**Protocol A3921104**

**EFFICACY, SAFETY AND TOLERABILITY OF TOFACITINIB FOR TREATMENT OF POLYARTICULAR COURSE JUVENILE IDIOPATHIC ARTHRITIS (JIA) IN CHILDREN AND ADOLESCENT SUBJECTS**

**Statistical Analysis Plan
(SAP)**

**Version:** 4.0

**Date:** 24 April 2019

# TABLE OF CONTENTS

CCI

## LIST OF TABLES

CCI

CCI

CCI

CCI

CCI

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study A3921104. 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.

The safety and effectiveness of tofacitinib for the treatment of RA has been demonstrated in adult subjects. The Sponsor is conducting a pediatric development program to determine the safety and efficacy of tofacitinib in subjects 2 to <18 years of age for the treatment of JIA.

As part of this pediatric program, a Phase 1 pharmacokinetic (PK) study of tofacitinib in JIA subjects (A3921103) has been completed, and an open-label, non-comparative, long-term extension study (A3921145) is currently ongoing.

This Phase 3 study is intended to provide evidence of efficacy and safety of tofacitinib in subjects with JIA.

Due to the availability of effective treatments for subjects with JIA, a randomized withdrawal study design was selected to limit exposure to placebo treatment.

### 2.1. Study Objectives

**Primary:**

- To compare the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA at Week 44/End of Study (Week 26 of the double-blind phase) as measured by the percentage of subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) after Week 18 of the open-label run-in phase.

**Secondary:**

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the percentage of subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by time to disease flare in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by achievement of JIA ACR 30, 50, 70, 90, 100 response at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in JADAS 27-CRP and JADAS-27 ESR, and percentage of subjects achieving JADAS minimum disease activity and inactive disease at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for treatment of signs and symptoms of JIA as measured by the JIA ACR inactive disease and clinical remission rate at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in each JIA ACR core set variable at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in CHQ responses at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in the Childhood Health Assessment Questionnaire (CHAQ) responses at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the occurrence of active uveitis (according to SUN criteria) in the double-blind phase;

- In subjects with ERA: To evaluate the efficacy of tofacitinib for the treatment of ERA as measured by changes from baseline in the Tender Entheseal Assessment, Modified Schober's Test, and Overall Back Pain and Nocturnal Back Pain responses at various time points in the double-blind phase;

- In subjects with PsA: To evaluate the efficacy of tofacitinib for the treatment of PsA as measured by changes from baseline in the BSA affected with psoriasis and PGA of psoriasis assessments at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib in the open-label run-in phase;

- To evaluate the taste acceptability of tofacitinib oral solution, if applicable, on Day 14 of the open-label run-in phase;

- To evaluate safety and tolerability of tofacitinib in subjects with JIA during the study;

- To evaluate the PK of tofacitinib in subjects with JIA during the open-label run-in phase.

CCI

## 2.2. Study Design

This is a randomized withdrawal, double-blind, placebo-controlled study of subjects from 2 to <18 years of age with JIA.

All eligible subjects enrolled in the study will initially receive open-label tofacitinib for 18 weeks (run-in phase).  At the end of the 18 week run-in phase, only subjects who achieve at least a JIA ACR 30 response will be randomized to the 26 week double-blind, placebo-controlled phase.  Subjects who do not achieve a JIA ACR 30 response at this time point will be discontinued from the study.  Subjects who experience a single episode of disease flare at any time during the study (including the open-label run-in and double-blind phase) will also be discontinued from the study.

CCI

Subjects who are eligible for the 26 week double-blind phase will be randomized (1:1 ratio) to either active tofacitinib or placebo.  For subjects with polyarticular course JIA (ie, extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features), randomization will be stratified by JIA category and baseline CRP (normal CCI , above normal CCI ).  For subjects with psoriatic and enthesitis-related arthritis, randomization will be stratified by JIA category.

CCI

Approximately 210 subjects will be enrolled in the open-label run-in phase.  Among subjects with polyarticular course JIA, stratification will target enrollment of at least 50% with a baseline CRP above the upper limit of normal.

The cohort of subjects with polyarticular course JIA will have at least 170 subjects enrolled in the run-in phase with the minimum number of JIA categories as follows: 24 with extended oligoarthritis, 20 with polyarthritis RF+, 62 with polyarthritis RF-, 20 with systemic JIA with active arthritis but without active systemic features. Additional cohorts (ie, psoriatic and enthesitis-related arthritis) will include a minimum of 20 subjects with psoriatic arthritis, and 20 subjects with enthesitis-related arthritis. The overall target minimum number of subjects to be enrolled in the study by age is as follows: 20 subjects 2 to <6 years, 20 subjects 6 to <12 years, and 20 subjects 12 to <18 years. The Sponsor will monitor enrollment and periodically notify investigator sites regarding the status of enrollment in the various JIA categories and age groups.

The duration of subject participation among those who complete the study (without discontinuation) is expected to be approximately 44 weeks. Pediatric blood tubes will be used (reduced volume) for testing to determine eligibility, monitor safety, and measure PK.

