Protocol B7981006

A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED, MULTI-CENTER STUDY TO ASSESS THE EFFICACY AND SAFETY PROFILE OF PF-06651600 IN SUBJECTS WITH MODERATE TO SEVERE ACTIVE RHEUMATOID ARTHRITIS WITH AN INADEQUATE RESPONSE TO METHOTREXATE

Statistical Analysis Plan
(SAP)

Version: 2

Date: 18-JAN-2018

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1. VERSION HISTORY

This SAP for study B7981006 is based on the protocol dated 22AUG2016.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	Derivation/update of the prior distribution for placebo response based on the review of baseline data. Changes made to Appendix 4	Availability and review of study baseline SDAI data. The prior placebo distribution depends on current study baseline data.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7981006. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Table 2. Study Objectives and Endpoints

Primary Objectives:	**Primary Endpoints:**
• To evaluate the efficacy of PF-06651600 at 8 weeks in subjects with moderate to severe active rheumatoid arthritis.	• Change from baseline in simple disease activity index (SDAI) at Week 8.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the safety of PF-06651600.	• Safety and tolerability of PF-06651600 versus placebo; vital signs, laboratory tests, adverse events (AEs) including infections, and Serious Adverse Events (SAEs).
• To assess other signs of clinical efficacy over 8 weeks.	• Change from baseline in SDAI at Weeks 1, 2, 4, and 6. • SDAI low disease activity scale and remission rates at Weeks 4, 6, and 8. • Disease activity score (DAS) low disease activity scale and remission rates at Weeks 4, 6, and 8: DAS28-3 (erythrocyte sedimentation

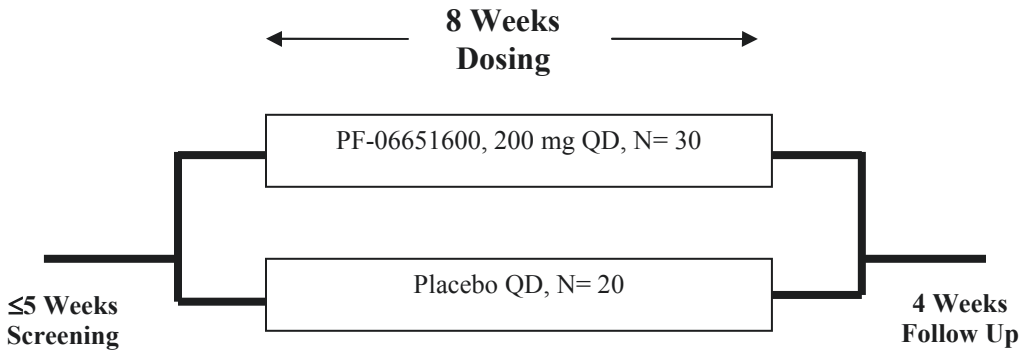
	rate (ESR)), DAS28-3 (C-reactive protein (CRP)), DAS28 -4 (ESR), and DAS28-4 (CRP). The following will also be calculated at Weeks 1, 2,4, 6, and 8: • Change from baseline in DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP). • Change from baseline in high sensitivity C-reactive protein (hsCRP). • Change from baseline in the Tender/Painful and Swollen Joint Count (28). • Change from baseline in the Physician's Global Assessment (PhGA) of Arthritis.
• To assess the effect of PF-06651600 on patient reported outcome measurements.	• Change from baseline in the Patient's Assessment of Arthritis Pain (PAAP) Visual Analogue Scale (VAS) and Patient's Global Assessment (PtGA) of Arthritis VAS at Weeks 1, 2, 4, 6, and 8. • Change from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Weeks 1, 2, 4, 6, and 8.
[redacted] CCI [redacted]	[redacted]
[redacted]	[redacted]

• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• Change from baseline in American College of Rheumatology 20 (ACR20), ACR50, and ACR70 responder rates.
• CCI [redacted] .	• CCI [redacted]

*Note: Analysis of exploratory endpoints may be further detailed in SAP or exploratory analysis plan. Samples collected for exploratory endpoints may or may not be analyzed and, if analyzed, may or may not be reported in the CSR.

2.2. Study Design

Figure 1. Study Design Schematic



Note: N indicates the total number of completers.

