Protocol B5381012

A RANDOMIZED COMPARATIVE STUDY ASSESSING THE SWITCHING BETWEEN PF-06410293 AND HUMIRA® IN COMBINATION WITH METHOTREXATE IN PARTICIPANTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS

Statistical Analysis Plan
(SAP)

Version: **2**

Date: **13 JUL 2021**

[redacted]

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 29 Aug 2019	Original 28 Jun 2019	N/A	N/A
2. draft	Amendment 1 19 May 2020	Update to align with protocol amendent 1 and clarificatio n/simplifica tion/comple tion of prior version	• Update the following sections to align with protocol amendment 1: ▪ Text update in the protocol title. ▪ Study design for TP4 and follow-up period (Section 2.2) ▪ The definitions of PK population (Section 4) ▪ The definition of treatment-emergent AEs (Section 3.5.1 and Section 6.1.3) ▪ The removal of TP2 to TP3 cumulative AE summary • Update/provide more details on AESI definition and immunogenic AE definition and medical evaluation (Section 3.5.1). • Exclude all subjects at site [redacted] from all the analysis populations due to violation of GCP principles (Section 4) • More details on Hypothesis and Decision rule (Section 5.1) • The analyses for C_{trough} in TP1 and TP2-TP4 are combined as TP1-TP4 analysis using safety-randomized population (Section 6.2.1). • Update/provide more detailed on ADA and NAb analysis (Section 6.2.2) • Clarification/simplificaiton of TP1 AE summary and provide more details on TP2 to TP4 AE summary including AESI and immunogenic AE (Section 6.6.1.1 and Section 6.6.1.2).

			• Clarification/simplication of Lab data analysis for TP1 and TP2-TP4. • Add COVID-19 related summary and analysis for protocol deviation, subject discontinuation, AE (Section 6.6.4) • Removal of the following analyses which won't impact the study conclusion: demographic summary for Safety-TP1 population and Safety-randomized population; concomitant medication and non-drug treatment summary for TP1 data; vital sign analysis for TP1 data; physical examination, MTX dose and medical history. • Additional typographic errors correction and editorial changes as necessary throughout the SAP.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B5381012. 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, Endpoints, and Estimands

The primary objective of the study is to evaluate interchangeability of PF-06410293 and Humira by examining adalimumab steady-state pharmacokinetics (PK) in a switching arm (following 3 switches between Humira and PF-06410293) as compared to a non-switching arm (receiving only Humira). The secondary objectives are

- To evaluate other serum adalimumab PK parameters in the switching arm and the non-switching arm.
- To evaluate the overall safety and tolerability of the switching arm and the non-switching arm.
- To evaluate immunogenicity of the switching arm and the non-switching arm.

2.1.1. Primary Estimand(s)

The primary estimand of this study is defined according to the primary objective and is in alignment with the primary endpoint. The primary estimands are the geometric mean ratio (GMR) and 90% confidence interval (CI) for AUC_{τ} and C_{max} to evaluate the PK equivalence

between the switching and non-switching arms, after 3 switches, in participants with RA who meet the PK population criteria that include criteria for the number and timing of missing doses, availability of PK sample data, adherence to background therapy, and major protocol deviations related to PK assessment (Section 4).

2.1.2. Secondary Estimand(s)

The secondary estimands are

- Other serum adalimumab PK parameters, including time at which C_{max} occurs (T_{max}), average concentration over the dosing interval (C_{av}), and apparent clearance (CL/F) obtained during the intensive PK sampling interval in participants who meet the PK population criteria. Pre-dose concentrations during multiple dosing (C_{trough}) obtained at scheduled PK sample timepoints will also be assessed in participants who meet the safety population criteria, for the switching arm and non-switching arm.

- Safety endpoints for the switching arm and non-switching arm in participants who meet the safety population criteria.

- Summarize percent of participants with antidrug antibodies (ADA), and neutralizing antibodies (NAb) and ADA/NAb titers over time for the switching arm and non-switching arm in participants who meet the Safety population criteria.