The study will be conducted over a period of approximately 3 years. CCI

CCI

CCI

CCI

CCI

## 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

### 3.1. Primary Endpoint

The primary endpoint of this study is:

- Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) by Week 44/End of Study (Week 26 of the double-blind phase).

Only disease flare during the double-blind phase will be counted as primary endpoint.

Disease flare (except assigning as flare after discontinuation) will be derived by the Centralized Coordinating Center (CCC) using Erythrocyte Sedimentation Rate (ESR) in real-time, and double-blind baseline will be used to determine disease flare. CCI

## 3.2. Secondary Endpoints

### 3.2.1. Key Secondary Endpoints

- Achieving JIA ACR 30-50-70 response at Week 44/End of Study (Week 26 of the double-blind phase); open-label run-in baseline will be used to determine ACR response.

CCI

- Change from double-blind baseline in CHAQ disability index at Week 44/End of Study (Week 26 of the double-blind phase).

- CCI

### 3.2.2. Secondary Endpoints in the Double-Blind Phase

- Disease flare and JIA ACR inactive disease during double-blind phase will be derived by the CCC using ESR in real-time, and other secondary endpoints during the double-blind phase will be derived by Pfizer. CCI

All secondary endpoints with data collected in the double-blind phase (from randomization/Week 18 to Week 44/EOS) are:

- Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase. CCI

CCI

- Time to disease flare in the double-blind phase. Time to disease flare is measured in number of days since randomization (day of disease flare – day of randomization +1) into the double-blind phase. CCI

- Achieving JIA ACR 30-50-70-90-100 response at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase; open-label run-in baseline will be used to determine ACR response;

- Change from double-blind baseline in JADAS-27 CRP, JADAS-27 ESR, and achieving JADAS minimum disease activity and inactive disease at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase;

- Achieving JIA ACR inactive disease at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase, and achieving clinical remission at week 44 (double-blind week 26); CCI

- Change from double-blind baseline in each JIA ACR core set variable at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase;

- Change from open-label run-in baseline in each JIA ACR core set variable at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase;

- Change from double-blind baseline in CHQ responses at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase;

- Change from double-blind baseline in CHAQ responses at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase.

- The 'each scheduled visit' means the visit in the visit window as defined in Appendix 9.3 throughout the study.

### 3.2.3. Secondary Endpoints in the Open-Label Run-in Phase

- Disease flare and JIA ACR inactive disease during open-label run-in phase and DB phase, and ACR 30 response at week 18 CCI

- The secondary efficacy endpoints with data collected in open-label run-in phase (from Day 1 to randomization/Week 18) are:

- Occurrence of disease flare at each scheduled visit in the open-label phase. CCI

- Time to disease flare in the open-label run-in phase. Time to disease flare is measured in number of days since Day 1 (day of disease flare – Day 1 +1) into the open-label run-in phase. Day 1 is defined as the day of first dose of study drug in open-label run-in phase. CCI

- Achieving JIA ACR 30-50-70-90-100 response at each scheduled visit in the open-label run-in phase; JIA ACR 30-50-70-90-100 response is determined based on the open-label run-in baseline.

- Change from open-label run-in baseline in JADAS-27 CRP, JADAS-27 ESR, and achieving JADAS minimum disease activity and inactive disease at each scheduled visit in the open-label run-in phase;

- Achieving JIA ACR inactive disease at each scheduled visit in the open-label run-in phase; percentage of subjects experiencing at least one JIA ACR inactive disease during open-label phase.

- Change from open-label run-in baseline in each JIA ACR core set variable at each scheduled visit in the open-label run-in phase.

- Change from open-label run-in baseline in CHQ responses at each scheduled visit in the open-label run-in phase.

- Change from open-label run-in baseline in CHAQ responses at each scheduled visit in the open-label run-in phase.

- Taste acceptability of tofacitinib oral solution (Like very much, Like a little, Not Sure, Dislike a little, Dislike very much), if applicable, on Day 14 of the open-label run-in phase.

- CCI

- The same secondary endpoints in the open-label run-in phase will also be calculated for ERA and PsA subjects.

### 3.2.4. Secondary Endpoints Specific for ERA and PsA in Both Open-Label Run-In Phase and Double-Blind Phase

- Secondary endpoints in both open-label run-in phase and double-blind phase are all ERA and PsA specific endpoints. For details of the derivation of these endpoints, see Appendix 9.2.9 to 9.2.10.

Open-label phase (Day 1 to randomization/Week 18):

- In subjects with ERA: Change from open-label run-in baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at each scheduled visit in the open-label run-in phase;

- In subjects with PsA: Change from open-label run-in baseline in the body surface area (BSA) affected with psoriasis and PGA of psoriasis assessments at each scheduled visit in the open-label run-in phase.

Double-blind phase (randomization/Week 18 to Week 44/EOS):

- In subjects with ERA: Change from double-blind baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase;

- In subjects with PsA: Change from double-blind baseline in the body surface area (BSA) affected with psoriasis and PGA of psoriasis assessments at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase.

- The 'each scheduled visit' means the visit in the visit window as defined in Appendix 9.2.3 throughout the study.