This is a Phase 2a, 8 week randomized double-blind, parallel group, placebo controlled, multi-center study to assess the efficacy and safety profile of PF-06651600 in seropositive subjects with moderate to severe active rheumatoid arthritis with an inadequate response to methotrexate (up to approximately 50% of subjects may also have had an inadequate response to 1 anti- tumor necrosis factor α (TNFα) biologic disease-modifying antirheumatic drug).

Up to approximately 60 subjects may be randomized globally into the study to ensure at least approximately 50 subjects complete 8 weeks of active dosing (assuming a dropout rate of approximately 15%). Subjects will participate in this study for approximately 16 weeks. This includes an up to 5-week screening period, an 8 week treatment period, and a 4 week follow-up period.

After an up to 5 week screening period, eligible subjects will be randomized to receive 200 mg twice a day (QD) of PF-06651600 or placebo (matching tablets for PF-06651600 QD) every day for 8 weeks in a blinded fashion.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint for this study is change from baseline in SDAI at Week 8. The SDAI is a continuous composite measure derived from components of the ACR Core Dataset at baseline (Day 1), Weeks 1, 2, 4, 6, and 8.

3.2. Secondary Endpoint(s)

- Change from baseline in SDAI at Weeks 1, 2, 4, and 6.
- SDAI low disease activity scale and remission rates at Weeks 4, 6, and 8.
- DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP) low disease activity scale and remission rates at Weeks 4, 6, and 8.

The following will also be calculated at Weeks 1, 2, 4, 6, and 8:

- Change from baseline in DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP).
- Change from baseline in hsCRP.
- Change from baseline in the Tender/Painful and Swollen Joint Count (28).
- Change from baseline in the PhGA of Arthritis.

3.3. Patient Outcomes Research (PRO) Endpoints

- Change from baseline in the PAAP VAS and PtGA of Arthritis VAS at Weeks 1, 2, 4, 6, and 8.
- Change from baseline in the HAQ-DI at Weeks 1, 2, 4, 6, and 8.

CCI [redacted]

- ACR20, ACR50, and ACR70 responder rates.
- CCI [redacted]

3.5. Baseline Variables

Below are baseline variables:

- Screening: Demographics and RA history, smoking history, medical history and non RA medications, history of alcohol and drug abuse, height, and weight.
- Day 1: Vital signs (pulse rate, blood pressure), temperature, and complete physical examination.

3.6. Safety Endpoints

Safety will be assessed by the spontaneous reporting of AEs, physical examinations and clinical laboratory results in all subjects who receive at least one dose of the investigational product. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns.

3.6.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.7.1).

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier-2 events: These are events that are not tier-1 but are "common". A Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) is defined as a tier-2 event if there are at least 4 in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

3.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the Pfizer reporting standards.

3.6.3. Vital Signs

Absolute values and changes from baseline in systolic and diastolic blood pressure, respiratory rate, pulse rate and temperature will be summarized by treatment and visit, according to Pfizer reporting standards.

3.6.4. Electrocardiogram (ECG)

Categorical summary tables will be summarized by treatment and visit using Pfizer reporting standards. A listing of ECG comments on findings and normal/abnormal results will be provided.

4. ANALYSIS SETS

4.1. Intent-to-Treat Analysis Set

An intent-to-treat (ITT) analysis set will include all subjects who were randomized to the study and received at least one dose of the randomized investigational drug (PF-06651600 or placebo).

4.2. Safety Analysis Set

The safety (SAF) analysis set is defined as those subjects who received at least one dose of the investigational drug.

4.3. Other Analysis Sets

None.

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analyses will occur after database lock after Last Subject Last Visit (LSLV).

5.1. Hypotheses and Decision Rules

The null hypothesis that the distribution of SDAI change from baseline at Week 8 is the same between the active and placebo arms will be tested using Bayesian framework outlined in Appendix 4. Statistical separation from the placebo will be observed if the probability of treatment effect Δ^* being greater than zero is over 90%.

5.2. General Methods

In general, number and percent will be presented for binary variables. Number, mean, standard deviation (or standard error of the mean), median, minimum, and maximum will be presented for continuous variables. In addition, graphics may be used to present the data.

5.2.1. Analyses for Binary Data

The normal approximation for the difference in binomial proportions will be used to assess the difference between active and placebo.