2.2. Study Design

This is an open-label, multi-national, 2-arm, randomized, parallel-group study designed to evaluate the interchangeability of the switching arm (PF-06410293 and Humira), compared to non-switching arm (Humira), in participants with moderately to severely active RA on background methotrexate (MTX). For purposes of this protocol, the treatment arm that includes switches between PF-06410293 and Humira will be referred to as the “switching” arm, while the treatment arm that comprises continuous Humira treatment will be referred to as the “non-switching” arm.

This study will enroll a maximum of approximately 420 participants so that approximately 314 evaluable participants complete the study.

Study treatment will be provided through 4 treatment periods. For the first 10 weeks, all participants will receive Humira [Treatment Period (TP) 1]. Upon completion of TP1, participants will be randomized (1:1 ratio) into either the switching or non-switching arm prior to dosing on Week 10. Randomization will be stratified by 3 body weight groups (Week 10 weight) (≥40 kg to <70 kg; ≥70 kg to <100 kg; ≥100 kg to ≤130 kg). Participants randomized to the non-switching arm will continue on Humira for the remainder of the study, and participants randomized to the switching arm will continue switching in each TP (TP2: PF-06410293; TP3: Humira; TP4: PF-06410293).

- Treatment Period 1 (Lead In Period) will begin with the first dose of investigational product on Week 0 (Day 1) and conclude with the completion of Week 10 pre-dose assessments.

- Treatment Period 2 will begin with the 1:1 randomization of the participants to either the switching arm or the non-switching arm at Week 10. Investigational product dosing for Week 10 will begin after the randomization process in the respective treatment arms and will conclude with the completion of Week 16 pre-dose assessments.

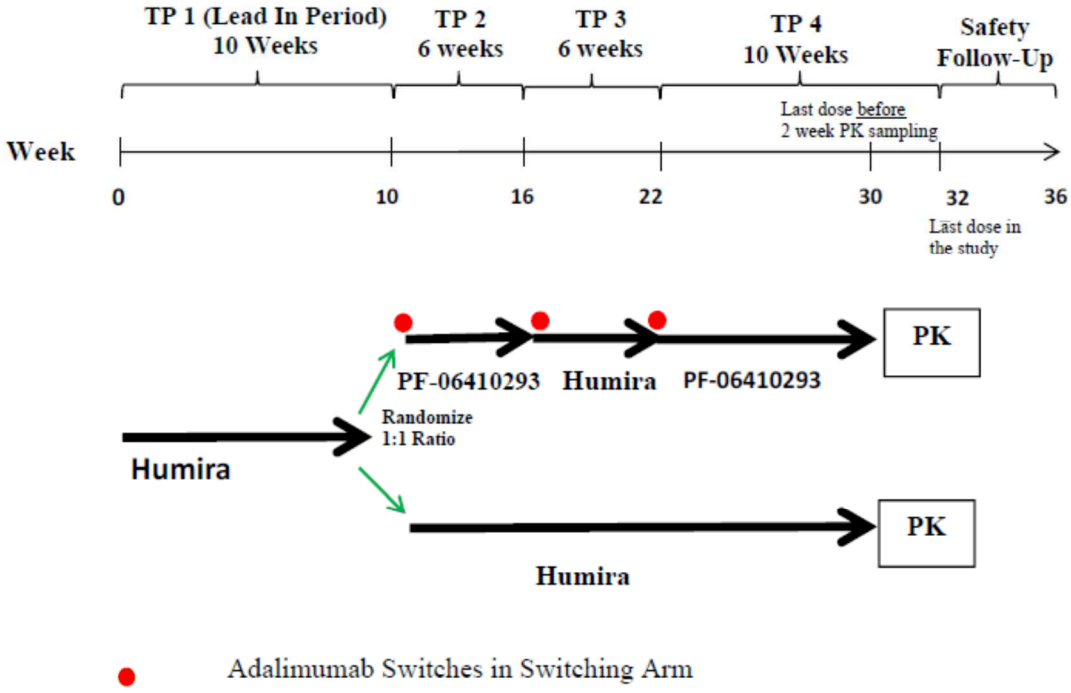
- Treatment Period 3 will begin with investigational product dosing on Week 16, and conclude with the completion of Week 22 pre-dose assessments.

