent dose of methylprednisolone suspension (up to 60 mg).

c. No more than 6 intra-articular (IA) or soft tissue corticosteroid injections may be administered per calendar year. The dose of corticosteroid injected at each time point should not exceed the anti-inflammatory equivalent dose of methylprednisolone suspension (up to 40 mg).

d. No more than 1 NSAID may be used on a chronic basis (≤ maximum recommended dose per local product information or local guidelines);

- An additional NSAID may be given as needed for acute conditions (≤ maximum recommended dose per local product information or local guidelines).

- Subjects may switch to a different NSAID at the discretion of the investigator.

e. Folic acid prophylaxis is recommended for all subjects receiving methotrexate;

f. Simple short-acting analgesics without anti-inflammatory action and/or short acting oral narcotic analgesics (such as acetominophen/paracetamol, codeine, dihydrocodeine, or tramadol, alone or in combination) may be used at the discretion of the investigator (≤ maximum recommended dose per local product information or local guidelines);

g. Physical therapy and therapeutic exercise;

h. Medications and treatments for acute or chronic conditions not listed under the prohibited treatments.

Additional permitted medications for subjects with PsA:

3. The dose and type of the following may be adjusted at the discretion of the investigator:

   a. Topical steroids and tar-based shampoos on all regions;

   b. Topical vitamin A or D analog preparations;

c. Anthralin.

6. STUDY PROCEDURES

6.1. Study Procedures for Subjects in the Active Treatment Period or Withdrawal/Re-treatment Period

Whenever possible, every effort must be made to ensure that the same investigator performs the investigator assessments (ie, physical assessment, Tanner Assessment, PGA of Disease Activity, Joint Assessment, BASMI, PGA of Psoriasis, Body Surface Area) for a subject throughout the study. Worksheets will be provided to the site to record the results of the assessments and must be maintained with the subject's source documents.

Throughout the study, the Patient/Parent Global Assessment, Pain Assessment, Duration of morning stiffness, Overall Back Pain and Nocturnal Pain will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years at the time of the assessment; these will be completed directly by subjects aged ≥18 years at the time of the assessment. The CHAQ will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years at the time of the assessment; the HAQ will be completed directly by subjects aged ≥18 years at the time of the assessment.

The health outcomes assessments (ie, CHAQ/HAQ) are for the purpose of exploring the subject's own perceptions about his/her quality of life. The investigator must not influence the subject's assessment. Every effort should be made by site personnel to maintain an unbiased assessment.

Refer to the Schedule of Activities flowchart of the protocol.

6.1.1. Active Treatment Period

6.1.1.1. Baseline Procedures for Subjects Planning to Participate in the Active Treatment Period

Baseline procedures may not commence until after the informed consent and assent (as applicable) have been signed. The study investigator or a sub-investigator will discuss with each subject and parent(s) (as applicable according to subject age and local guidelines) the nature of the study, its requirements, and its restrictions.

Every attempt should be made to complete the study B1801023 baseline visit on the same day as the study 0881A1-3338 Week 96 visit. For subjects planning to continue investigational product, the baseline visit (Day 1) of study B1801023 must occur within 6 weeks of the last dose of investigational product received in study 0881A1-3338.

The following baseline procedures and assessments must be completed for all subjects in the active treatment period:

1. Sign and date informed consent/assent for active treatment period.

2. Review inclusion/exclusion criteria that apply to all subjects and that apply to subjects planning to continue investigational product in study B1801023.

    - Those subjects who do not meet entry criteria for continuing investigational product in study B1801023 will be asked to participate in the observational period in study B1801023.

3. Collect/update contact information, including primary care physician or other treating physician.

4. For female subjects, evaluate childbearing potential. The evaluation must be documented in the subject's source documents.

5. Female subjects who, in the opinion of the investigator, are of childbearing potential will have a urine pregnancy test, which must be preformed within 7 days before the baseline visit; this includes subjects who are menstruating at the time of the visit. If a pregnancy test was collected at the week 96 visit in study 0881-3338, and the visit occurred within 7 days of the baseline visit, a urine pregnancy test does not have to be repeated as long as the test result was negative. For these subjects, a negative test result must be available before dispensing and administration of investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

6. As appropriate, discuss sexual activity. For those subjects who either plan on becoming sexually active or who are sexually active, discuss requirement for highly effective methods of contraception (refer to Section 4.3.2 for female subjects and Section 4.3.3 for male subjects). The discussion must be documented in the subject's source documents.

7. BASMI and its components (Intermalleolar Distance, Cervical Rotation, Modified Schober's Test, Lateral Flexion, and Tragus to Wall Distance) only for ERA subjects.

8. Prior and concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event. Medications reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must be recorded on the appropriate CRF.

9. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions. Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must be recorded on the appropriate CRF.

The following additional baseline procedures and assessments must be completed for subjects in the active treatment period with >14 days between the study 0881A1-3338 week 96 visit and the study B1801023 baseline visit:

10. Physical examination (performed by a physician).

    - The physical examination will include completion of the Tanner Assessment for subjects <18 years or who have a score of <5 on 1 or more applicable domain(s).

11. Vital signs: Temperature, blood pressure (mmHg) and pulse rate (beats/min, after sitting for at least 5 minutes).

12. Height (cm).

13. Weight (kg):

14. Laboratory evaluations (ie, hematology, blood chemistry, and CRP).

15. PGA of Disease Activity.

16. Patient/Parent Global Assessment, according to the subject's age at the time of the assessment.

17. Pain Assessment. The Pain Assessment should be completed before the Joint Assessment.

18. Duration of Morning Stiffness.

19. Joint Assessment including joints with limitation of motion.

20. Overall Back Pain and Nocturnal Back Pain (ERA subjects only).

21. BSA (PsA subjects only).

22. PGA of Psoriasis (PsA subjects only).

23. CHAQ or HAQ, according to the subject's age at the time of the assessment.

24. Randomization/Registration.

Once all baseline procedures have been completed and it has been confirmed that the subject is eligible to enter the active treatment period, the study staff will use the IWR/IVR to allocate investigational product packages. The investigational product, investigational product instructions, subject diary and reminder card for their next scheduled visit will then be dispensed to the subject.

For subjects with ≥7 days since the previous dose of investigational product in study 0881A1-3338, the first dose of investigational product in study B1801023 may be administered at the study site to maintain the QW dosing schedule.

6.1.1.2. Active Treatment Period – Month 3 to Month 96 Visits

For subjects in the active treatment period, study visits will be scheduled at the study site at Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, and 96 (within ±14 days of the projected visit date based on the actual baseline visit date).

The following safety and efficacy evaluations will be performed at all visits during the active treatment period unless otherwise indicated:

1. Collect/update contact information, including primary care physician or other treating physician.

2. Concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event.

3. Physical examination (performed by a physician at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

    - The physical examination will include completion of the Tanner Assessment for subjects <18 years or who have a score of <5 on 1 or more applicable domain(s).

4. Vital signs: Temperature, blood pressure (mmHg) and pulse rate (beats/min, after sitting for at least 5 minutes).

5. Height (cm, at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

6. Weight (kg):

    - For subjects who are <18 years of age and who weigh ≤62 kg (at all visits).

    - For subjects who are ≥18 years of age or weigh >62 kg (at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

7. Laboratory evaluations (ie, hematology, blood chemistry, and CRP, at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only). Additional testing may be performed according to local guidelines or standard of care and for follow-up of abnormal laboratory test results.