The normal-approximation to the test statistic for the difference in binomial random variables is calculated as

$$Z_i = \frac{\hat{p}_i - \hat{p}_c}{\sqrt{\frac{\hat{p}_i(1-\hat{p}_i)}{n_i} + \frac{\hat{p}_c(1-\hat{p}_c)}{n_c}}}$$

where $\hat{p}$ refers to the relative frequency, n to sample size, the subscript c refers to the control group (eg, placebo) and the subscript i refers to the active group.

Two-sided 95% confidence intervals are formed by:

$$(\hat{p}_i - \hat{p}_c) \pm Z_{0.975}\sqrt{\frac{\hat{p}_i(1-\hat{p}_i)}{n_i} + \frac{\hat{p}_c(1-\hat{p}_c)}{n_c}}$$

5.2.2. Analyses for Continuous Data

Mixed Effect Model Repeat Measurement (MMRM) for Longitudinal Continuous Data:

The fixed effects of treatment, visit, and treatment-by-visit interaction will be included, along with patient as a random effect. Unstructured covariance matrix will be assumed.

When modeling the change from baseline values, the variable of visit will start with the first post-baseline visit, and the actual baseline value will be included as a covariate. At each visit, estimates of mean values and the mean differences between the active treated group and the placebo group will be derived from the model. The corresponding p-values, standard errors and 95% confidence intervals will also be derived from the model.

Below is an example of potential statistical analysis system (SAS) code:

```
PROC MIXED DATA=XXX;
  CLASS SUBJID TREATMENT VISIT;
  MODEL CHGBASE=TREATMENT VISIT TREATMENT*VISIT BASE/ALPHA=0.05 DDFM=KR;
  REPEATED VISIT/SUBJECT=SUBJID TYPE=UN;
  LSMEANS TREATMENT*VISIT/ALPHA=0.05 CL DIFF;
RUN;
```

Analysis of Covariance (ANCOVA) for Non-longitudinal Continuous Data:

The non-longitudinal continuous data will be analyzed by ANCOVA with treatment as the factor. When modelling change from baseline values, the actual baseline value will be included as a covariate. Active dose group will be contrasted versus placebo.

Below is an example of potential SAS code:

```
PROC MIXED DATA=XXX;
  CLASS TREATMENT;
  MODEL CHGBASE=TREATMENT BASE/ALPHA=0.05;
  LSMEANS TREATMENT/ALPHA=0.05 CL PDIFF;
RUN;
```

5.2.3. Analyses for Categorical Data

The frequency and percentage for each category will be presented.

5.2.4. Analyses for Time to Event Data

None.

5.3. Methods to Manage Missing Data

In general, for descriptive statistics missing values will not be imputed. In addition, for safety endpoints missing values will not be imputed. Unless there is an explicit instruction, missing values will be used for lower limits of detection and quantitation.

5.3.1. Binary Endpoint

For the binary response endpoints (eg, SDAI remission rates), subjects with missing values will be handled by:

- non-responder imputation (NRI) method, ie, setting any missing values to be non-responsive (0)
- will be used as observed (ie, excluding any missing values from analysis)

5.3.2. Continuous Endpoints

For non-patient reported outcome variables, the missing values will be handled as following:

- For continuous endpoints measured longitudinally, the missing values post-baseline will be handled in a linear mixed-effect model with repeated measures for this continuous variable, where the values are assumed to be missing at random.
- For the continuous endpoint not measured longitudinally, the post-baseline missing values will be:
  - as observed (ie, excluding any missing values from analysis);
  - imputed using last observation carried forward (LOCF).

For PRO endpoints, rules suggested by the developers of these PROs will be followed in calculating the values of a given component at a scheduled assessment. If these rules are not enough for imputing a value, then the missing values will be handled in the same way as non-patient reported outcome variables.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The primary efficacy analysis will be conducted on simple disease activity index (SDAI) change from baseline at Week 8. Analysis will include data on PF-06651600 and placebo arms.

Analyses of the primary endpoint will be based on ITT population.

6.1.1. Primary Analysis

The primary analysis will be based on the Bayesian analysis outlined in Appendix 4.

6.1.2. Sensitivity/Robustness Analyses

There are 3 sets of analyses.