- Treatment Period 4 will begin with investigational product dosing on Week 22 and continue through Week 30, where onsite investigational product dosing is scheduled at Weeks 22, 24, 26, 28, and 30, followed by a 2-week PK sampling period from Week 30 to Week 32. TP4 will conclude with end of treatment (EoT) assessments and final dose administration at Week 32.

    - The 2-week PK sampling period within TP4 starts with Week 30 predose PK collection and ends with predose PK collection on Week 32.

- Safety Follow-Up Period begins after the last investigational product dosing on Week 32, and concludes at completion of the Week 36 assessments. All participants (including early discontinuations) will be followed for at least 28 calendar days from the date of their last dosed investigational product. Week 36 safety follow up may be conducted via phone.

Figure 1. Study Design



TP = Treatment Period.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoints are C_{max} and AUC_{τ} obtained during the intensive PK sampling interval.

3.2. Secondary Endpoint(s)

The secondary endpoints are

- Other serum adalimumab PK parameters and serum concentration, including T_{max}, C_{av}, and CL/F obtained during the intensive PK sampling interval and C_{trough} obtained at scheduled PK sample timepoints.

- Safety endpoints including adverse events (AEs), laboratory test and vital signs. More detailed information is provided in Section 3.5.

- ADA and NAb endpoints including percent of participants with ADA/NAb and ADA/NAb titers over time.

3.3. Other Endpoint(s)

Other endpoints include demographic and baseline characteristics, such as participant age, sex, height, weight, race, ethnicity, and medical history, and study drug administration.

3.4. Baseline Value

For the TP1 summary, the baseline value is defined as the most recent measurement prior to the first dose of investigational product in TP1. For the TP2 to TP4 summary, the baseline value is defined as the most recent measurement prior to the first dose of investigational product after randomization in TP2.

3.5. Safety Endpoints

3.5.1. Adverse Events

A treatment-emergent adverse event (TEAE) for TP1 summary is defined as any adverse event that occurs after the beginning of the study treatment in TP1 and before the first dose of investigational product administrated after randomization in TP2.

A treatment-emergent adverse event (TEAE) for TP2 to TP4 summary is defined as any adverse event that occurs after the first dose of investigational product administrated after randomization in TP2. Adverse events of special interest (AESI) include Targeted medical events (TME) which are defined for Adalimumab biosimilar program and are maintained in a list in the product's Safety Review Plan.

Immunogenic adverse effects include injection-site reactions (ISRs); medically evaluated AEs that meet Sampson Criteria[1], and medically evaluated AEs identified by broad MedDRA SMQ for Hypersensitivity/Anaphylaxis /Angioedema; medically evaluated AEs identified as potential Cytokine storm, and medically evaluated AEs tidentified as potential Delayed immune responses.

3.5.2. Laboratory Data

Laboratory data include hematology, chemistry, and urine routine safety laboratory tests results at each visit.

3.5.3. Vital Sign Data

Vital signs endpoints include body temperature, pulse rate, respiratory rate, and blood pressure.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

All subjects at site CCI will be excluded from all the analysis populations due to violation of GCP principles (i.e., suspected falsification of study records).

Population	Description
Enrolled Population	All participants who are enrolled in TP1. This population will be used for participant accountability in TP1.
Safety Population for TP1 (Safety-TP1)	All participants who are enrolled in TP1 and receive at least one dose of investigational product in TP1. This population will be used for the TP1 safety analyses.
Intent-to-Treat Population (ITT-Randomized)	All participants who are randomized to a study treatment group at Study Week 10. This population will be used for participant accountability during TP2 through TP4.
Safety Population (Safety-Randomized)	All participants who are randomized and receive at least one dose of investigational product following the randomization at Study Week 10. The Safety Population will be used for the safety analyses during TP2 and beyond, ADA and NAb analyses and the secondary PK endpoint (C_{trough}).
PK population	All randomized participants who are dosed to initiate the Week 30 steady-state PK profile, remain on background MTX with no major protocol deviations influencing the PK assessment, such as a miss dose (the first dose of the study in TP1 cannot be missed, no more than 1 missed dose allowed per TP except Week 32 dose, no more than 2 missed doses allowed in TP1 through TP4 except Week 32 dose, participants can only miss or have an incomplete dose for either the first or second dose in TP4 (but not both), and the study doses on Weeks 26, 28, and 30 cannot be missed or incomplete), and have at least 1 primary endpoint (AUC_{τ} or C_{max}). The last study dose in TP4 on week 32 after the PK assessments is not included in the definition of the population for analyses and can be missed or be incomplete. Subjects will be excluded from the PK population in case of missed PK sample(s) which significantly affect the calculation of PK parameters. The PK population will be used for the primary PK analysis and other secondary PK endpoint analyses (T_{max}, C_{av}, and CL/F).

