Protocol A3921215

A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PHASE 3 STUDY TO DEMONSTRATE NON-INFERIORITY FOR THE EFFICACY OF A ONCE DAILY DOSE OF TOFACITINIB MODIFIED RELEASE TABLET TO A TWICE DAILY DOSE OF THE IMMEDIATE RELEASE TABLET IN ADULT PATIENTS WITH RHEUMATOID ARTHRITIS ON BACKGROUND METHOTREXATE

Statistical Analysis Plan (SAP)

Version: **3.0**

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[redacted]

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

NOTE: This Statistical Analysis Plan was amended after blinded data had been sent to the University of Wisconsin, which analyzed the data to report to the Data Safety Monitoring Board (DSMB). The data sets were sent on March 5 2015. None of the amended text resulted from or is otherwise based upon the review of data by DSMB.

Amendment 2

Changes from the previous version (version 2.0, December 2, 2016) have been made for results of blinded data review.

- Corrected the method of multiple imputation for DAS28 missing values in Section 7.
- Added analysis of herpes zoster events defined by MedDRA Preferred Terms in Section 8.2.3.1 and Appendix 4.
- Added creatine kinase for descriptive, model analysis and summary of abnormalities in Section 8.2.3.2.
- Changed the use of percent change from baseline value instead of change from baseline value in triglyceride in Section 8.2.3.2.

Amendment 1

Changes from the previous version (version 1.0, January 14, 2015) have been made for the issuance of a protocol amendment, results of blinded data review and observation of document review at Quality Gate.

- Statistical null hypothesis and alternative hypothesis were added in Section 4.1.
- Corrected definition of the difference between treatment groups in primary endpoint to in Section 4.2 and Section 8.2.1 as per protocol amendment.
- Definition of subgroups was clarified in Section 8.2.1.2.
- Analyses of safety data were clarified in Section 8.2.3.1 for adverse events, Section 8.2.3.2 for laboratory data, Section 8.2.3.3 for vital signs, Section 8.2.3.4 for electrocardiogram and Section 8.2.3.5 for physical examination.
- New Section 8.2.4 was added for analyses of other data and clarified in Section 8.2.4.1 for baseline summaries, Section 8.2.4.2 for study treatment exposure and Section 8.2.4.3 for concomitant medications and non-drug treatments.
- Added the definition of DAS28-3(CRP), DAS28-3(ESR), SDAI and CDAI as versions of the disease activity score in Appendix 2.1. Although these two endpoints are not pre-defined efficacy endpoint but will be available for further analysis if need be.

- Added Definition of Hyperlipidemia (Screen Shots) by ATP III in Appendix 3.
- Other minor revisions.

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicised***.

Tofacitinib is a potent, selective inhibitor of the Janus Kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. The immediate release (IR) formulation of tofacitinib has been approved for the treatment of rheumatoid arthritis (RA) as a twice daily (BID) regimen. Tofacitinib is being developed for the treatment of psoriasis (PsO, oral and topical), spondylarthropathies (ankylosing spondylitis [AS] and psoriatic arthritis [PsA]) and inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]).

The modified release (MR) formulation of tofacitinib is being studied as a disease-modifying antirheumatic drug (DMARD) for the once daily (QD) treatment of RA. The MR QD regimen has the potential to improve drug compliance of patients, patient convenience, and to offer additional dosing options for patients.

This study will seek to compare the efficacy and safety of the MR 11 mg QD regimen to the IR 5 mg BID regimen for the treatment of RA.