8. For female subjects, evaluate childbearing potential. The evaluation must be documented in the subject's source documents.

9. Female subjects who, in the opinion of the investigator, are of childbearing potential will have a urine pregnancy test at each visit; this includes subjects who are

menstruating at the time of the visit. For these subjects, a negative test result must be available before dispensing and/or administration of investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

10. As appropriate, discuss sexual activity. For those subjects who either plan on becoming sexually active or who are sexually active, discuss highly effective methods of contraception (refer to Section 4.3.2 for female subjects and Section 4.3.3 for male subjects). The discussion must be documented in the subject's source documents.

11. PGA of Disease Activity (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only).

12. Patient/Parent Global Assessment, according to the subject's age at the time of the assessment (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only).

13. Pain Assessment. The Pain Assessment should be completed before the Joint Assessment (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only).

14. Duration of Morning Stiffness (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only).

15. Joint Assessment (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only).

16. Overall Back Pain and Nocturnal Back Pain (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only [ERA subjects only]).

17. BASMI Assessments (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only [ERA subjects only]).

18. BSA (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only [PsA subjects only]).

19. PGA of Psoriasis (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only [PsA subjects only]).

20. CHAQ or HAQ, according to the subject's age at the time of the assessment (at months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 only).

21. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions.

22. Perform drug accountability.

23. Collect and review diary card dispensed at the previous visit.

    - For each dose, the site personnel will calculate the total volume (mL) delivered from the syringe(s) and the total dose (mg).

24. Use the IWR/IVR to allocate investigational product packages (except at month 96).

25. Dispense investigational product, investigational product instructions, and the subject diary (except at month 96).

26. Dispense the reminder card for next scheduled visit.

27. Complete the End of Treatment Subject Summary CRF (only at month 96).

6.1.2. Withdrawal/Re-treatment Period

6.1.2.1. Baseline Procedures for Subjects Planning to Enter Directly into the Withdrawal/Re-treatment Period

The following section is only applicable to subjects who enter directly into the withdrawal/re-treatment period at the baseline visit of study B1801023.

Baseline procedures may not commence until after the informed consent and assent (as applicable) have been signed. The study investigator or a sub-investigator will discuss with each subject and parent(s) (as applicable according to subject age and local guidelines) the nature of the study, its requirements, and its restrictions.

Every attempt should be made to complete the study B1801023 baseline visit on the same day as the study 0881A1-3338 week 96 visit. The baseline visit (day 1) must occur within 14 days of the last dose of investigational product received in study 0881A1-3338.

The following baseline procedures and assessments must be completed for all subjects entering into the withdrawal/re- treatment period:

1. Sign and date informed consent/assent for withdrawal/re-treatment period.

2. Review inclusion/exclusion criteria that apply to all subjects and that apply to subjects planning to enter the withdrawal/re-treatment period.

    - Those subjects who do not meet entry criteria for withdrawal/re-treatment period may be evaluated to determine whether participation in the active treatment period or observational period is appropriate.

3. Collect/update contact information, including primary care physician or other treating physician every.

4. For female subjects, evaluate childbearing potential. The evaluation must be documented in the subject's source documents.

5. Female subjects who, in the opinion of the investigator, are of childbearing potential will have a urine pregnancy test, which must be performed within 7 days before the baseline visit; this includes subjects who are menstruating at the time of the visit. If a pregnancy test was collected at the week 96 visit in study 0881-3338, and the visit occurred within 7 days of the baseline visit, a urine pregnancy test does not have to be repeated as long as the test result was negative. For these subjects, a negative test result must be available before dispensing and administration of investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

6. As appropriate, discuss sexual activity. For those subjects who either plan on becoming sexually active or who are sexually active, discuss requirement for highly effective methods of contraception (refer to Section 4.3.2 for female subjects and Section 4.3.3 for male subjects). The discussion must be documented in the subject's source documents.

7. BASMI and its components (Intermalleolar Distance, Cervical Rotation, Modified Schober's Test, Lateral Flexion, and Tragus to Wall Distance) only for ERA subjects.

8. Prior and concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event. Medications reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must be recorded on the appropriate CRF.

9. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions. Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must be recorded on the appropriate CRF.

10. Registration/Randomization.

11. Dispense reminder card for next scheduled visit.

The following additional baseline procedures and assessments do not need to be completed for subjects in the withdrawal/re-treatment period as long as the each procedure was completed within 14 days of the study 0881A1-3338 week 96 visit and the study B1801023 baseline visit:

12. Physical examination (performed by a physician).

- The physical examination will include completion of the Tanner Assessment for subjects <18 years or who have a score of <5 on 1 or more applicable domain(s).

13. Vital signs: Temperature, blood pressure (mmHg) and pulse rate (beats/min, after sitting for at least 5 minutes).

14. Height.

15. Weight (kg).

16. Laboratory evaluations (ie, hematology, blood chemistry, and CRP).

17. PGA of Disease Activity.

18. Patient/Parent Global Assessment, according to the subject's age at the time of the assessment.

19. Pain Assessment. The Pain Assessment should be completed before the Joint Assessment.

20. Duration of Morning Stiffness.

21. Joint Assessment including joints with limitation of motion.

22. Overall Back Pain and Nocturnal Back Pain (ERA subjects only).

23. BSA (PsA subjects only).

24. PGA of Psoriasis (PsA subjects only).

25. CHAQ or HAQ, according to the subject's age at the time of the assessment.

6.1.2.2. Withdrawal Period

Subjects who are eligible and consent to participate in the withdrawal period will have the following visits conducted:

- Subjects who enter directly into the withdrawal period will have the first post baseline visit conducted at the study site 1 month (±7 days) after the baseline visit.

- Subjects who participated in the active treatment period of study B1801023 will have the first withdrawal visit conducted at the study site 1 month (±7 days) after the active treatment early withdrawal visit.

- Subsequent visits will occur at the study site every 3 months after the baseline or active treatment early withdrawal visit for up to a year and then every 6 months thereafter. Subsequent visits must be scheduled within ±14 days of the projected visit date based on the actual date of the baseline or active treatment period early

withdrawal visit. Subjects who do not experience disease relapse will continue in the withdrawal period for a total of 96 months from the time of the baseline visit in study B1801023.

The following assessments will be performed at all visits during the withdrawal period unless otherwise indicated:

1. Ensure that the subject meets inclusion/exclusion criteria that apply to the withdrawal period.

2. Those subjects who do not meet entry criteria for the withdrawal period will be asked to participate in the observational period.

3. Ensure the most recent version(s) of the informed consent/assent for withdrawal/re-treatment period has been signed and dated.

4. Collect/update contact information, including primary care physician or other treating physician.

5. Concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event.

6. Physical examination (performed by a physician and conducted at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

    - The physical examination will include completion of the Tanner Assessment for subjects <18 years or who have a score of <5 on 1 or more applicable domain(s).

7. Vital signs: Temperature, blood pressure (mmHg) and pulse rate (beats/min, after sitting for at least 5 minutes).

8. Height (cm, at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

9. Weight (kg):

    - For subjects who are <18 years of age and who weigh ≤62 kg (at all visits).

    - For subjects who are ≥18 years of age or weigh >62 kg (at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

10. Laboratory evaluations (ie, hematology, blood chemistry, and CRP).

11. For female subjects, evaluate childbearing potential. The evaluation must be documented in the subject's source documents.