The determination of PK population independent of the PK test results will be finalized prior to the releasing of the study database.

Protocol deviations independent of PK test results will be determined on an ongoing basis per data review. Any participant with major protocol deviations that affect PK assessment as determined by the study team will be excluded from the PK population. Major protocol deviations may include: Missing or incomplete dosing (the first dose of the study in TP1 cannot be missed, no more than 1 missed dose allowed per TP except Week 32 dose, no more than 2 missed doses allowed in TP1 through TP4 except Week 32 dose, participants can only miss or have an incomplete dose for either the first or second dose in TP4 (but not both), and the study doses on Weeks 26, 28, and 30 cannot be missed or incomplete). During the conduct of the study, it is possible that other deviations will be identified that can impact PK assessments, which can result in additional deviations to those noted above.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

null hypothesis: H01 $\frac{\mu_s}{\mu_{ns}} < 0.8$ or H02 $\frac{\mu_s}{\mu_{ns}} > 1.25$

alternative hypothesis: Ha $0.8 \leq \frac{\mu_s}{\mu_{ns}} \leq 1.25$

μ_s: geometric mean for the switching arm

μ_{ns} : geometric mean for the non- switching arm

Interchangeability will be established statistically if the 90% CI for the GMR is within 80.00% to 125.00% for both C_{max} and AUC_{τ}.

5.2. General Methods

The analyses for TP1 (lead-in period) will be performed for Humira group. The analyses for TP2 and beyond will be performed by treatment groups (switching arm vs non-switching arm).

5.2.1. Analyses of Variance (ANOVA)

ANOVA will be used for comparing switching arm vs non-switching arm for C_{max} and $AUC\tau$. GMR and the associated 90% 2-sided CI are will be obtained using analysis of ANOVA applied to log-transformed data, with terms for treatment and randomization stratification factor (body weight categories).

5.3. Methods to Manage Missing Data

In general, no missing data will be imputed. For PK data, the following rules apply.

5.3.1. Concentrations below the limit of quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In the listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

5.3.2. Deviations, missing concentrations and anomalous values

In summary tables and plots of mean profiles of PK, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample);

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the PK analyst.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. C_{max} and AUC_{τ}

The serum concentrations between Week 30 and Week 32 will be analyzed for the PK population using standard non-compartmental analysis to estimate the PK parameters (C_{max}, AUC_{τ}, T_{max}, C_{av}, and CL/F) for each individual participant.

C_{max} and AUC_{τ} are the primary endpoints. The primary analysis for C_{max}, and AUC_{τ} will be ANOVA with terms for treatment and randomization stratification factor (body weight categories) to compare switching arm and non-switching arm in log-transformed data in PK population. The mean difference and the confidence intervals (CI) for the differences will be obtained using ANOVA model. The mean differences and the CI will be exponentiated to provide estimates of geometric mean ratio (GMR) and the 90% confidence intervals for the ratio. Interchangeability will be established statistically if the 90% CI for the GMR is within 80.00% to 125.00% for both endpoints.

C_{max} and AUC_{τ} will also be summarized descriptively for switching arm and non-switching arm. In addition, the primary endpoints will be summarized by ADA and NAb status at week 30.