2.1. Study Design

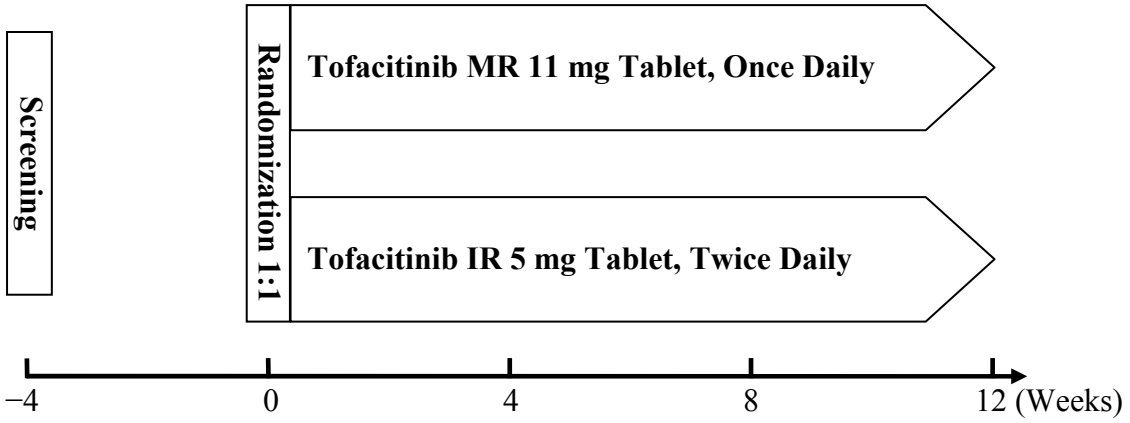
This is a multicenter, randomized, double blind, parallel group, phase 3 study to evaluate efficacy and safety of tofacitinib MR 11 mg QD tablet compared to IR 5 mg BID tablet following 12 weeks treatment in patients with moderate to severe RA on a stable background of methotrexate (MTX).

Subjects will be randomized in a 1:1 ratio for the 2 treatment arms with a total sample size of approximately 200 subjects; there will be approximately 100 subjects randomized into the 11 mg MR QD group and approximately 100 patients into the 5 mg IR BID group.

The study design schematic for the study is represented in Figure 1.

Figure 1. Study Design

Approximately 100 per arm, N=200



2.2. Study Objectives

Primary Objective

1. *To demonstrate the non-inferiority for efficacy of tofacitinib MR 11 mg QD to IR 5 mg BID for the treatment of signs and symptoms in patients with active RA on a stable background of* MTX*, as measured by Disease Activity Score 28-4 (C-reactive protein) [DAS28-4(CRP)] change from Baseline at Week 12.*

Secondary Objectives

1. *To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for the treatment of signs and symptoms of RA, as measured by DAS28-4 erythrocyte sedimentation rate (ESR) change from Baseline, American College of Rheumatology 20% improvement (ACR20), ACR50, ACR70 responses, remission, and Low Disease Activity (LDA), at Week 12.*

2. *To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for physical function status as measured by health assessment questionnaire-disability index (HAQ-DI) change from Baseline at Week 12.*

3. *To evaluate the similarity in effects on patient's health outcome measures (change from Baseline in short form 36 health survey (SF-36), functional assessment of chronic illness therapy (FACIT) fatigue and euro quality of life-5 dimensions questionnaire [EQ-5D]) of tofacitinib MR 11 mg QD and IR 5 mg BID at Week 12.*

4. *To evaluate the safety and tolerability of tofacitinib MR 11 mg QD in comparison with IR 5 mg BID in patients.*

Other Objective

The efficacy and health outcome objectives will also be evaluated at other post-Baseline visits.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis of the study data will be performed for use outside the data monitoring committee (DMC).

Final analyses will follow the official database release.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The primary hypothesis associated with the statistical objective is to demonstrate non-inferiority of tofacitinib MR 11 mg QD to IR 5 mg BID as measured by DAS28-4(CRP) change from baseline at Week 12. The null hypothesis is that the treatment difference (tofacitinib MR 11 mg QD – IR 5 mg BID) is 0.6 or more, and the alternative hypothesis is that the treatment difference is less than 0.6.

4.2. Statistical Decision Rules

If the upper *bound of the 2-sided 95% confidence interval (type-I error [alpha] of 0.025 in each tail) for the difference in change from baseline in DAS28-4(CRP) between the two arms (MR 11 mg QD – IR 5 mg BID) is less than 0.6, then the treatment of tofacitinib MR 11 mg QD will be declared to be non-inferior to that of tofacitinib IR 5 mg BID.*

5. ANALYSIS SETS

5.1. Full Analysis Set

The full analysis set (FAS) *will include all subjects who were randomized and received at least one dose of the randomized investigational drug.*

5.2. 'Per Protocol' Analysis Set

The Per Protocol Analysis Set (PPAS) will be a subset of the FAS dataset. The PPAS *will include all randomized subjects who completed the 12 week study with no important protocol deviations that could impact the efficacy analysis. The list of potentially important protocol deviations (pIPDs) and the subjects to be excluded from the 'Per Protocol' analysis set will be identified, reviewed, and finalized prior to the release of the database.*

5.3. Safety Analysis Set

The Safety Analysis Set will include *all subjects who were randomized and received at least one dose of the randomized investigational drug. By definition, it is identical to the full analysis set defined above.*

5.4. Other Analysis Sets

None.