12. Female subjects who, in the opinion of the investigator, are of childbearing potential will have a urine pregnancy test; this includes subjects who are menstruating at the time of the visit. Pregnancy tests will also be done whenever one menstrual cycle is

missed during the withdrawal period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

13. As appropriate, discuss sexual activity. For those subjects who either plan on becoming sexually active or who are sexually active, discuss highly effective methods of contraception (refer to Section 4.3.2 for female subjects and Section 4.3.3 for male subjects). The discussion must be documented in the subject's source documents.

14. PGA of Disease Activity.

15. Patient/Parent Global Assessment, according to the subject's age at the time of the assessment.

16. Pain Assessment. The Pain Assessment should be completed before the Joint Assessment.

17. Duration of Morning Stiffness.

18. Joint Assessment.

19. Overall Back Pain and Nocturnal Back Pain (ERA subjects only).

20. BASMI Assessments (ERA subjects only).

21. BSA (PsA subjects only).

22. PGA of Psoriasis (PsA subjects only).

23. CHAQ or HAQ, according to the subject's age at the time of the assessment.

24. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions.

25. Dispense reminder card for next scheduled visit (except at month 96).

26. Complete the End of Phase Subject Summary CRF for the withdrawal period (at the month 96 visit only).

27. Complete the End of Study Summary CRF (at the month 96 visit only).

6.1.2.3. Re-Treatment Period

Subjects who are eligible for re-treatment with investigational product will have study visits conducted at the study site every 3 months after the re-treatment assessment visit. Visits must be scheduled within ±14 days of the projected visit date based on the actual date of the re-treatment assessment visit. Subjects who remain eligible for re-treatment will continue in

the re-treatment period for a total of 96 months (±14 days) from the time of the baseline visit in study B1801023.

The following assessments will be performed at all visits during the re-treatment period:

1. Ensure that the subject meets the inclusion/exclusion criteria that apply to the re-treatment period.

2. Those subjects who do not meet entry criteria for the re-treatment period will be asked to participate in the observational period.

3. Ensure the most recent version(s) of the informed consent/assent for withdrawal/re-treatment period has been signed and dated.

4. Collect/update contact information, including primary care physician or other treating physician.

5. Concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event.

6. Physical examination (performed by a physician and conducted at months 12, 24, 36, 48, 60, 72, 84, and 96 months only).

    - The physical examination will include completion of the Tanner Assessment for subjects <18 years or who have a score of <5 on 1 or more applicable domain(s).

7. Vital signs: Temperature, blood pressure (mmHg) and pulse rate (beats/min, after sitting for at least 5 minutes).

8. Height (cm, at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

9. Weight (kg):

    - For subjects who are <18 years of age and who weigh ≤62 kg (at all visits).

    - For subjects who are ≥18 years of age or weigh >62 kg (at months 12, 24, 36, 48, 60, 72, 84, and 96 only).

10. Laboratory evaluations (ie, hematology, blood chemistry, and CRP) at months 3, 6, 9, 12, and every 6 months thereafter.

11. For female subjects, evaluate childbearing potential. The evaluation must be documented in the subject's source documents.

12. Female subjects who, in the opinion of the investigator, are of childbearing potential will have a urine pregnancy test; this includes subjects who are menstruating at the time of the visit. Pregnancy tests will also be done whenever one menstrual cycle is

missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

13. As appropriate, discuss sexual activity. For those subjects who either plan on becoming sexually active or who are sexually active, discuss highly effective methods of contraception (refer to Section 4.3.2 for female subjects and Section 4.3.3 for male subjects). The discussion must be documented in the subject's source documents.

14. PGA of Disease Activity at months 3, 6, 9, 12, and every 6 months thereafter.

15. Patient/Parent Global Assessment, according to the subject's age at the time of the assessment at months 3, 6, 9, 12, and every 6 months thereafter.

16. Joint Assessment at months 3, 6, 9, 12, and every 6 months thereafter.

17. Pain Assessment. The Pain Assessment should be completed before the Joint Assessment at months 3, 6, 9, 12, and every 6 months thereafter.

18. Duration of Morning Stiffness at months 3, 6, 9, 12, and every 6 months thereafter.

19. Overall Back Pain and Nocturnal Back Pain (ERA subjects only) at months 3, 6, 9, 12, and every 6 months thereafter.

20. BASMI Assessments (ERA subjects only) at months 3, 6, 9, 12, and every 6 months thereafter.

21. BSA (PsA subjects only) at months 3, 6, 9, 12, and every 6 months thereafter.

22. PGA of Psoriasis (PsA subjects only) at months 3, 6, 9, 12, and every 6 months thereafter.

23. CHAQ or HAQ, according to the subject's age at the time of the assessment at months 3, 6, 9, 12, and every 6 months thereafter.

24. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions.

25. Perform drug accountability.

26. Collect and review diary card dispensed at the previous visit.

    - For each dose, the site personnel will calculate the total volume (mL) delivered from the syringe(s) and the total dose (mg).

27. Use the IWR/IVR to allocate investigational product packages (except at month 96).

28. Dispense investigational product, investigational product instructions, and the subject diary (except at month 96).

29. Dispense the reminder card for next scheduled visit.

30. End of treatment subject summary (month 96 only).

6.1.3. Active Treatment Period Follow-up Visit

The follow-up visit will only be completed for subjects who are receiving investigational product in either the active treatment period or the re-treatment period approximately 96 months after the baseline visit in study B1801023. The follow-up visit will occur at the study site 30 days (±7 days) after the month 96 visit.

The following information will be collected at the follow-up visit:

1. Concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event.

2. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions.

3. Complete the End of Study Subject Summary CRF.

6.1.4. Active Treatment Period and Re-Treatment Period Early Withdrawal Visits

Active Treatment Period Early Withdrawal Visit:

- Subjects in the active treatment period who receive at least 1 dose of investigational product in the active treatment period of study B1801023 and withdraw before completion of the month 96 visit are required to complete the active treatment early withdrawal visit at the study site. The active treatment early withdrawal visit should occur as soon as possible after the decision has been made to withdraw the subject from investigational product. At the active treatment early withdrawal visit, the subject will be asked to participate in either the withdrawal/re-treatment period or the observational period as appropriate

Re-Treatment Period Early Withdrawal Visit:

- Subjects in the re-treatment period who withdraw from investigational product before completion of the month 96 visit are required to complete the re-treatment early withdrawal visit at the study site. At the early withdrawal visit, the subject will be asked to participate in the observational period. Subjects may not enter the withdrawal/re-treatment period more than once during the study. Once the subject is in the observational period, he or she cannot resume investigational product for the remaining time in the study.

The following safety and efficacy evaluations will be performed at the early withdrawal visit:

1. Collect/update contact information, including primary care physician or other treating physician.

2. Concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event.

3. Physical examination (performed by a physician).

    - The physical examination will include completion of the Tanner Assessment for subjects <18 years or who have a score of <5 on 1 or more applicable domain(s). The Tanner Assessment does not need to be repeated if it was performed within 2 months before the early withdrawal visit.

4. Vital signs: Temperature, blood pressure (mmHg) and pulse rate (beats/min, after sitting for at least 5 minutes).

5. Height (cm).

6. Weight (kg).

7. Laboratory evaluations (ie, hematology, blood chemistry, and CRP).

8. For female subjects, evaluate childbearing potential. The evaluation must be documented in the subject's source documents.