### 3.3. Other Endpoints

### 3.3.1. PK Endpoints

- Plasma tofacitinib concentrations during the open-label run-in phase.

CCI

CCI

### 3.5. Safety Endpoints

The safety endpoints of this study are:

- Occurrence of active uveitis (according to SUN criteria) at each scheduled visit in the open-label run-in and double-blind phase;

- Incidence and severity of adverse events, with focus on serious infections, cytopenias, malignancies, cardiovascular diseases and gastrointestinal perforations;

- Incidence of clinical laboratory abnormalities and change from baseline in clinical laboratory values;

- Incidence of abnormalities in physical examination and incidence of significant changes from baseline at final visit for physical examination;

- Incidence of vital sign abnormalities and change from baseline in vital sign measures;

- Validated assessments of growth and pubertal development (Tanner Stage of Development);

The 'each scheduled visit' means the visit in the visit window as defined in Appendix 9.2.3 throughout the study.

### 4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures. Table 2 listed all the analysis sets and their corresponding analyses in the study.

**Table 2.    Summary of Different Analysis Sets**

| Analysis set | Brief description | Efficacy analysis | Safety analysis |
|---|---|---|---|
| DBFAS | Subjects randomized to DB phase, received at least one dose of study medication in DB phase, reported under randomized treatment | None | None |
| DBJAS | pJIA subjects in DBFAS | Primary endpoint, key secondary endpoints and secondary endpoints in DB phase for pJIA | None |
| DBERA | ERA subjects in DBFAS | Secondary endpoints in DB phase for ERA, ERA specific endpoints in DB phase | None |
| DBPsA | PsA subjects in DBFAS | Secondary endpoints in DB phase for PsA, PsA specific endpoints in DB phase | None |
| DBJPP | Subjects with no major protocol violations in the DBJAS | Primary endpoint | None |
| DBSAS | Subjects received at least one dose of study medication in DB phase, reported under received treatment | None | All DB safety analyses |
| OLFAS | Subjects enrolled, received at least one dose of study medication in OL phase | Taste acceptability | All OL safety analyses |
| OLJAS | pJIA subjects in OLFAS | Secondary endpoints in OL phase for pJIA | None |

| Analysis set | Brief description | Efficacy analysis | Safety analysis |
|---|---|---|---|
| OLERA | ERA subjects in OLFAS | Secondary endpoints in OL phase for ERA, ERA specific endpoints in OL phase | None |
| OLPsA | PsA subjects in OLFAS | Secondary endpoints in OL phase for PsA, PsA specific endpoints in OL phase | None |

## 4.1. Double-Blind Full Analysis Set (DBFAS)

The double-blind full analysis set (DBFAS) consists of all subjects randomized to the double-blind phase who received at least one dose of study medication in the double-blind phase. Subjects will be reported under the treatment they were randomized to. In this study, no efficacy analyses will be performed on the DBFAS, all efficacy analyses will be done on the following subsets of the DBFAS.

### 4.1.1. Double-Blind Polyarticular Course JIA Analysis Set (DBJAS)

The double-blind polyarticular course JIA analysis set (DBJAS) consists of all subjects included in the DBFAS with polyarticular course JIA. The double-blind polyarticular course JIA analysis set is the primary efficacy analysis set of the study.

### 4.1.2. Double-Blind ERA Analysis Set (DBERA)

The double-blind ERA analysis set (DBERA) consists of all subjects included in the DBFAS with ERA.

### 4.1.3. Double-Blind PsA Analysis Set (DBPsA)

The double-blind PsA analysis set (DBPsA) consists of all subjects included in the DBFAS with PsA.

## 4.2. Double-Blind Polyarticular Course JIA Per Protocol Analysis Set (DBJPP)

The double-blind polyarticular course JIA per-protocol analysis set (DBJPP) will consist of all subjects included in the double-blind polyarticular course JIA analysis set (see Section 4.1.1) who have no major protocol violations with regard to inclusion criteria, exclusion criteria, or study conduct.

Inclusion in the DBJPP analysis set will be determined prior to un-blinding of the study. Efficacy results for the DBJPP analysis set will be produced as part of a sensitivity analysis, supporting the analysis of the primary endpoint.

If there are few major protocol deviations impacting the primary analysis, the study team will decide whether to have a DBJPP analysis or not before un-blinding of the study.

See the definition of protocol deviations that relate to statistical analysis/populations in Appendix 9.4.

### 4.3. Double-Blind Safety Analysis Set (DBSAS)

The double-blind safety analysis set (DBSAS) consists of all subjects who have received at least one dose of study medication in double-blind phase.  Subjects will be reported under the treatment which they received.

### 4.4. Other Analysis Sets

### 4.4.1. Open-Label Run-In Phase Full Analysis Set (OLFAS)

The open-label run-in phase full analysis set (OLFAS) consists of all subjects who were enrolled into the open-label run-in phase of the study and received at least one dose of study medication in the open-label run-in phase.  This will be the same as the open-label run-in safety analysis set.

### 4.4.2. Open-Label Run-In Polyarticular Course JIA Analysis Set (OLJAS)

The open-label run-in polyarticular course JIA analysis set (OLJAS) consists of all subjects included in the OLFAS with polyarticular course JIA.