5.5. Treatment Misallocations

If a patient was:

- Randomized but not treated, then the patient will be excluded from all analyses according to the definitions of FAS, PPAS and Safety Analysis Set given above. The patient will be included in the disposition summaries.

- Treated but not randomized, then the patient will be excluded from all analyses according to the definitions of FAS, PPAS and Safety Analysis Set given above. The patient will be included in safety data listings.

- Randomized but took incorrect treatment, then the patient will be reported under his/her randomized treatment group for all analyses based on FAS and Safety Analysis Set, but will be omitted from analyses based on PPAS. Medication errors will be listed.

5.6. Protocol Deviations

The following sections describe any protocol deviations that relate to the statistical analyses.

It is possible that unexpected deviations will arise, becoming known only after the study has been active for a long period of time; hence more deviations may be added. A full list of protocol deviations for the study report will be compiled prior to database closure. As of this writing, the protocol deviations can all be found in Sections 5.6.1 and 5.6.2 below.

The list of patients along with the excluding protocol deviation will be put into the trial master file.

5.6.1. Deviations Assessed Prior to Randomization

Granted exceptions to the inclusion or exclusion criteria are not expected to occur. Any patient who enters the study when the inclusion or exclusion criteria would have prevented entry will be considered to have had a protocol deviation.

5.6.2. Deviations Assessed Post-Randomization

Only protocol deviations that are thought to effect the efficacy of tofacitinib will be considered. Each of the cases will be reviewed by the team and a clinical judgment made in

each particular circumstance as to whether efficacy would have been effected in the cases of these specific classes of protocol deviations assessed post randomization:

- Patients who receive prohibited concomitant medications;
- Patients who interrupt therapy for longer than allowed (less than 80% compliant during the double-blind study treatment period);
- Patients who were randomized but took incorrect treatment;
- Patients whose background RA medications are changed in violation of protocol.

Each patient's presence on the list of exclusion from the per-protocol analysis means that there was at least one deviation for that patient clinically judged to effect efficacy.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

6.1.1. Primary Efficacy Endpoint

- *Change from Baseline in DAS28-4(CRP) at Week 12.*

6.1.2. Secondary Efficacy Endpoints

- *Change from Baseline in DAS28-4(ESR) at Week 12.*
- *ACR20, ACR50 and ACR70 response at Week 12.*
- *Remission at Week 12, as assessed by: DAS28-4(CRP) < 2.6 and DAS28-4(ESR) < 2.6.*
- *LDA at Week 12, as assessed by: DAS28-4(CRP) ≤ 3.2 and DAS28-4(ESR) ≤ 3.2.*
- *Change from Baseline in HAQ-DI at Week 12.*
- *HAQ-DI response (decrease of at least 0.22) at Week 12.*
- *Change from Baseline in the SF-36 8 domain scores and 2 component scores at Week 12.*
- *Change from Baseline in the FACIT-Fatigue scale at Week 12.*
- *Change from Baseline in the EQ-5D at Week 12.*

6.1.3. Other Efficacy Endpoints

- *Primary and secondary efficacy endpoints at other selected post-baseline scheduled visits.*

6.2. Safety Endpoints

- *All adverse events (AEs), including serious adverse events (SAEs).*
- *Clinically significant abnormal laboratory parameters.*

6.3. Other Endpoints

None.

6.4. Covariates

The baseline values of the efficacy endpoint will be used as covariates when the treatment effect is assessed on the change from baseline for the efficacy endpoints.

7. HANDLING OF MISSING VALUES

In general, missing values will not be imputed for descriptive statistics.

For continuous efficacy endpoints, 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.

In addition, if the DAS28 values post-baseline are missing, method of multiple imputation (MI) will be used to impute any missing DAS28 values. The SAS MI procedure will be used to impute missing DAS28 values for each group. One thousand (1000) complete data sets will be generated and analyzed using the SAS MIANALYZE procedure to combine results from these complete sets.