9. Female subjects who, in the opinion of the investigator, are of childbearing potential will have a urine pregnancy test; this includes subjects who are menstruating at the time of the visit. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

10. As appropriate, discuss sexual activity. For those subjects who either plan on becoming sexually active or who are sexually active, discuss highly effective methods of contraception (refer to Section 4.3.2 for female subjects and Section 4.3.3 for male subjects). The discussion must be documented in the subject's source documents.

11. PGA of Disease Activity.

12. Patient/Parent Global Assessment, according to the subject's age at the time of the assessment.

13. Pain Assessment. The Pain Assessment should be completed before the Joint Assessment.

14. Duration of Morning Stiffness.

15. Joint Assessment.

16. Overall Back Pain and Nocturnal Back Pain (ERA subjects only).

17. BASMI Assessments (ERA subjects only).

18. BSA (PsA subjects only).

19. PGA of Psoriasis (PsA subjects only).

20. CHAQ or HAQ, according to the subject's age at the time of the assessment.

21. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions.

22. Perform drug accountability.

23. Collect and review diary card dispensed at the previous visit.

    - For each dose, the site personnel will calculate the total volume (mL) delivered from the syringe(s) and the total dose (mg).

24. Dispense reminder card for next scheduled visit.

25. Review inclusion/exclusion and discuss the option of entering into the observational period or the withdrawal/re-treatment period as appropriate.

    - For subjects being withdrawn from the active treatment period who are being considered for participation in the withdrawal/re-treatment period, review inclusion/exclusion criteria that apply to the withdrawal/re-treatment period.

    - Those subjects who do not meet entry criteria for the withdrawal/re-treatment period will be asked to participate in the observational period. This includes subjects who have previously or are currently participating in the withdrawal/re-treatment period.

    - Sign and date informed consent/assent for the observational period or the withdrawal/re-treatment period, as appropriate. There will be separate informed consents for participation in the observational and withdrawal/re-treatment periods.

26. Complete the appropriate End of Phase Subject Summary CRF. Separate subject summaries will be completed at the time of withdrawal from each of the active treatment period, and/or re-treatment period.

6.1.5. Re-Treatment Assessment Visit for Subjects in the Withdrawal Period

Subjects in the withdrawal period who experience disease relapse will be seen for a re-treatment assessment visit at the study site, which should occur as soon as possible after disease relapse. Subjects requiring re-treatment per the investigator's clinical judgment and who are otherwise eligible will be offered the option to re-start treatment with investigational product.

Subjects who are in the withdrawal period and discontinue (eg, for adverse events) or are ineligible for re-treatment with investigational product for any reason will be seen for a re-treatment assessment visit at the study site and asked to participate in the observational period. Once the subject is in the observational period, he or she can not resume investigational product for the remaining time in the study.

The following safety and efficacy evaluations will be performed at the re-treatment assessment visit:

1. Collect/update contact information, including primary care physician or other treating physician.

2. Concomitant medications (DMARDs, corticosteroids, NSAIDs, and anti-infective agents) and non-drug treatments received due to an adverse event.

3. Physical examination (performed by a physician).

    - The physical examination will include completion of the Tanner Assessment for subjects <18 years or who have a score of <5 on 1 or more applicable domain(s). The Tanner Assessment does not need to be repeated if it was performed within 2 months before the re-treatment assessment visit.

4. Vital signs: Temperature, blood pressure (mmHg) and pulse rate (beats/min, after sitting for at least 5 minutes).

5. Height (cm).

6. Weight (kg):

7. Laboratory evaluations (ie, hematology, blood chemistry, and CRP).

    - For subjects entering the re-treatment period, all laboratory evaluations must be completed before administration of the first dose of the investigational product. Results of the re-treatment assessment visit laboratory tests are not required for investigational product administration, but must be reviewed as soon as possible after the re-treatment assessment visit and before the first visit in the re-treatment period. If the re-treatment assessment visit laboratory results are consistent with the laboratory abnormalities described in the exclusion criteria in Section 4.2.3.1 or the results are determined to be clinically significant by the investigator, the

tests should be repeated and decisions regarding continuation of investigational product must be discussed with the sponsor's Clinical team.

8. For female subjects, evaluate childbearing potential. The evaluation must be documented in the subject's source documents.

9. Female subjects who, in the opinion of the investigator, are of childbearing potential will have a urine pregnancy test; this includes subjects who are menstruating at the time of the visit. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

10. As appropriate, discuss sexual activity. For those subjects who either plan on becoming sexually active or who are sexually active, discuss highly effective methods of contraception (refer to Section 4.3.2 for female subjects and Section 4.3.3 for male subjects). The discussion must be documented in the subject's source documents.

11. PGA of Disease Activity.

12. Patient/Parent Global Assessment, according to the subject's age at the time of the assessment.

13. Pain Assessment. The Pain Assessment should be completed before the Joint Assessment.

14. Duration of Morning Stiffness.

15. Joint Assessment.

16. Overall Back Pain and Nocturnal Back Pain (ERA subjects only).

17. BASMI Assessments (ERA subjects only).

18. BSA (PsA subjects only).

19. PGA of Psoriasis (PsA subjects only).

20. CHAQ or HAQ, according to the subject's age at the time of the assessment.

21. Adverse events, including malignancies, serious adverse events, infections, medically important infections, and injection site reactions.

22. Review inclusion/exclusion criteria and discuss the option of entering into the observational period or the re-treatment period as appropriate.

- For subjects experiencing disease relapse who are being considered for participation in the re-treatment period, review inclusion/exclusion criteria that apply to the re-treatment period.

- Those subjects who do not meet entry criteria for the re-treatment period will be asked to participate in the observational period.

- For subjects entering into the observational period, sign and date informed consent/assent for the observational period.

- For subjects entering the re-treatment period, assure that the most recent version of the withdrawal/re-treatment period informed consent/assent has been signed.

23. Dispense reminder card for next scheduled visit.

24. Complete the End of Phase Subject Summary CRF for the withdrawal period.

For subjects who will be participating in the re-treatment period: Once all of the re-treatment assessment visit procedures have been completed and it has been confirmed that the subject is eligible to enter the re-treatment period, the study staff will use the IWR/IVR to allocate investigational product packages. Investigational product, investigational product instructions, and subject diary will then be dispensed to the subject. The first dose of investigational product in the re-treatment period may be administered at the study site.

6.1.6. Observational Period Follow-up Visits for Subjects Who Participated in the Active Treatment Period and/or Withdrawal/Re-treatment Period

Subjects who participate in the active treatment period and/or withdrawal/re-treatment period and are no longer eligible to participate in one of these periods will be asked to continue to be followed in the observational period for a total of 96 months from the time of the baseline visit in study B1801023:

- The first observational period follow-up visit will occur at the study site and will be scheduled 30 days (±7 days) after the active treatment early withdrawal visit or the re-treatment assessment visit or re-treatment early withdrawal visit. For subjects who enter the observational period after discontinuing from the withdrawal period, this visit may be waived as long as the subject had already been seen at the study site ≥30 days after the most recent dose of investigational product in either study 0881A1-3338 or study B1801023.

- The subsequent follow-up visits will occur by telephone every 6 months (±4 weeks) after the first follow-up visit. For subjects who enter the observational period after discontinuing from the withdrawal period and are eligible to waive the first observational period follow-up visit, the subsequent observational period follow-up visits will occur by telephone every 6 months (±4 weeks) after the re-treatment assessment visit.

- For subjects <18 years of age, telephone contacts will be conducted with the subject's parent or legal representative/guardian.

- For subjects aged ≥18 years, telephone contacts may be conducted with the subjects or the subject's parent or legal representative/guardian.