Set 1:

The sensitivity analysis will be based sensitivity prior models on the Bayesian analysis outlined in Appendix 4.

Set 2:

- Missing data imputation
  - Observed
  - LOCF
- ANCOVA (see Section 5.2.2)
  - Baseline SDAI as a covariate
  - Baseline SDAI and previous anti-TNF use as covariates

Set 3:

- Missing data imputation – none (Observed).
- MMRM (see Section 5.2.2) for analysis of change from baseline in SDAI at Weeks 1, 2, 4, 6, and 8.
  - Baseline SDAI as a covariate
  - Baseline SDAI and previous anti-TNF use as covariates

6.2. Secondary Endpoint(s)

6.2.1. SDAI

Analysis of number of subjects with SDAI remission (SDAI≤3.3) and SDAI low disease activity (SDAI≤11) at Weeks 4, 6, and 8:

- ITT population set
- Missing data imputation
  - Observed

    - NRI
- Normal approximation

Analysis of change from baseline in SDAI at Weeks 1, 2, 4, 6, and 8:

- ITT population set
- Missing data imputation – none (Observed)
- MMRM

6.2.2. DAS

For DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP), analysis of number of subjects with DAS28 remission (DAS<2.6) and DAS28 low disease activity (DAS28<3.2) at Weeks 4, 6, and 8:

- ITT population set
- Missing data imputation
    - Observed
    - NRI
- Normal approximation

Analysis of change from baseline in DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP)SDAI at Weeks 1, 2, 4, 6, and 8:

- ITT population set
- Missing data imputation – none (Observed)
- MMRM

6.2.3. hsCRP

Analysis of change from baseline in hsCRP at Weeks 1, 2, 4, 6, and 8:

- ITT population set
- Missing data imputation – none (Observed)
- MMRM

6.2.4. Tender/Painful and Swollen Joint Count

Analysis of change from baseline in the Tender/Painful and Swollen Joint Count (28) at Weeks 1, 2, 4, 6, and 8:

- ITT population set
- Missing data imputation – none (Observed)
- MMRM

6.2.5. PhGA of Arthritis

Analysis of change from baseline in PhGA of arthritis at Weeks 1, 2, 4, 6, and 8:

- ITT population set
- Missing data imputation – none (Observed)
- MMRM

6.3. PRO Endpoints

Analysis of change from baseline in for outcomes research endpoints at Weeks 1, 2, 4, 6, and 8:

- Endpoints are PAAP VAS, PtGA VAS, and HAQ-DI
- ITT population set
- Missing data imputation – none (Observed)
- MMRM

6.4. CCI [redacted], only ACR20, ACR50, and ACR70 rate will be summarized:

- CCI [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

Additional statistical analyses of other exploratory endpoints (including PK analysis) will be provided in a separate document.

6.5. Subset Analyses

Summary statistics for the SDAI endpoints will be presented by baseline smoking status and by previous anti-TNF use.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Demographics and medical history variables as defined in Section 3.5 will be summarized by treatment group.

6.6.2. Study Conduct and Subject Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed in the ITT analysis set, and as well as for safety. Frequency counts will be supplied for subject discontinuations by treatment.

Data will be reported in accordance with Pfizer reporting standards.

6.6.3. Study Treatment Exposure

A summary of compliance and the number of doses received as well as the median total dose by visit and treatment group will be provided.

6.6.4. Concomitant Medications and Non-Drug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

6.7. Safety Summaries and Analyses

Safety analysis will be based on the SAF analysis set.

All clinical AEs, SAEs, treatment-emergent signs and symptoms (TEAEs), withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, blood pressure, pulse rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data, ECGs and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly.

6.7.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

The analyses of adverse events under the 3-tier approach are considered exploratory. There will be no adjustment for multiple comparisons or stratification factors in the analyses unless specified.

Nominal p-values (Tier-1 events only) and 95% confidence intervals (Tier-1 and Tier-2 events) will be provided for between treatment differences in the percentage of patients with events. Reporting p-values and confidence intervals will follow Pfizer standards.

6.7.2. Laboratory Data

Laboratory data will be listed and summarized by treatment and visit in accordance with the Pfizer reporting standards.