For binary efficacy endpoints, last observation carried forward (LOCF) mixed components method will be used to impute any missing components in binary composite endpoints before dropout for any reason. Only post-baseline values will be carried forward. Any subject whose response status at any time cannot be determined even after the imputation above will be counted as a non-responder at that time (non-responder imputation, NRI). This includes all visits after dropout for any reason.

Also as a sensitivity check, the “as-is” values of the binary efficacy endpoints will be analyzed. That is, the values of binary composite endpoints will be calculated without applying any imputation to the components.

In addition, missing values for safety endpoints will not be imputed.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

In general, number and percent will be presented for binary variables, and number, mean, standard deviation, standard error of the mean, minimum, 1st, 2nd and 3rd quartiles and maximum will be presented for continuous variables. In addition, graphics may be used to present the data.

8.1. Statistical Methods

8.1.1. Analysis of Longitudinal Continuous Data

The analysis will be conducted using a linear mixed effect model with repeated measures (MMRM), which will include treatment (tofacitinib MR 11 mg QD and IR 5 mg BID)*, visit, and treatment by visit interaction as fixed effects. Subjects will be a random effect and unstructured covariance will be assumed* for the within-subject errors. If there are convergence problems with this model, sequential structures will be applied until the problems resolved; autoregressive 1 and compound symmetry.

If there is modeling of actual values, the explanatory variable of visit will include baseline as one of the longitudinal values. 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, the mean differences between the treatment groups and the associated 2-sided 95% confidence interval (type-I error [alpha] of 0.025 in each tail) will be derived from the model.

8.1.2. Analysis of Non Longitudinal Continuous Data

The same approach as in Section 8.1.1 will be applied, except that the model will not include visit, treatment-by-visit interaction, or patient as a random effect. In this case, the model is an analysis of covariance (ANCOVA) model.

8.1.3. Analysis of Binary Data

The normal approximation for the difference in binomial proportions will be used to estimate the 95% confidence interval.

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 a comparator group (i.e., tofacitinib IR 5 mg BID) and the subscript i refers to a test group (i.e., tofacitinib MR 11 mg QD).

Two-sided 95% confidence intervals are formed by:

$$(\hat{p}_i - \hat{p}_c) \pm 1.96\sqrt{\frac{\hat{p}_i(1-\hat{p}_i)}{n_i} + \frac{\hat{p}_c(1-\hat{p}_c)}{n_c}}$$

In addition, this method will also be used in all secondary analyses involving binary variables.

8.2. Statistical Analyses

8.2.1. Analysis of Primary Efficacy Endpoints

The primary endpoint DAS28-4(CRP) change from baseline will be analyzed using MMRM described in Section 8.1.1 on the FAS. The patient is required to have a baseline and at least one non-missing on-study assessment of DAS28-4(CRP) to be included the analysis. Missing values will not be imputed.

Non-inferiority of tofacitinib MR 11 mg QD to IR 5 mg BID will be concluded if the upper bound of the 2-sided 95% confidence interval of differences between the treatment groups (MR 11 mg QD – IR 5 mg BID) at Week 12 is less than the pre-specified non-inferiority margin of 0.6.

8.2.1.1. Sensitivity/Robustness Analyses

To support the interpretation of the primary analyses, some robustness or sensitivity analyses will be performed for the primary endpoint. However, the conclusions (non-inferiority) for comparison of the primary endpoint between tofacitinib MR 11 mg QD and IR 5 mg BID group is purely based on results of the primary analysis.

One of the robustness analyses is 'Per Protocol' analysis, that is, the same primary analysis for the primary endpoint will be conducted using PPAS rather than the FAS.

Other robustness analyses will be performed using the FAS as follows:

- MMRM model described in Section 8.1.1 with compound symmetry instead of unstructured covariance. Missing values will not be imputed.
- MMRM model described in Section 8.1.1 with unstructured covariance. Missing values will be imputed using the method of MI as described in Section 7.
- ANCOVA model described in Section 8.1.2 at Week 12. Missing values will not be imputed.

8.2.1.2. Subset Analysis

For DAS28-4(CRP) change from baseline, subgroup analysis will be performed by following subsets at baseline/screening:

- Sex (Male, Female),
- Body weight (<55 kg, ≥55 kg),
- Age (<65 years old, ≥65 years old),
- Rheumatoid factor at screening (Negative, Positive),
- Disease duration (<5 years, ≥5 years),
- Methotrexate dose at baseline (≤8 mg/week, >8 mg/week) and
- DAS28-4(CRP) at baseline (≤5.1, >5.1).