### 4.4.3. Open-Label Run-In ERA Analysis Set (OLERA)

The open-label run-in ERA analysis set (OLERA) consists of all subjects included in the OLFAS with ERA.

### 4.4.4. Open-Label Run-In PsA Analysis Set (OLPsA)

The open-label run-in PsA analysis set (OLPsA) consists of all subjects included in the OLFAS with PsA.

### 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

### 5.1.1. Hypotheses

The primary hypothesis is that among subjects who achieve ACR30 response at Week 18, those who remain on tofacitinib will have a lower rate of disease flare up to Week 44/EoS compared to those on placebo.

From statistical perspective, the primary null hypothesis is

$$H_0 : p_t - p_c = 0,$$

and the primary alternative hypothesis is

$$H_0 : p_t - p_c \neq 0 ,$$

where $p$ refers to the proportion of disease flare by Week 44/End of Study (Week 26 of the double-blind phase) for polyarticular course JIA subjects, the subscript c refers to the control group (placebo) and the subscript t refers to the treatment group.

Tofacitinib will be considered superior to placebo with respect to occurrence of disease flare by Week 44/End of Study (EoS) (Week 26 of the double-blind phase) for polyarticular course JIA subjects if the test for difference in the occurrence rate results in a p-value (two-sided) less than 0.05.

### 5.1.2. Statistical Decision Rules

In order to preserve type I error, each endpoint will be assessed sequentially using gate-keeping or step-down approach where statistical significance can be claimed for the second endpoint only if the first endpoint in the sequence meets the requirements for significance.

CCI

Analyses other than primary and key secondary analyses will not be strictly controlled for Type I error.

### 5.2. General Methods

In addition to the statistical analyses given below, all efficacy endpoints as described in Section 3 will be summarized descriptively. In general, number and percent will be presented for binary variables; number, mean, median, standard deviation, quartiles, minimum, and maximum will be presented for continuous variables; estimates of median event-free time and survival probabilities by Kaplan-Meier method will be presented for time-to-event endpoints.

### 5.2.1. Analyses for Binary Data

### 5.2.1.1. Normal Approximation Approach

Binary endpoints will be analyzed using the normal approximation approach for the binomial populations for double-blind polyarticular course JIA analysis set (DBJAS).

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

$$Z = \frac{\hat{p}_t - \hat{p}_c}{\sqrt{\dfrac{\hat{p}_t(1-\hat{p}_t)}{n_t} + \dfrac{\hat{p}_c(1-\hat{p}_c)}{n_c}}}$$

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

Two-sided 95% confidence intervals are formed by:

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

CCI

CCI

## 5.2.2. Analyses for Continuous Data

For the continuous secondary endpoints, a mixed-effect model with repeated measures (MMRM) will be applied. CCI
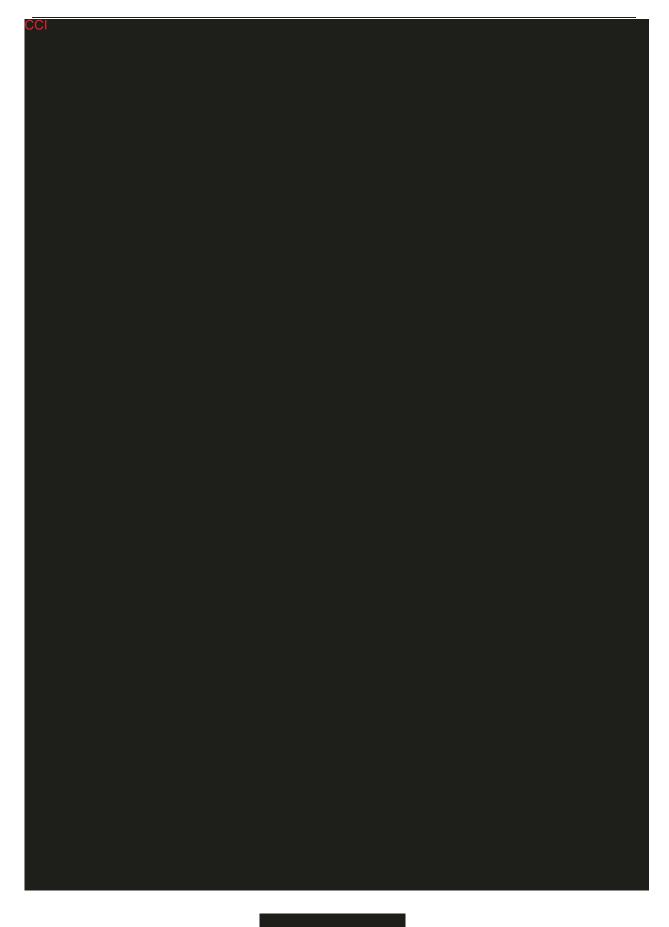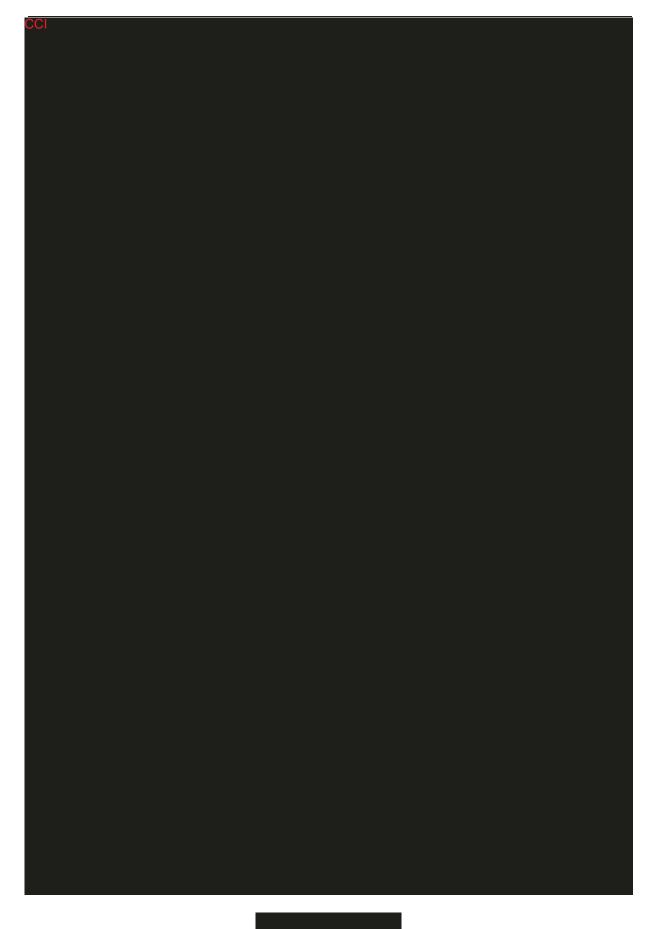
CCI