- The number of telephone contacts will be adjusted based on when the subject enters the observational period.

- The final observational period follow-up visit will occur by telephone 96 months (±4 weeks) after the baseline visit of study B1801023.

The following safety evaluations will be performed at the follow-up visits:

1. Ensure the informed consent/assent for observational period is signed and dated.

2. Collect/update contact information, including primary care physician or other treating physician (except at the final month 96 follow-up visit).

3. Concomitant medications (DMARDs, including any immunosuppressives or anti-TNFs and/or other immunosuppressive biologic agents; corticosteroids; and anti-infective agents taken for medically important infections) and non-drug treatments received due to an adverse event.

4. Serious adverse events, malignancies, and medically important infections.

5. Complete the End of Study Subject Summary CRF (at the final follow-up visit or upon early withdrawal from the study).

6.2. Study Procedures for Subjects Entering Directly into the Observational Period

Subjects who discontinue investigational product prior to completing 96 weeks of active treatment in study 0881A1-3338 or do not meet eligibility criteria for continuing investigational product in study B1801023 will be asked to participate in the observational period of study B1801023. The initial baseline visit will be conducted at the study site, and subsequent study visits will be conducted via telephone at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96. The month 6 to month 96 visits must occur within a window of ±4 weeks of the projected visit date based on the actual baseline visit date.

6.2.1. Baseline Procedures for Subjects Entering Directly into the Observational Period

Baseline procedures may not commence until after the informed consent and assent (as applicable) have been signed. The study investigator or a sub-investigator will discuss with each subject and parent(s) (as applicable according to the subject's age and local guidelines) the nature of the study, its requirements, and its restrictions.

The following baseline procedures and assessments must be completed for all subjects in the observational period:

1. Sign and date informed consent/assent.

2. Review inclusion/exclusion criteria that apply to all subjects.

3. Collect/update contact information, including primary care physician or other treating physician.

4. Prior and concomitant medications (DMARDs, including any immunosuppressives or anti-TNFs and other immunosuppressive biologic agents; corticosteroids; and anti-infective agents taken for medically important infections) and non-drug treatments received due to an adverse event.

5. Serious adverse events, malignancies, and medically important infections (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s) and/or hospitalization). Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must be recorded on the appropriate CRF.

6.2.2. Observational Period – Month 6 to Month 96

For subjects in the observational period, study visits will be conducted via telephone at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 (within ±4 weeks of the projected visit date based on the actual baseline visit date). Subjects should receive reminder cards for their next scheduled telephone visit.

- For subjects <18 years of age, telephone contact will be conducted with the subject's parent or legal authorized representative/guardian.

- For subjects aged ≥18 years, telephone contact may be conducted with the subject or the subject's parent or legal representative/guardian.

The following safety evaluations will be performed at all visits unless otherwise indicated:

1. Collect/update contact information, including primary care physician or other treating physician (except at month 96).

2. Concomitant medications (DMARDs, including any anti-TNFs and/or other immunosuppressive biologic agents; corticosteroids; and anti-infective agents taken for medically important infections) and non-drug treatments received due to an adverse event.

3. Serious adverse events, malignancies, and medically important infections.

4. Complete the End of Study Subject Summary CRF (at month 96 or upon early withdrawal from the study).

6.3. Subject Withdrawal

The Pfizer Clinical team must be consulted as soon as possible if any of the following occur during the active treatment period, or the withdrawal/re-treatment period in order to determine whether the subject should continue receiving investigational product or for consideration of whether re-treatment with investigational product should be allowed:

- Any medically important infection (ie, an infection requiring parenteral [IV, IM] anti-infective agent(s), and/or hospitalization).
- Subjects with clinical signs and symptoms suggestive of active tuberculosis should have investigational product withheld until a diagnosis can be confirmed. If diagnosis of tuberculosis is confirmed, investigational product must be discontinued.
    - The 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 other than surgical joint interventions (open or arthroscopic), investigational product should be withheld for a period of time prior to the procedure; the specific duration should be determined according to the investigator's clinical judgment.
    - 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 more than 4 consecutive doses of investigational product are missed due to AEs, infections, or surgery or if more than 2 consecutive doses are missed due reasons other than AEs, infections, or surgery (eg, subject forgot to take investigational product or away from home without enough investigational product). Note: Tapering of the investigational product (ie, prescription or receipt of a dose lower than that described in Section 5 or less than once-weekly on an average basis) is not allowed.
- Lack of compliance with the protocol, including protocol required schedule of study visits and/or procedures.

Subjects MUST be withdrawn from investigational product if any of the following occurs during the active treatment period or withdrawal/re-treatment period:

- Pregnancy;
- Suspected Sepsis;
- Any infection meeting seriousness criteria other than hospitalization (refer to serious adverse event Section 8.5);

- Confirmed blood dyscrasia, demyelinating disorders (such as multiple sclerosis or optic neuritis), lupus-like syndrome or development of hypersensitivity to etanercept;
- Confirmed malignancy other than squamous cell, basal cell carcinoma or cervical carcinoma in situ;
- Receipt of any live (attenuated) vaccines:
    - At any time while receiving investigational product in the active treatment period or the re-treatment period;
    - Within 4 weeks after the last dose of investigational product in the active treatment period and within 8 weeks after the last dose of investigational product in the re-treatment period;
- Surgical joint intervention (open or arthroscopic);
- Tapering of the investigational product (ie, prescription or receipt of a dose lower than that described in Section 5 or less than once-weekly on an average basis);
- Withdrawal of consent;
- Principal investigator's decision;
- Sponsor decision.

Subjects may withdraw from the study at any time (active, withdrawal/re-treatment or observational period) 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 site.

If a subject does not return for a scheduled visit in the active treatment period, or the withdrawal/re-treatment period, or cannot be reached for a scheduled observational period phone call every effort should be made to contact the subject. The number and type 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 the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

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.

Refer to Section 6.1.4 for procedures to be performed for subjects in the active treatment period or re-treatment period and withdraw from investigational product before completion of the Month 96 visit.

Refer to Section 6.1.5 for procedures to be performed for subjects in the withdrawal period who experience disease relapse before completion of the Month 96 visit and are being considered for participation in the re-treatment period.

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 which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely fashion.

7.1. Safety Assessments

For subjects in the active treatment period, and the withdrawal/re-treatment period, safety will be assessed using the following measures:

1. Physical examinations will be performed by a physician. Any clinically significant abnormalities or worsening of medical history conditions should be recorded on the source documents and the appropriate adverse event CRF.

    - The physical examination will include the Tanner Stage Assessment for subjects <18 years of age or who have a score of <5 on 1 or more applicable domain(s). The sexual maturity rating of each subject will be determined according to the criteria adapted from Tanner. Female subjects will be classified on a scale of 1 to 5 across the following 2 maturity domains: breast and pubic hair characteristics. Male subjects will be classified on a scale of 1 to 5 across the following 3 maturity domains: pubic hair, penis and testes characteristics.

2. Vital sign measurements will include temperature, blood pressure and pulse rate (after sitting for at least 5 minutes).

    - A sitting blood pressure will be obtained by qualified site personnel and should be taken using the same arm throughout the study. If possible, a different arm should be used for the collection of blood samples.

3. Height and Weight.

4. Subjects will be evaluated for adverse events (infectious and noninfectious), serious adverse events, malignancy, and medically important infections.

- Infectious and noninfectious adverse events will be recorded on separate CRFs.