8.2.2. Analysis of Secondary and Other Efficacy Endpoints

All analyses of secondary and other efficacy endpoints are based on the FAS.

The change from baseline in longitudinal continuous variables (i.e. DAS28-4(ESR), HAQ-DI, other 6 components of the ACR criteria, the 8 domains and 2 component scores of SF-36) will each be analyzed using the MMRM model as described in Section 8.1.1 and the missing values will not be imputed.

The change from baseline in non-longitudinal continuous variables (i.e. EQ-5D utility score and FACIT fatigue scale) will each be analyzed using ANCOVA model as described in Section 8.1.2 and the missing values will not be imputed.

Binary variables (i.e. the ACR variables [ACR20, ACR50 and ACR70], DAS28 responses [DAS28 ≤3.2, DAS28 <2.6] which include DAS28-4[CRP] and DAS28-4[ESR], and decrease [at least 0.22] in HAQ-DI) will be analyzed using the normal approximation to the difference in response rates, as described in Section 8.1.3. The missing values will be handled according to the approach described in Section 7.

8.2.3. Analysis of Safety Data

The safety analysis will be conducted on the safety analysis set.

The Sponsor has standard (i.e., used for all its clinical trials) summary displays and listings for MedDRA-coded adverse events, demography, medical history, length of time in study and discontinuation, concomitant and concurrent medications, physical examination, ECG, laboratory tests, weight, pulse rate, and blood pressure. These standards, called Pfizer Data Standards, will be utilized in the reporting of these routine safety variables (Pfizer Data Standards Rulebook).

8.2.3.1. Adverse Events

Adverse events will be listed and summarized within treatment group in accordance with the Pfizer Data Standards. Adverse events, serious adverse events and discontinuation due to adverse event will also be summarized by subsets described in Section 8.2.1.2.

Adverse events met following the Standardised MedDRA Queries (SMQs) will be summarized within treatment group.

- Hypertension
- Congestive Heart Failure
- Dyslipidaemia
- Erythropenia
- Leukopenia
- Acute Renal Failure
- Ischemic Heart Disease
- Ischemic Cerebrovascular Disease
- Myocardial Infarction
- Possible Drug-Related Hepatic Disorders

Serious infection events and treated infection events will be summarized per visit, respectively.

Herpes zoster events defined by MedDRA Preferred Terms in Appendix 4 will be summarized within treatment group.

Adverse events reviewed in the following adjudication/review committees will be listed.

- Cardiovascular safety endpoints adjudicated by the Cardiovascular Endpoint Adjudication Committee (CV-EAC).
- Malignancies adjudicated by Malignancy Adjudication Committee (MAC)
- Opportunistic infections reviewed by the Opportunistic Infection Review Committee (OIRC).
- Hepatic events reviewed by the Hepatic Event Review Committee (HERC).

- Gastrointestinal perforation events reviewed by Gastrointestinal Perforation Review Committee (GIPRC).
- Interstitial lung disease (ILD) events reviewed by the Interstitial Lung Disease Review Committee (ILDRC).
- Potentially malignant tumors, suspicious lymphadenopathy, possible extranodal lymphoproliferative disorder (LPD) reviewed by the central pathologists.

8.2.3.2. Laboratory Data

Laboratory data will be listed and summarized within treatment group in accordance with the Pfizer Data Standards. Incidence of laboratory test abnormalities (including without regard to baseline abnormality) will be summarized within each treatment group.

For each planned time point, actual values and changes from baseline values will be summarized within each treatment with descriptive statistics. The changes from baseline values will be analyzed using the MMRM model as described in Section 8.1.1. Instead of changes form baseline, percent changes from baseline will be analyzed in lipid tests (total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride). Laboratory tests to be analyzed for absolute and (percent) changes from baseline values are listed in Table 1.