6.2. Secondary Endpoint(s)

6.2.1. Other PK endpoints

Secondary PK parameters (T_{max}, C_{av} and CL/F) and serum concentrations collected between Week 30 and Week 32 will be summarized descriptively for switching arm and non-switching arm using PK population. C_{trough} collected in TP1 through TP4 will summarize descriptively by each visit using Safety-Randomized population for switching and non-switching arm.

For serum concentration during week 30 to week 32, mean concentration time plot, median concentration time plots and individual concentration time plots on both linear and semi-log scales will be provided for PK population by switching and non-switching arms. For C_{trough}, box plots will be provided using using Safety-Randomized population by switching and non-switching arm for data collected in TP1 through TP4.

In addition, the summarization for secondary PK parameters (T_{max}, C_{av} and CL/F), serum concentrations collected between Week 30 and Week 32 will be provided by ADA and NAb status at week 30. The plots for serum concentration during week 30 to week 32 will be provided by ADA and NAb status at week 30. C_{trough} at each visit will also be summarized and plotted by ADA and NAb status at the corresponding visit.

6.2.2. Anti-drug antibody (ADA) and Neutralizing Anti-Drug Antibody (NAb) Results

For the ADA and NAb data, the percentage of participants with positive ADA and NAb will be calculated and summarized for the Safety-Randomized population by each visit for TP1 through TP4. The magnitude (titer) and time of first positive sample will also be described.

ADA and NAb status at the end of study will be used to characterized the participants response as either persistent or transient. For participants with at least one ADA/NAb positive sample, persistent response is defined as ADA/NAb positive at the last sample, and transient response is defined as having had at least one ADA/NAb positive sample, and an ADA/NAb negative at last sample.

In addition, the impact of ADA and NAb on PK over time will be assessed as specified in section 6.1.1 and 6.2.1.

6.2.3. Safety endpoints

The analyses and summary for safety endpoints is provided in Section 6.6.

6.3. Other Endpoint(s)

The summary for other endpoints including demographic and baseline characteristic, study drug administration is provided in section 6.5.

6.4. Subset Analyses

PK data over time will be assessed by ADA and NAb status. Please see the details in Section 6.1.1 and 6.2.1.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Participant disposition

Participant disposition will be summarized for enrolled population and ITT-Randomized population and will include the number and percentage of participants enrolled, randomized, treated, status, reason/description and other relevant data.

6.5.2. Participant demographics, Baseline characteristics

Demographics and baseline characteristics (age, sex, height, weight, race, ethnicity, etc.) will be summarized descriptively using Enrolled population, , ITT- Randomized population, and PK population.

6.5.3. Study Treatment Exposure

Study drug exposure (total number of doses, duration of treatment, total number of participants with any missed doses, etc.) will be summarized descriptively using Safety-TP1 population by Humira arm and Safety-Randomized population by switching arm and non-switching arm.

6.5.4. Concomitant Medications and Nondrug Treatments

Collected prior and concomitant medications will be coded by WHO medical dictionary; participants who received these medications will be summarized using Safety-Randomized population from TP2 to TP4 by switching arm and non-switching arm.

6.6. Safety Summaries and Analyses.

Unless otherwise specified, safety analyses for TP1 will be performed using the Safety-TP1 population for the Humira arm. Safety analyses for TP2 and beyond will be performed using Safety-Randomized populations by switching arm and non-switching arm.

6.6.1. Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system.

Unless otherwise specified, AE analyses for TP1 will be performed using the Safety-TP1 population for the Humira arm. AE analyses for TP2 and beyond will be performed using Safety-Randomized populations by switching arm and non-switching arm. Treatment-emergent adverse events definitions for TP1 and TP2 and beyond are provided in section 3.5.1.

6.6.1.1. Adverse Event for TP1

Adverse events (including overall summary of treatment-emergent adverse events; treatment-related adverse events; adverse events classified as Grade 3 or higher; adverse event leading to discontinuation; and SAEs) will be summarized for the Humira arm. All-causality TEAE and SAE will be also summarized by body system and preferred term according to MedDRA terminology.