- Medically important infections are defined as infections that require parenteral anti-infective agents (IV, IM) and/or hospitalization.

- Infections considered preventable by vaccination will be reported on the infectious adverse event CRF.

5. Injection site reactions (symptoms, action taken, number, and frequency) will be monitored throughout the study and will be graded for intensity according to the Symptom Occurrence Scale (Itching, Redness, Swelling, Pain, Ulceration). Injection site reactions need to be clearly differentiated from symptoms associated with the technique of administering subcutaneous injections (eg, physical injury to blood vessels).

6. Clinical laboratory evaluations including blood chemistry, hematology, and urinalysis.

For subjects in the observational period, safety will be assessed through collection of the following information via telephone contact:

1. Subjects will be evaluated for serious adverse events, malignancy, and medically important infections.

   - Infectious and noninfectious serious adverse events will be recorded on separate CRFs.

   - Medically important infections are defined as infections that require parenteral anti-infective agents (IV, IM) and/or hospitalization.

7.2. Laboratory Evaluations

As much as possible, only one 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 laboratory ranges and certifications for the sponsor designated central laboratory.

All laboratory tests with values 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 recorded on the appropriate adverse event CRF. In addition, additional laboratory testing may be performed according to local guidelines or standard of care and for follow-up of abnormal laboratory test results.

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:

1. Pregnancy test (performed locally with material provided by the central laboratory): For female subjects, who in the opinion of the investigator are biologically capable of having children, a urine pregnancy test must be performed within 7 days prior to the baseline (day 1) visit and at each of the visits in the active treatment period during the withdrawal/re-treatment period, including the early withdrawal visit(s) and the re-treatment assessment visit; this includes subjects who are menstruating at the time of the visit. A negative urine pregnancy test must be obtained prior to administration and dispensing of investigational product at each of the visits in the active treatment period and the re-treatment period. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period and withdrawal/re-treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

2. Serum chemistry: alkaline phosphatase, alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), and total bilirubin.

3. Hematology: white blood cell (WBC) count including differential, red blood cell (RBC) count, hemoglobin, and platelet count.

4. CRP evaluation.

5. Evaluation of potential Hy's Law cases: Repeat testing will include AST, ALT, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. At the discretion of the investigator, additional testing for acute hepatitis A, hepatitis B, or hepatitis C may also be performed at the site's local laboratory.

7.3. Efficacy Assessments

For subjects in the active treatment period, and in the withdrawal/re-treatment period, efficacy will be assessed.

1. The following assessments will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years; these will be completed directly by subjects aged ≥18 years at the time of the assessment.

    - Patient/Parent Global Assessment: The subject or parent will assess all the ways that arthritis affects the subject using a scale between 0 and 10 on a 21-circle VAS with 0 = Very Well and 10 = Very Poor. This is to be completed in a manner that does not bias the investigator's assessment of the subject.

- Pain Assessment: The subject or parent will assess how much pain the subject has had because of his/her illness in the past week (0-10 on a 21-circle VAS with 0= no pain and 10=very severe pain). The Pain Assessment should be completed before the joint assessment.

- Duration of morning stiffness: Based on the investigator questioning the subject or parent, the time elapsed when the subject awoke in the morning and was able to resume normal activities without stiffness will be provided in minutes and cannot exceed 1440 minutes within 24 hours; If morning stiffness was continuing at the time of assessment or was unusual compared to the recent past, the average duration of stiffness over the past 3 days should be reported.

- Overall Back Pain and Nocturnal Back Pain ([0-100 mm VAS with 0= no pain and 100= most severe pain], ERA subjects only).

2. PGA of Disease Activity: The investigator will estimate the subject's overall disease activity for the current day by using a scale between 0 and 10 on a 21-circle VAS with 0 = No Activity and 10 = Maximum Activity. This is to be completed in a manner that does not bias the Patient/Parent Global Assessment

3. Number of active joints, defined as joints with swelling or, in the absence of swelling, joints with limitation of motion with pain and /or tenderness. Joint assessors will assess 68 joints for swelling, 69 joints for limitation of motion, and 75 joints for pain and/or tenderness on motions as follows: 0=no swelling, limitation of motion, or pain and/or tenderness on motion; 1=any swelling, limitation of motion, or pain and/or tenderness on motion; JR = joint replacement; NE=not evaluable

4. Number of joints with limited range of motion. Joint assessors will assess 69 joints for limited range of motion as follows: 0=no limited range of motion; 1=any limited range of motion; JR = joint replacement; NE=not evaluable

5. Laboratory measure of inflammation (CRP)

6. BASMI consists of 5 clinical measurements to reflect axial status (ERA subjects only):

   - Intermalleolar Distance: The subject should lie supine with the knees straight and feet pointing straight up. The subject is asked to separate the legs as far as possible and the distance between the medial malleoli is measured (in cm to the nearest tenth of a cm). Measure two tries.

   - Cervical Rotation: The subject should be in the neutral position. The subject is then asked to turn the head as far as possible to the right and then to the left. Use a inclinometer to measure two tries on the right side and two tries on the left side in degrees (to the nearest degree).

   - Modified Schober's Test: With the subject standing erect, place a mark in the midpoint of a line that joins the posterior superior iliac spines (baseline mark).

Place another mark 10 cm above the first (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 the two marks. The full measurement between the two lines should be recorded to the nearest tenth of a centimeter.

- Lateral Flexion: The subject should stand as close to the wall as possible with shoulders level and outer edges of feet 30 cm apart and feet parallel (neutral position). The distance between the subject's middle fingertip and the floor is measured in cm (to the nearest tenth of a cm). The patient is asked to bend sideways without bending the knees or lifting the heels while attempting to keep the shoulders in the same place (flexion position). The distance between the subject's middle fingertip and the floor is re-measured. Measure two tries on the right side and two tries on the left side.

- 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 tenth of a cm) from both the right side and left side. Measure two tries on the right side and two tries on the left side.

7. BSA will be measured as the percentage of BSA affected by psoriasis using the palm method; the subject's palm will be used for the calculation, with 1 of the subject's palms to PIP and thumb equal to 1% of BSA (PsA subjects only).

8. PGA of Psoriasis will assess the amount of induration, erythema, and scaling averaged over all psoriatic lesions on a scale of 0-5 (PsA subjects only).

7.4. Health Outcome Assessments

Health outcomes will be assessed using the CHAQ and HAQ.

The CHAQ will be completed by the subject's parent or legal representative/guardian for subjects aged <18 years at the time of the assessment; HAQ will be completed directly by subjects aged ≥18 years at the time of the assessment.

The health outcomes assessments (ie, CHAQ/HAQ) are for the purpose of exploring the subject's own perceptions about his/her quality of life. The investigator must not influence the subject's assessment. Every effort should be made by site personnel to maintain an unbiased assessment.

7.4.1. Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ, derived from the adult HAQ, is a parent-administered, reliable and valid assessment of functional disability and discomfort in pediatric subjects with rheumatic diseases. The parent of the pediatric subject is asked to report the subject's ability to perform activities of daily living, over the past week, in the following eight domains: dressing, arising, eating, walking, hygiene, reach, grip, and common activities distributed among a

total of 30 items. Each item within a domain is scored on a 4-point Likert scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Not Applicable is also included as an option. The highest score reported for a domain determines the score for that domain. If aids or devices are used, or assistance is required, the minimum score for that functional area is 2. The Disability Index is calculated as the mean of the eight functional areas.[19] The English version of the CHAQ is included in Appendix 2. The appropriate language form will be used for each participating country.