Table 1. Laboratory Tests for Absolute and (Percent) Change from Baseline Values

Descriptive Statistics[a]	Descriptive Statistics[a] and Model Analysis[b]
Platelet	Neutrophil Count
Hemoglobin	Lymphocyte Count
Creatinine Clearance (Cockcroft-Gault)	Serum Creatinine
ALT	Total Cholesterol
AST	LDL-C
Bilirubin	HDL-C
Lymphocyte Subset Count CD3+	Triglyceride
Lymphocyte Subset Count CD3−CD19+	Ratio of Total Cholesterol/HDL-C
Lymphocyte Subset Count CD3+CD4+CD8−	Ratio of LDL-C/HDL-C
Lymphocyte Subset Count CD3+CD4−CD8+	Creatine Kinase
Lymphocyte Subset Count CD3+CD16+CD56+	
Lymphocyte Subset Count CD3−CD16+CD56+	
Lymphocyte Subset Count CD3−CD16+CD56−	
Lymphocyte Subset Count CD3−CD16−CD56+	
Lymphocyte Subset Count CD3−CD16−CD56−	
Ratio of Lymphocyte Subset Count CD4/CD8	

ALT = alanine transaminase , AST = aspartate transaminase, LDL-C = low density lipoprotein-cholesterol, HDL-C = high density lipoprotein-cholesterol, CD = cluster of differentiation
a. Descriptive statistics of actual and change from baseline values per visit
b. MMRM model analysis of change from baseline values per visit

The following laboratory test abnormalities will be listed and summarized within each treatment group.

- Neutropenia
- Lymphopenia
- Decreased hemoglobin
- Hyperlipidemia classified by ATP III criteria defined in Appendix 3
- Increased liver function test values as multiple of upper limit of normal in patients with normal at baseline and without regard to baseline abnormality
- Drug-induced Liver Injury (DILI) in patients with normal at baseline and without regard to baseline abnormality
- Laboratory values met protocol criteria for monitoring and discontinuation
- Increased creatine kinase values as multiple of upper limit of normal in patients with normal at baseline and with abnormal at baseline

Maximum LDL-cholesterol value on-treatment versus baseline value will be summarized in shift table.

8.2.3.3. Vital Signs

For each planned time point, actual values and change from baseline values in blood pressure, weight and body mass index will be summarized within each treatment with descriptive statistics.

The changes from baseline values in blood pressure will be analyzed using the MMRM model as described in Section 8.1.1.

Subjects with hypertension will be listed and summarized per visits classified by JNC7[3] criteria;

- Stage 1 (140 ≤ systolic blood pressure (SBP) ≤ 159 mmHg or 90 ≤ diastolic blood pressure (DBP) ≤99),
- Stage 2 (SBP ≥160 or DBP ≥ 100).

All values in blood pressure meeting the categorical criteria of potential clinical concern will be listed. All planned and unplanned post-dose time points will be counted in these categorical summaries.

All vital signs values will be listed.

8.2.3.4. Electrocardiogram

Interpretation and comments on findings in ECG at Screening will be listed.

8.2.3.5. Physical Examination

Physical examination data will be listed within treatment group in accordance with the Pfizer Data Standards. New/intensified physical examination findings from Screening to Week 12/End of Treatment will also be presented.

8.2.4. Analysis of Other Data

8.2.4.1. Baseline Summaries

A breakdown of demographic data will be provided for age, race, weight, body mass index and height. Each will be summarized by sex at birth and 'All Subjects' with tables and listings presented in accordance with the Pfizer Data Standards. Use adult age categories for the demographic summaries (<18, 18-44, 45-64, and ≥65).

Also, medical history and primary diagnosis will be tabulated and listed in in accordance with the Pfizer Data Standards.

The following pre-treatment characteristic will be summarized:

- Rheumatoid Factor at screening (Positive and Negative)

8.2.4.2. Study Treatment Exposure

Duration of exposure will be presented in tables and listings in accordance with the Pfizer Data Standards.

8.2.4.3. Concomitant Medications and Non-Drug Treatments

All prior and concomitant medications as well as non-drug treatments will be provided in tables and listings in accordance with the Pfizer Data Standards.

The following rheumatoid arthritis medications use will be summarized by treatment group:

- Previously taken anti-TNF inhibitors
- Previously taken other biologic DMARDs
- Previously taken traditional (conventional synthetic) DMARDs other than methotrexate
- Previously taken glucocorticoids
- New lipid lowering medications taken

- New DMARDs taken (that may have been Protocol Violations)
- New NSAIDs/COX-2 inhibitors taken
- New hypertension medications taken
- Concomitant glucocorticoids taken
- New glucocorticoids taken

Frequency and type of medication will be summarized categorically by treatment group. Descriptive statistics of doses of background methrotrexate at baseline will also be summarized.