6.6.1.2. Adverse Event for TP2 and Beyond

Adverse events (including overall summary of treatment-emergent adverse events; treatment-related adverse events; adverse events classified as Grade 3 or higher; adverse event leading to discontinuation; and SAEs, etc.) will be summarized by switching arm and non-switching arm. All-causality TEAE and SAE will be also summarized by body system and preferred term according to MedDRA terminology.

AESI will be summarized by body system and preferred term according to MedDRA terminology and also by AESI categories, subcategories and preferred term.

6.6.1.2.1. Effect of Immunogenicity on Safety

Immunogenic adverse effect during TP2 and beyond will be summarized for 2 subgroups of safety-randomized population: ADA positive in TP1 and ADA negative in TP1 subgroups (if applicable):

- Percentage of participants with ISR AEs (as per the investigators)
- Percentage of participants with medically evaluated AEs that meet Sampson's Criteria
- Percentage of participants with medically evaluated potential Hypersensitivity, Angioedema, Anaphylaxis, Cytokine Storm, and Delayed immune responses

The identification of participants with AEs that meet Sampson criteria and the statistical summary will be provided in a supplemental statistical specification.

6.6.1.2.2. AESI Summary for Individual Period

The summary of AESI will be provided by switching arm and non-switching arm for individual switching periods (TP2, TP3, TP4).

The safety analysis population for each individual period TP2/TP3/TP4 (Safety-TP2/TP3/TP4) is defined as all participants who are randomized and receive at least one dose of investigational product in TP2/TP3/T4.

TEAE for TP2 is defined as any adverse event that occurs after the first dose of investigational product administrated in TP2 and before the first dose of investigational product administratd in TP3. TEAE for TP3 is defined as any adverse event that occurs after the first dose of investigational product administrated in TP3 and before the first dose of investigational product administratd in TP4. TEAE for TP4 is defined as any adverse event that occurs after the first dose of investigational product administrated in TP4.

6.6.2. Laboratory Data

The incidence of Lab abnormality will be summarized in TP1 for Safety-TP1 population and in TP2 through TP4 for Safety-Randomized population. The summary for Lab data by Maximum CTC Grade will be provided in TP2 through TP4 for Safety-Randomized population. eDISH Analysis will be provided in TP2 through TP4 for Safety-Randomized population.

6.6.3. Vital Signs

The vital sign data at each visit will be summarized for TP2 through TP4 data using Safety-Randomized population. The mean change from baseline to week 32/EOT/ET will be provided for Safety-Randomized populations. Baseline definitions for vital sign data will be consistent with Section 3.4.

6.6.4. COVID-19 Related Summary

Protocol Deviation, subject discontinuation, AE and SAE related to COVID-19 will be listed and/or summarized by Humira group for TP1 data and by switching and non-switching arms for TP2-TP4 data.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor will conduct ongoing reviews of the data during the course of the study for the purpose of safety.

7.2. Interim Analyses and Summaries

No interim analyses and summaries will be provided since no formal interim analyses is planned for this study.

8. REFERENCES

(1) Sampson H.A., et al. [2006]. Second Symposium on the Definition and Management of Anaphylaxis: Summary Report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Annals of Emergency Medicine, 47. 373 - 380.

9. APPENDICES

Appendix 1. SMQ MedDRA V24.0 Listings

SMQ MedDRA V24.0 listings could be found through the link

https://www.meddra.org/how-to-use/support-documentation/english/welcome

Appendix 2. List of Abbreviations

Abbreviation	Term
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
AUC	area under the curve
AUCτ	area under the concentration - time curve over the dosing interval
C_{av}	average concentration
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum observed concentration
C_{trough}	predose concentration during multiple dosing
EoT	End of Treatment
ET	Early Termination
GMR	geometric mean ratio
MedDRA	Medical dictionary for regulatory activities
MTX	methotrexate
NAb	neutralizing antibodies
ND	not done
NS	no sample
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA query
TEAE	treatment-emergent adverse event
T_{max}	time at which Cmax occurs
TP1	treatment period 1
TP2	treatment period 2
TP3	treatment period 3
TP4	treatment period 4
WHO	World Health Organization