CCI

CCI

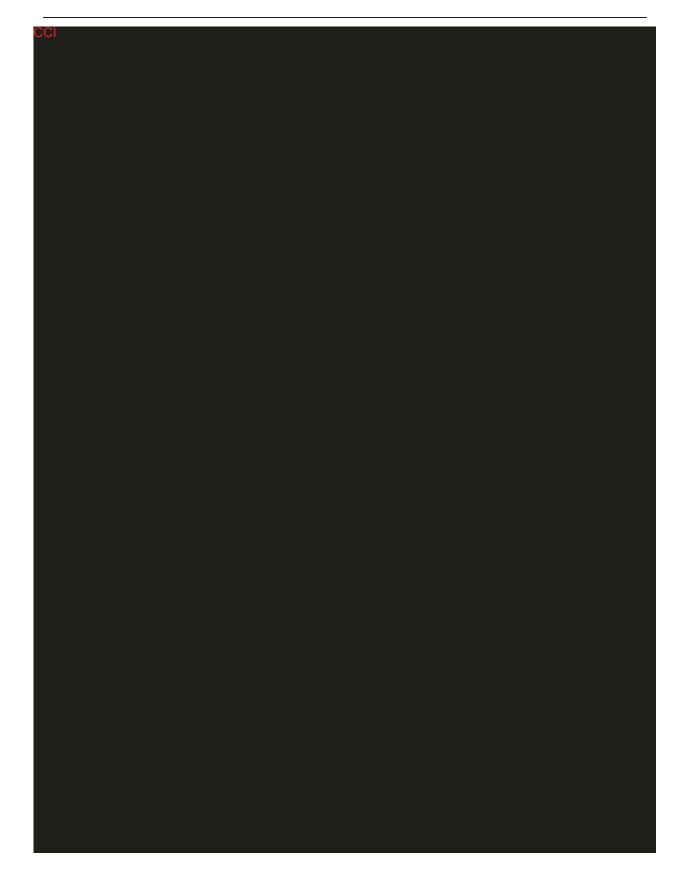### 5.2.3. Analyses for Time to Event Data

The Kaplan-Meier plot will be generated for the secondary endpoint of time to flare. The log rank test will be used to compare the treatment groups.

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

## 6.3. Other Endpoint(s)

### 6.3.1. Analysis of PK Endpoints

Please see details in the protocol and PMAP (or population PK modeling plan).

### 6.3.2. Analysis of Exploratory Endpoints

Exploratory or pooled analyses, if conducted utilizing the biobanked genomic and/or biomarker samples from this study, will be documented in a separate analysis plan.

## 6.4. Subset Analyses

The primary endpoint, key secondary endpoints and some secondary endpoints (occurrence of disease flare, achieving ACR 30/50/70 and JIA ACR inactive disease at each scheduled visit in double-blind phase; time to disease flare in double-blind phase) and open-label run-in baseline demographic characteristics will be summarized by JIA category, open-label run-in baseline C-Reactive Protein (normal and above normal), geographical region (North America [US and Canada], South and Central America [Brazil, Argentina, Mexico], European Union [Poland, Belgium, Great Britain, Spain], All Other [Ukraine, Turkey, Russia, Australia and Israel]), baseline body weight (<40 kg, ≥40 kg), and age (2 to <6 years, 6 to <12 years and 12 to <18 years) by treatment and visit. Inferential statistics and forest plot for treatment comparison by the aforementioned subgroups will be performed at week 26 of the double-blind phase for the efficacy endpoints if appropriate. For time to disease flare, Kaplan-Meier analysis will be replicated for each JIA category, open-label run-in baseline CRP and age group, separately.