6.7.3. Vital Signs

Absolute values and changes from baseline in systolic and diastolic blood pressure, respiratory rate, pulse rate and temperature will be listed summarized by treatment and visit in accordance with the Pfizer reporting standards.

6.7.4. Electrocardiogram

Categorical summary tables will be summarized by treatment and visit using Pfizer reporting standards. A listing of ECG comments on findings and normal/abnormal results will be provided.

6.7.5. Physical Examination

All physical exam data will be provided in the listings.

7. INTERIM ANALYSES

No interim analysis is planned. Final analyses will follow the official database release.

8. REFERENCES

None.

9. APPENDICES

Appendix 1. SUMMARY OF EFFICACY ANALYSES

All efficacy analyses will be based on ITT set. Treatment groups will be PF-06651600 and placebo.

Primary Efficacy Endpoint	Statistical Method	Missing Data
Change from baseline in SDAI at Week 8	ANCOVA with baseline SDAI as a covariate	Observed
Change from baseline in SDAI at Week 8	ANCOVA with baseline SDAI as a covariate	LOCF
Change from baseline in SDAI at Week 8	ANCOVA with baseline SDAI and anti-TNF use as covariates	Observed
Change from baseline in SDAI at Week 8	ANCOVA with baseline SDAI and anti-TNF use as covariates	LOCF
Change from baseline in SDAI at Week 8	Bayesian analysis of posterior distributions of the SDAI scores and placebo adjusted change from baseline	-

Secondary Efficacy Endpoints	Statistical Method	Missing Data
SDAI remission and low disease activity at Weeks 4, 6, and 8	Normal approximation	Observed
SDAI remission and low disease activity at Weeks 4, 6, and 8	Normal approximation	NRI
DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP) remission and disease activity at Weeks 4, 6, and 8	Normal approximation	Observed
DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP) remission and disease activity at Weeks 4, 6, and 8	Normal approximation	NRI

Change from baseline in SDAI at Weeks 1, 2, 4, 6, and 8	MMRM	Observed
Change from baseline in DAS28 (eg, DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP)) at Weeks 1, 2, 4, 6, and 8	MMRM	Observed
Change from baseline in hsCRP at Weeks 1, 2, 4, 6, and 8	MMRM	Observed
Change from baseline in in the Tender/Painful and Swollen Joint Count (28) at Weeks 1, 2, 4, 6, and 8	MMRM	Observed
Change from baseline in PhGA of Arthritis at Weeks 1, 2, 4, 6, and 8	MMRM	Observed

Outcomes Research Endpoints	**Statistical Method**	**Missing Data**
Change from baseline in in PAAP VAS and PtGA of Arthritis VAS at Weeks 1, 2, 4, 6, and 8	MMRM	Observed
Change from baseline in in the HAQ-DI at Weeks 1, 2, 4, 6, and 8	MMRM	Observed
CCI [redacted]		CCI [redacted]
ACR20, ACR50, and ACR70 at Weeks 4, 6, and 8	CCI [redacted]	[redacted]
ACR20, ACR50, and ACR70 at Weeks 4, 6, and 8	CCI [redacted]	[redacted]

Appendix 2. DETAILS OF VISIT WINDOWS

Visit windows will be used for efficacy variables, and for any safety data that display/summarize by study visit. For other endpoints (eg, ECG, vital signs), visit windows will be applied for summary statistics by study visits if required.

Visit Label	Target Day	Definition [Day window]
Screening		Days -35 to Day 0
Baseline	Day 1, Randomization	Day 1
Week 1	8	Days 2 to 11
Week 2	15	Days 12 to 22
Week 4	29	Days 23 to 36
Week 6	43	Days 37 to 50
Week 8	57	Days 51 to 64
Follow Up/End of Study		
Week 10	71	Days 65 to 78
Week 12	85	Days 79 to -

For the lab values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls within 40 days before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

For the other values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

If two or more visits fall into the same window, keep the one closest to the Target Day. If two visits are equaled distant from the Target Day in absolute value, the later visit should be used.

Safety analysis may follow Pfizer standard.