9. REFERENCES

1. Pfizer Inflammation Statistics Rulebook For Rheumatoid Arthritis Version 2.0
2. Pfizer Data Standards Rulebook.
3. U.S. NIH - Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

Appendix 1. DETAILS OF VISIT WINDOWS

Visit windows will be used for efficacy and safety summaries that will conduct evaluations or assessments in schedule visits and display by visit.

Table 2. Details of Visit Windows

Visit Label	Target Day	Definition [Day window]
Screening	0	Days −34 to 0
Baseline	Day 1, Randomization	Day 1
Week 4	29	Days 2 to 43
Week 8	57	Days 44 to 71
Week 12	85	Days 72 to

If the calculated study day for the labeled 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 values fall into the same visit window, keep the one closest to the Target Day. If the study day of two values are equal distant from the Target Day in absolute value, the later value should be used.

Subjects' observations will be excluded from visit windows if the data was collected more than 7 days off study drug.

(Safety analysis may follow Pfizer standard)

Appendix 2. DATA DERIVATION DETAILS

Appendix 2.1. Miscellaneous Notes Regarding Endpoints

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
- A 20% improvement from baseline in the swollen joint count
- A 20% improvement from baseline in *at least 3* of the following 5 variables:
    1. Patient's Global Assessment of Arthritis (VAS)
    2. Physician's Global Assessment of Arthritis (VAS)
    3. Patient's Assessment of Arthritis Pain (VAS)
    4. HAQ disability index
    5. C-Reactive Protein (CRP)

ACR50 and ACR70 are defined analogously.

There are many forms of the DAS. The DAS used in this protocol is the DAS using the the 28-count subsets of tender/painful joints and swollen joints, together with either CRP or erythrocyte sedimentation rate ESR, to derive the DAS28-4(CRP), DAS28-3(CRP) or DAS28-4(ESR) and DAS28-3(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.

DAS28 improvement in RA[†] are categorized using the following EULAR response criteria:

[+] 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.

[†] See http://www.das-score.nl/ as of 30 November, 2016

EULAR Response Criteria

	DAS28 improvement (decline in DAS)		
DAS28 (at current visit)	**≤ 0.6**	**0.6 < - ≤ 1.2**	**>1.2**
≤ 3.2	none	moderate	good
3.2 < - ≤ 5.1	none	moderate	moderate
> 5.1	none	none	moderate

There are three categories then, in order: no improvement, moderate improvement, and good improvement. That is, good improvement is the highest kind of improvement. Implicitly, the category "no improvement" also includes a worsening of RA. Hence, relative to Baseline, a patient can only have: a 0 change in categories; a change of "1" category or a change of "2" categories.

The Simplified Disease Activity Index (SDAI) will be calculated per the following formula:

SDAI= TJC28+SJC28+GH/10+PGA/10+CRP/10;

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, PGA stands for Physician's Global Assessment of Arthritis on a 100 mm VAS and CRP is in mg/L.

The Clinical Disease Activity Index (CDAI) will be derived similarly, except that the CRP component will not be part of the calculation.

Appendix 2.2. 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"
- 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 3. ATP III SCREEN SHOTS

ATP III "At A Glance" is available here at this link: http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm That page at this link is pasted below.

ATP III At-A-Glance: Quick Desk Reference

- STEP 1: Determine lipoprotein levels - obtain complete lipoprotein profile after 9- to 12-hour fast
- STEP 2: Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent)
- STEP 3: Determine presence of major risk factors (other than LDL)
- STEP 4: If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk
- STEP 5: Determine risk category
- STEP 6: Initiate therapeutic lifestyle changes (TLC) if LDL is above goal
- STEP 7: Consider adding drug therapy if LDL exceeds levels shown in Step 5 table
- STEP 8: Identify metabolic syndrome and treat, if present, after 3 months of TLC
- STEP 9: Treat elevated triglycerides

STEP 1: Determine lipoprotein levels - obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

- LDL Cholesterol - Primary Target of Therapy

<100	Optimal
100-129	Near Optimal/Above Optimal
130-159	Borderline High
160-189	High
≥190	Very high

- Total Cholesterol

<200	Desirable
200-239	Borderline High
≥240	High

- HDL Cholesterol

<40	Low
≥60	High

STEP 2: Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

STEP 3: Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dl)*
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

* HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.
Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

STEP 4: If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk (see Framingham tables).