As said in Section 6.2.2 to 6.2.4, for ERA subjects and PsA subjects, only descriptive statistics will be reported by treatment and visit.

## 6.5. Baseline and Other Summaries and Analyses

None.

## 6.6. Safety Summaries and Analyses

Safety analysis will be performed for polyarticular course JIA, ERA and PsA subjects combined together. Safety data will be reported separately for the open-label run-in phase using OLFAS and the double-blind phase using DBSAS. In addition, AE will be reported using the entire exposure period (both open-label run-in phase and double-blind phase) while the subjects are exposed to tofacitinib.

For occurrence of active uveitis (according to SUN criteria) at each scheduled visit in the open-label run-in and double-blind phase, descriptive statistics will be reported. Visit window in Appendix 9.3 will be used.

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

- Safety laboratory tests will be summarized according to Pfizer standards.

- Special attention will be given to the following safety endpoints: serious infections, cytopenias, malignancies, cardiovascular diseases, gastrointestinal perforations and validated assessments of growth and pubertal development.

### 6.6.1. Adverse Events

Adverse events will be summarized according to Pfizer data standards for each phase and for the entire study period while the subjects are exposed to tofacitinib.  For the AE reported over entire study period, subjects randomized to the placebo group will only have their events and exposure during the open-label run-in phase counted, and there will be no comparisons performed.

For AE reporting for each phase, AEs will not be double counted across phases.  Counting of AEs will be based on start date of AE.  If the start date of an AE is in the open label phase, the end date of the AE in the double blind phase and severity of AE remained the same or became lower in both phases, then the AE will be counted in open lable phase, not in the double blind phase.  However, if the same AE started in the open label phase, and get worse in severity in the double blind phase, then the AE will be counted in both phases.  In all these analyses attention will be restricted to assessments that occurred no more than 28 calendar days after the last dose of study drug.

AEs of special interest in double-blind phase and over the entire study period while the subjects are exposed to tofacitinib will be analyzed using incidence rates (IR), including death, serious infections, opportunistic infections excluding TB, tuberculosis, herpes zoster, malignancy excluding NMSC, NMSC (non-melanoma skin cancer), lymphoma, MACE (Major Adverse Cardiovascular Events), gastrointestinal perforations, and Interstitial Lung Disease (ILD). Adverse events of macrophage activation syndrome (MAS) will be analyzed using IR. The MAS, Deep vein thrombosis (DVT), and Pulmonary embolism (PE) will be listed.

CCI

CCI

## 7. INTERIM ANALYSES

No interim analysis is planned, except for the safety review by DSMB.

Final analyses will be conducted after requirements for final release of the randomization codes have been met, and the official database is released.

An independent Data Safety Monitoring Board (DSMB), a group of experts external to Pfizer, will review accumulating safety data from this study on an ongoing basis within the context of the Phase 3 pediatric program as well as adult program. Based on these reviews, the DSMB will have the capacity to make recommendations to Pfizer that might impact the future conduct of the trial. The recommendations made by the DSMB to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. The DSMB will have access to unblinded treatment information from concurrently ongoing double-blind studies during the clinical trial. The management and process of this committee will be in accordance with Pfizer's Standard Operating Procedures and will be documented in the DSMB Charter. The DSMB members will all be individuals who are independent of Pfizer. A DSMB Liaison will be appointed; this is an individual who represents Pfizer to coordinate communications and facilitates access to Pfizer's resources, but is not involved in the study design, study management, site management, data accrual, or study analysis. Records of DSMB meetings, interactions with Pfizer contacts, assessments and recommendations and materials reviewed will be maintained and kept proprietary and confidential by the DSMB. Further information about the DSMB can be found in the DSMB Charter, which outlines the operating procedures of the committee, including specific description of the scope of their responsibilities, including a plan where communication timelines are defined.

## 8. REFERENCES

1.  Chan ISF, Zhang Z. (1999). Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics*, 55:1201–1209.

2.  J. Kalbeisch and R. Prentic. *The Statistical Analysis of Failure Time Data*. Wiley, New York, 1980.

3.  Landgraf JM,. Abetz L Ware JE.. In:Child-Health Questionnaire(CHQ): a user's manual. Boston, MA: Health Institute, New England Medical Center; 1996: 34-52, 90-95.

4.  R. Little, J. Wang, X. Sun, T. Hong, E. Suh, M. Lee, T. Sarich, L. Oppenheimer, A. Plotnikov, J. Wittes, N. Cook-Bruns, P. Burton, M. Gibson, and S. Mohanty. The treatment of missing data in a large cardiovascular clinical outcomes study. *Clinical Trials*, 13(3):344-351, 2016.