Appendix 3. DATA DERIVATION DETAILS

A patient is said to have achieved the ACR20 criteria[+] when all of the following bulleted points are true:

- A 20% improvement from baseline in the tender/painful joint count (TCJ28).
- A 20% improvement from baseline in the swollen joint count (SJC28).
- A 20% improvement from baseline in *at least 3* of the following 5 variables:
    1. PhGA of Arthritis;
    2. PAAP VAS;
    3. PtGA of Arthritis VAS;
    4. HAQ disability index;
    5. Results of ESR or CRP blood test (both of which test for inflammation).

ACR50 and ACR70 are defined analogously.

There are many forms of the DAS. The DAS used in this study is the DAS using the 28-count subsets of tender/painful joints and swollen joints, together with either CRP or ESR, to derive the DAS28-3 (CRP), DAS28-4 (CRP), or DAS28-3 (ESR) and DAS28-4 (ESR), which are calculated using the following formulae, respectively:

DAS28-4(ESR) = (0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70*ln(ESR) + 0.014*GH

DAS28-3(ESR) = [0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70*ln(ESR)]*1.08 + 0.16

DAS28-4(CRP) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

DAS28-3(CRP) = [0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1)] * 1.10 + 1.15

where TJC28 is number of painful joints out of 28 joints, SJC28 is number of swollen joints out of 28 joints, GH is the general health or patients' global assessment of disease activity on a 100 mm VAS, ln is the natural logarithm, ESR is in mm/first hour, and CRP is in mg/L.

Handling Missing Joint Counts:

- A missing painful/tender assessment or one NOT DONE at *baseline* is set to "not painful/tender";
- A missing swollen assessment or one NOT DONE at *baseline* is set to "not swollen";

[+] Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis. Arthritis Rheum 1995; 38:727-35.

- A missing painful/tender assessment or one NOT DONE *post baseline* is set to "painful/tender";

- A missing swollen assessment or one NOT DONE at *post baseline* is set to "swollen".

Note that joints marked NOT APPLICABLE are not to be counted in the summation of swollen and painful/tender joints at baseline and post baseline.

Any *new* NOT APPLICABLE for a joint POST BASELINE is set to "painful/tender" and "swollen".

Any intra-articular injection (baseline and post baseline) sets the joint status to "painful/tender" and "swollen" - on or after the date of the injection.

Appendix 4. ADDITIONAL METHODOLOGY DETAILS

Details of Bayesian analysis of posterior distributions of the SDAI scores

Notation/Definitions

$i = 1,2,\ldots,n;$ *where n is the total number of patients*
$x_i^B =$ *Baseline SDAI score for Patient i*
$x_i^W =$ *Week W SDAI score for Patient i*
$y_i = -(x_i^W - x_i^B)$; *negative change from baseline SDAI at Week W for Patient i*
$I_i^D = \begin{cases} 1, if\ Patient\ i\ received\ Treatment\ D \\ 0, otherwise. \end{cases}$
$A =$ *Active terated group*
$P =$ *Placebo treated group*

Primary Model – Bayesian Analysis of Covariance

$$y_i = \mu_P^* I_i^P + (\mu_P^* + \Delta^*) I_i^A + \beta(x_i^B - \mu^B) + \varepsilon_i,$$
$$where\ \varepsilon_i \sim N(0, \sigma_\varepsilon^2)$$

Prior Models:

$\mu_P^* \sim N(13.7, \sigma^2 = 25)$
$\Delta^* \sim N(0, 10^3)$
$\beta \sim N(0, 10^3)$
$\sigma_\varepsilon^2 =$ *Noninformative inverse gamma* $IG(0.001, 0.001)$

Note: μ_P^H is calculated based on commensurability between the historic and current study baseline patient profiles including both arms. The baseline profiles were based on baseline SDAI score prior ant-TNF exposure status. Geographic data was not used in the assessment of the prior distribution.

At least two alternative sensitivity prior models will be considered for μ_P^H, with one being a noninformative prior $N(0, 10^3)$. Also sensitivity models will be considered with ε_i modeled using t distribution with three degrees of freedom.

Data visualization techniques

Table shells of figures displaying the primary endpoint results (see below) will be provided in programming document.

- Distribution of treatment effect Δ^*.
- Display of change from baseline by treatment group based on Bayesian Analysis of Covariance.
- Display of change from baseline by treatment group based on Bayesian Analysis of Covariance vs baseline SDAI.