7.4.2. Health Assessment Questionnaire (HAQ)

The HAQ assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0-3 with 0 representing "no difficulty," 1 as "some difficulty," 2 as "much difficulty," and 3 as "unable to do." Any activity that required assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited functional status. The English version of the HAQ is included in Appendix 3. The appropriate language form will be used for each participating country.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. 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 adverse event 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 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 at least 96 months after the baseline visit in study B1801023. In addition, for subjects who are either in the active treatment period or the re-treatment period at Month 96, serious adverse events will be collected until 30 days after the last dose of 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 CRF from the time the subject enters either the active treatment period or withdrawal/re-treatment period at the baseline visit of study B1801023 through the subject's last visit in the active treatment period and/or the withdrawal/re-treatment period of the study and for 30 days after the last dose of investigational product for those subjects who are in either the active treatment period or the re-treatment period at Month 96.

For subjects in the active treatment period:

All adverse events (serious and non-serious), including infections, medically important infections, injection site reactions, and malignancy must be recorded on the CRF from the time the informed consent is signed through the Month 96 visit or upon early withdrawal from the study. All adverse events will be collected for the duration of the active treatment period and for 30 days after the last dose of investigational product for those subjects who are either in the active treatment period or the re-treatment period at Month 96.

Events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must also be recorded on the appropriate CRF.

For subjects in the withdrawal/re-treatment period:

All adverse events (serious and non-serious), including infections, medically important infections, injection site reactions, and malignancy must be recorded on the CRF from the time the informed consent is signed through the duration of the withdrawal/re-treatment period. All adverse events will be collected for the duration of the withdrawal/re-treatment period and for 30 days after the last dose of investigational product for those subjects who are in either the active treatment period or the re-treatment period at Month 96.

For subjects entering directly into the withdrawal/re-treatment period at the baseline visit of study B1801023, events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must also be recorded on the appropriate CRF.

For subjects in the observational period:

All serious adverse events (including serious infections), malignancy and medically important infections must be recorded on the CRF from the time the informed consent is signed or when the subject enters the observational period through the Month 96 visit.

For subjects entering into the observational period at the baseline visit of study B1801023, events reported as ongoing at the final study 0881A1-3338 visit as well as events starting between the final study 0881A1-3338 visit and baseline visit of study B1801023 must also be recorded on the appropriate CRF.

8.3. Definition of an Adverse Event

An adverse event 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 adverse events 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. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event 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 (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

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

8.5. 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 adverse event when it is associated with a serious adverse 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 adverse event 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.

8.5.1. Other Reportable Information

If a subject experiences any of the following events, the event must be reported to Pfizer in the same manner and time frame as a serious adverse event:

- Amyotrophic lateral sclerosis;
- Demyelination and multiple sclerosis;
- Guillain-Barré Syndrome;
- Malignancy, including lymphoma (excluding squamous cell or basal cell carcinoma or cervical carcinoma in situ);
- Cutaneous T-cell lymphoma, including mycosis fungoides;
- Progressive Multifocal Leukoencephalopathy (PML).

8.5.2. 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).

8.5.3. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) concurrent with abnormal elevations in total bilirubin 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 concurrent with a total bilirubin value ≥2 times the upper limit of normal with no evidence of hemolysis and an alkaline phosphatase value ≤2 times the upper limit of normal or not available.
- For subjects with preexisting ALT **or** AST **or** total bilirubin values above the upper limit of normal, 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 times the upper limit of normal, or ≥8 times the upper limit of normal (whichever is smaller).

Concurrent with

- For subject with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 time the upper limit of normal or if the value reaches ≥3 times the upper limit of normal (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 (GGT), 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 serious adverse events.

8.6. 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 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 adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pretreatment 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 adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical adverse event;
- Pre-planned 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 non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. 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 adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes

significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 adverse event; 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 a serious adverse event 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 serious adverse event reporting requirements, if applicable.

8.9. 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 EIU 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 EIU Form. This must be done irrespective of whether an adverse event 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 EIU 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 congental 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 serious adverse events.

Additional information about pregnancy outcomes that are reported as serious adverse events 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 serious adverse events. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy 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.

8.10. 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 nvestigative site file.

8.11. Withdrawal Due to Adverse Events (See Also the section Subject Withdrawal)

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

When a subject withdraws because of a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events. In addition to recording observed or spontaneously volunteered adverse events, certain additional data will be solicited from the subjects in this study via questionnaires. These additional data will be collected and evaluated in a different manner than the observed or volunteered adverse events as detailed in the statistical analysis section. Given these differences, no attempt will be made to resolve any apparent discrepancies between or volunteered adverse events and the questionnaire data collected. Questionnaire data will be presented in separate tables, figures, and data listings, and will be reviewed in the final study report. Adverse event incidence rates will not be calculated from these solicited data.

8.13. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event 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 a serious adverse event 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 adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes 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 serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event 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.

8.13.2. NonSerious Adverse Event Reporting Requirements

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

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse events 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, 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 sample size for this safety extension protocol, as agreed upon with regulatory authorities, is not based on efficacy considerations; rather, all eligible subjects who either complete or discontinue from study 0881A1-3338 will be asked to participate in study B1801023. The anticipated enrollment is approximately 100 subjects.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

The primary endpoint in this study are are related to safety. Efficacy endpoints are secondary.

9.2.2. Analysis of Secondary Endpoints for Subjects in the Active Treatment Period, and Withdrawal/Re-treatment Period

The secondary efficacy endpoints will be analyzed in the active treatment period and the withdrawal/re-treatment period. For the overall population as well as each of the JIA subpopulations, descriptive statistics will be provided for each study endpoint at all time points in the study. For categorical endpoints, the summary statistics will contain the frequency, percentage, and 95% confidence interval (CI) for the percentage. For continuous endpoints, the summary statistics will contain the number of observations, mean, standard

deviation, median, minimum, maximum, and 95% CI of the mean for both raw data and the change from baseline. The observed data analysis, ie, without imputation for missing data, will be the focus of the efficacy summaries. The baseline visit from study 0881A1-3338 will be used for the calculation of change from baseline results where applicable. Summaries with last observation carried forward (LOCF) imputation may also be provided.

9.3. Analysis of Health Outcomes Assessments for Subjects in the Active Treatment, and Withdrawal/Re-treatment Period

The CHAQ and HAQ will be summarized in the same way as the efficacy endpoints. CHAQ and HAQ results will be summarized separately as well as for the combined CHAQ/HAQ results for subjects who switch to the adult version over the course of the trial.

9.4. Safety Analysis

9.4.1. Safety Analysis All Subjects

The incidence of malignancies, serious adverse events and medically important infections will be summarized as frequency and percentage, as well as adjusted rate per 100 subject-years of exposure to etanercept along with 95% confidence intervals. In addition to showing cumulative rates over the entire study period (including both 0881A1-3338 and B1801023), rates will also be categorized by year for each year from 1 to 10. Safety presentations will be provided for overall populations and by each JIA subpopulations; separate summaries for subjects in the active treatment period, withdrawal/re-treatment period and the observational period will also be provided.

Incidence of malignancies may be compared to external data sources to generate standardized incidence ratios (SIRs) to aid interpretation. Due to the small sample size and expected rarity of the events, this approach may be of limited value.