5.  CCI

6.  Diggle P. J., Liang K.-Y., and Zeger S. L. *Analysis of Longitudinal Data*. Oxford: Clarendon Press, 1994.

7.  McCullagh P., and Nelder J. A. *Generalized Linear Models*. 2nd ed. London: Chapman & Hall, 1989.

8.  CCI

9.  Singh G, Athreya BH, Fries JF, et al. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994; 37(12):1761–9

# 9. APPENDICES

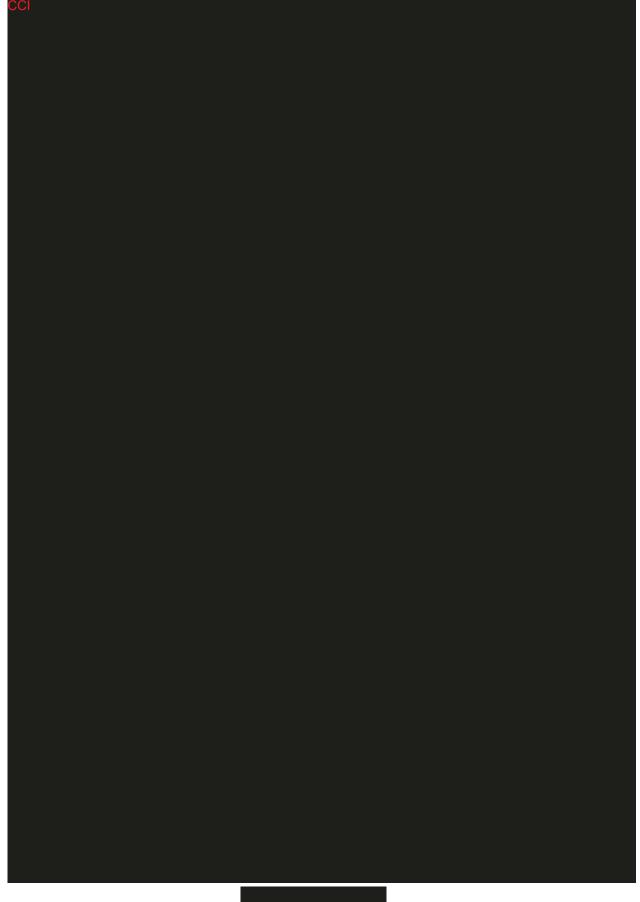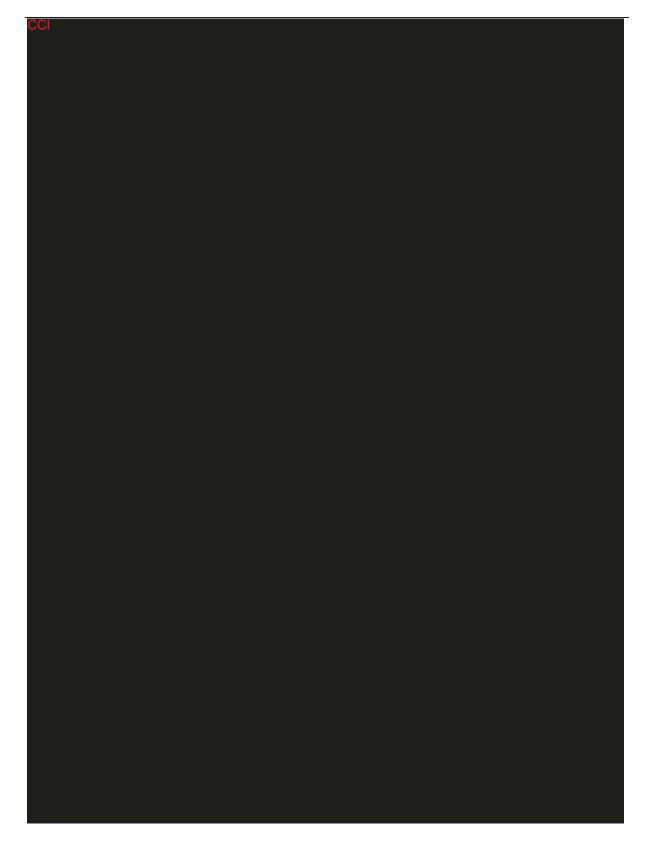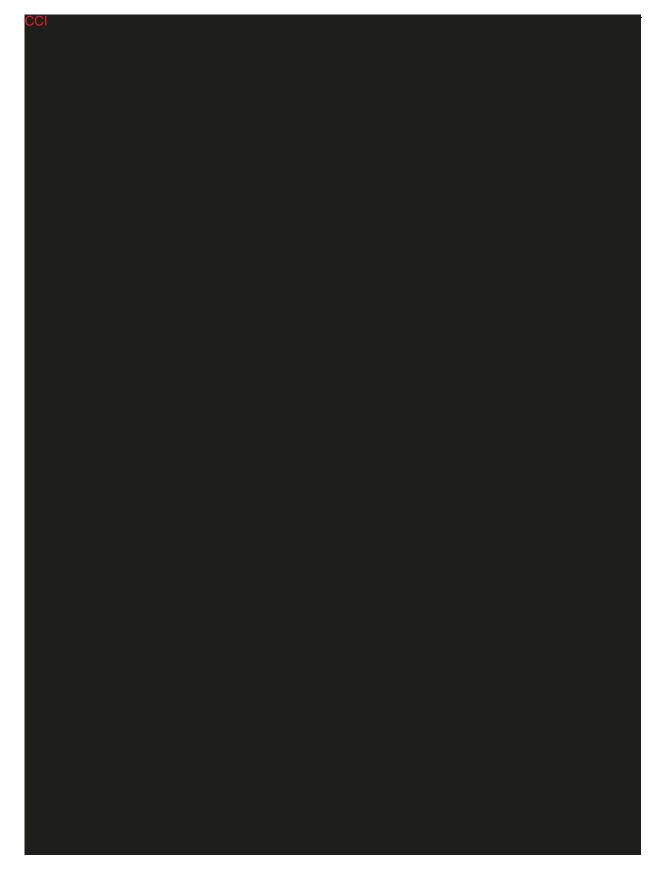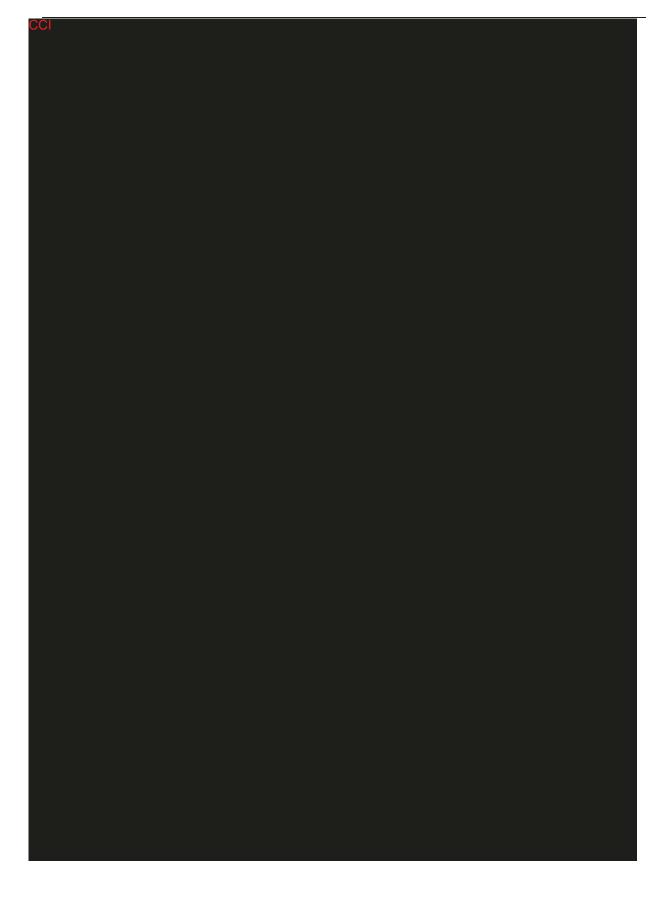## 9.1. SUMMARY OF EFFICACY ANALYSES