Three levels of 10-year risk:

- >20% -- CHD risk equivalent
- 10-20%

- <10%

STEP 5: Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor**	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
** Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

STEP 6: Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

TLC Features

- TLC Diet:
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2g/day) as therapeutic options to enhance LDL lowering
- Weight management
- Increased physical activity

STEP 7: Consider adding drug therapy if LDL exceeds levels shown in Step 5 table:

- Consider drug simultaneously with TLC for CHD and CHD equivalents
- Consider adding drug to TLC after 3 months for other risk categories.

Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG CoA reductase inhibitors (statins)	Lovastatin (20-80 mg), Pravastatin (20-40 mg), Simvastatin (20-80 mg), Fluvastatin (20-80 mg), Atorvastatin (10-80 mg), Cerivastatin (0.4-0.8 mg)	LDL-C ↓18-55% HDL-C ↑5-15% TG ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs*
Bile acid Sequestrants	Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	LDL-C ↓15-30% HDL-C ↑3-5% TG No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL
Nicotinic acid	Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g)	LDL-C ↓5-25% HDL-C ↑15-35% TG ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease
Fibric acids	Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate (1000 mg BID)	LDL-C ↓5-20% (may be increased in patients with high TG) HDL-C ↑10-20% TG ↓20-50%	Dyspepsia Gallstones Myopathy	Absolute: • Severe renal disease • Severe hepatic disease

* Cyclosporine, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).

STEP 8: Identify metabolic syndrome and treat, if present, after 3 months of TLC.

Clinical Identification of the Metabolic Syndrome - Any 3 of the Following:

Risk Factor	Defining Level
Abdominal obesity* Men Women	Waist circumference** >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol Men Women	 <40 mg/dl <50 mg/dl
blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

** Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

Treatment of the metabolic syndrome

- Treat underlying causes (overweight/obesity and physical inactivity):
  - Intensify weight management
  - Increase physical activity
- Treat lipid and non-lipid risk factors if they persist despite these lifestyle therapies:
  - Treat hypertension
  - Use aspirin for CHD patients to reduce prothrombotic state
  - Treat elevated triglycerides and/or low HDL (as shown in Step 9 below)

STEP 9: Treat elevated triglycerides.

ATP III Classification of Serum Triglycerides (mg/dL)

<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

Treatment of elevated triglycerides (≥150 mg/dL)

- Primary aim of therapy is to reach LDL goal.
- Intensify weight management.
- Increase physical activity.
- If triglycerides are ≥200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total - HDL) 30 mg/dL higher than LDL goal.

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

If triglycerides 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal:

- intensify therapy with LDL-lowering drug, or
- add nicotinic acid or fibrate to further lower VLDL.

If triglycerides ≥500 mg/dL, first lower triglycerides to prevent pancreatitis:

- very low-fat diet (≤15% of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid
- when triglycerides <500 mg/dL, turn to LDL-lowering therapy.

Treatment of low HDL cholesterol (<40 mg/dL)

- First reach LDL goal, then:
- Intensify weight management and increase physical activity.
- If triglycerides 200-499 mg/dL, achieve non-HDL goal.
- If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent, consider nicotinic acid or fibrate.

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Appendix 4. HERPES ZOSTER

Herpes zoster is defined as an adverse event with one of the following MedDRA version 19.1 Preferred Terms (Preferred Codes):

- Genital herpes zoster (10072210)
- Herpes zoster (10019974)
- Herpes zoster cutaneous disseminated (10074297)
- Herpes zoster disseminated (10065038)
- Herpes zoster infection neurological (10061208)
- Herpes zoster meningitis (10074259)
- Herpes zoster meningoencephalitis (10074248)
- Herpes zoster meningomyelitis (10074251)
- Herpes zoster necrotising retinopathy (10074253)
- Herpes zoster oticus (10063491)
- Herpes zoster pharyngitis (10074245)
- Ophthalmic herpes zoster (10030865)

Additionally, if there are any events that are adjudicated as any type of herpes zoster (including herpes zoster, two adjacent dermatomes which is considered a special interest infection rather than an opportunistic infection), the events will be included in the herpes zoster analyses, regardless of the reported MedDRA Preferred Terms.