9.4.2. Safety Analysis for Subjects in the Active Treatment Period, and Withdrawal/re-treatment Period:

The occurrence of all adverse events (infectious and noninfectious), infections considered preventable by vaccination, and injection site reactions as well as treatment-emergent adverse events, potentially clinically important laboratory measurements, and premature discontinuations during the study will be summarized as using frequency and percentage, as well as adjusted rate per 100 subject-years of exposure to etanercept.

For laboratory data, vital sign measurements, and other continuous safety data, the number of observations, mean, standard deviation, median, minimum, maximum, and 95% CI of the mean will be summarized by visit for raw data and the change from baseline. Height, weight, BMI, and Tanner scores will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum by age group. Height, weight and BMI will also be compared with data from standardized growth charts.

9.5. Interim Analysis

No formal statistical interim analyses are planned. However, a descriptive analysis will be performed at a minimum of every 2 years after subjects have either completed or withdrawn from the study at the corresponding time point based on the time of initial entry into study B1801023. In addition, summaries of safety and efficacy assessments will be produced at intervals to satisfy regulatory obligations and the requirements of the Data Monitoring Committee.

9.6. Data Monitoring Committee

This study will use an Internal Review Committee (IRC) to help assure the safety of study participants. The IRC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter which describes and governs the IRC's activities. The recommendations made by the IRC to alter the conduct of the study will be forwarded to the appropriate Pfizer team member as identified in the IRC Charter for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety and/or efficacy data to regulatory authorities, as appropriate. In this instance, such disease-related efficacy endpoints are not reported individually as SAEs.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Global Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB/IEC, 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.

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 Case Report Form (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 is true. Any corrections to entries made in the CRFs, 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 investigator’s 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, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, 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 to 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 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 (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC 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 Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 1996 and/or 2008 as mandated by local law).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by an alpha-numerical code consisting of a numbering system provided by Pfizer and year of birth. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent and assent forms must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent documents(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC, and available for inspection.

At the baseline visit, the following must occur according to local regulatory guidelines before any study specific activity is performed:

- The investigator must ensure that each study subject and/or his/her legal representative/guardian, 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 and/or the subject's legal representative/guardian.

- The investigator will retain the original of each subject's signed consent and assent forms.

12.4. Subject Recruitment

Only subjects who were previously enrolled in study 0881A1-3338 will be included in B1801023. Therefore advertisements will not be used for this study.

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 which 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 sufficient 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 Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit in the study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue the development of Etanercept 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 7 days. 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 the results of studies through posting the results of this study 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 United States (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 pre-specified 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 has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) 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, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. 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, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

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Appendix 1. Abbreviations

Abbreviation	Term
ACR	American College of Rheumatology
ALT	alanine aminotransferase
AS	ankylosing spondylitis
AST	aspartate aminotransferase
BASMI	Bath Ankylosing Spondylitis Metrology Index
BSA	Body Sure Area
CHAQ	Childhood Health Assessment Questionnaire
CRP	c-reactive protein
CSR	clinical study report
CTA	clinical trial application
DMARD	disease-modifying antirheumatic drug
eCRF	electronic case report form
EIU	Exposure in-utero
EMA	European Medicines Agency
ERA	enthesitis-related arthritis
FDA	US Food and Drug Administration
FDAAA	US Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HAQ	Health Assessment Questionnaire
IB	investigator's brochure
IEC	independent ethics committee
ILAR	International League of Associations for Rheumatology
IRC	Internal Review Committee
IV	intravenous
IM	intra-muscular
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWR/IVR	interactive web response/interactive voice response
JIA	juvenile idiopathic arthritis
LFT	liver function test
LOCF	last observation carried forward
LSLV	last subject last visit
NSAID	nonsteroidal anti-inflammatory drug
PCD	primary outcome completion date
Pedi	pediatric
PGA	Physician's Global Assessment
PhRMA	Pharmaceutical Research and Manufacturers of America
PsA	psoriatic arthritis
PUVA	psoralen + ultraviolet A
QW	once weekly
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
SAE	serious adverse event
SC	subcutaneous
SGOT	serum glutamic pyruvic transaminase
SGPT	serum glutamic oxaloacetic transaminase
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
UVA	ultraviolet A
UVB	ultraviolet B
VAS	visual analogue scale
WBC	white blood cell

Appendix 2. Sample of Childhood Health Assessment Questionnaire

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please check the one response which best describes your child's usual activities (averaged over an entire day) **OVER THE PAST WEEK. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS**. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". **For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY ILLNESS, please mark it as "NOT Applicable".**

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicabl
DRESSING & GROOMING					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo his/her hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
ARISING					
Is your child able to:					
- Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a crib?	☐	☐	☐	☐	☐
EATING					
Is your child able to:					
- Cut his/her own meat?	☐	☐	☐	☐	☐
- Lift up a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
Is your child able to:					
- Walk outdoors on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

*** Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

- Cane	☐	- Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)	☐
- Walker	☐	- Built up pencil or special utensils	☐
- Crutches	☐	- Special or built up chair	☐
- Wheelchair	☐	- Other (Specify:_____)	☐

*** Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

- Dressing and Grooming	☐	- Eating	☐
- Arising	☐	- Walking	☐

Sample of Childhood Health Assessment Questionnaire cont.

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
HYGIENE					
Is your child able to:					
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to:					
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out trash, vacuuming, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

*** Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

- Raised toilet seat	☐	- Bathtub bar	☐
- Bathtub seat	☐	- Long-handled appliances for reach	☐
- Jar opener (for jars previously opened)	☐	- Long-handled appliances in bathroom	☐

*** Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

- Hygiene	☐	- Gripping and opening things	☐
- Reach	☐	- Errands and chores	☐

Appendix 3. Sample of Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE©
Stanford University School of Medicine
Division of Immunology & Rheumatology

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mo	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipp long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Full HAQ-Ph 37

Sample of Health Assessment Questionnaire cont.

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Raised toilet seat
- ☐ Bathtub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Bathtub bar
- ☐ Long-handled appliances for reach
- ☐ Long-handled appliances in bathroom
- ☐ Other (Specify:_____)

Appendix 4. Joint Assessment

Please enter one of the following four codes for each of the joints:
0 = No swelling; No pain and/or tenderness on motion; No limitation of motion
1 = Any swelling; Any pain and/or tenderness on motion; Any limitation of motion
JR = Joint replacement
NE = Not evaluable

Legend:

Swell: swelling
Pain: pain &/or tenderness on motion
LOM: limitation of motion

RIGHT SIDE

Swell	Pain	LOM	JOINTS	Swell	Pain	LOM
			Temporo-mandibular			
			Sterno-clavicular			
			Acromion-clavicular			
			Shoulder			
			Elbow			
			Wrist			
			MCP I			
			MCP II			
			MCP III			
			MCP IV			
			MCP V			
			PIP I			
			PIP II			
			PIP III			
			PIP IV			
			PIP V			
			DIP II			
			DIP III			
			DIP IV			
			DIP V			
			Hip			
			Knee			
			Ankle			
			Talocalcaneal joints			
			Intertarsal joints			
			MTP I			
			MTP II			
			MTP III			
			MTP IV			
			MTP V			
			TOE I			
			TOE II			
			TOE III			
			TOE IV			
			TOE V			
			Sacroiliac joints			
			Cervical spine			
			Thoracic spine			
			Lumbar spine			

LEFT SIDE

Abbreviations:
MCP=metacarpophalangeal; **PIP**=proximal interphalangeal; **DIP**=distal interphalangeal; **MTP**=metatarsophalangeal
Assessor's Signature:_____