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

s

.

al

,

CCI

CCI

CCI
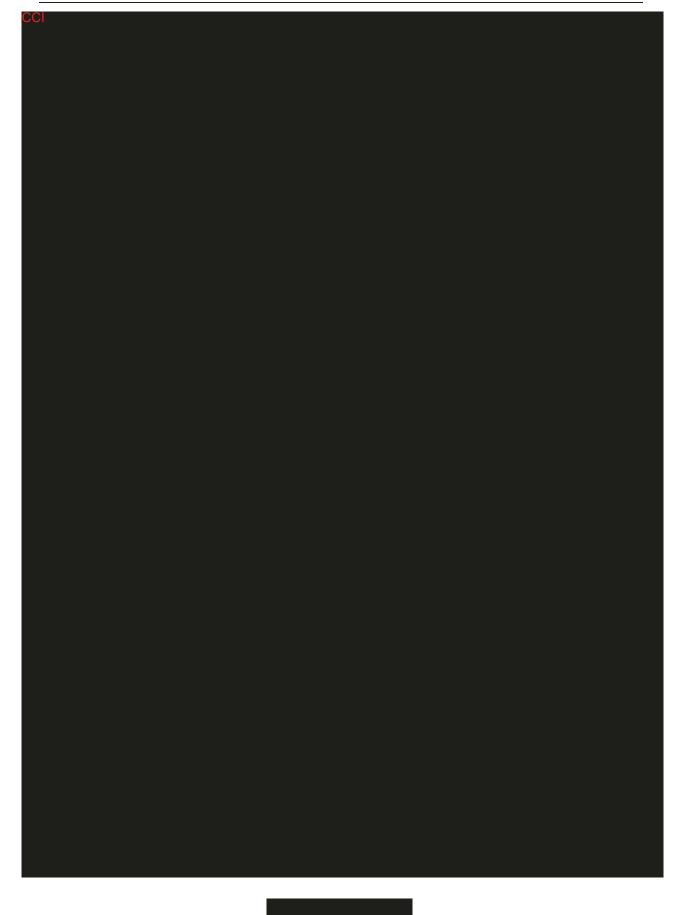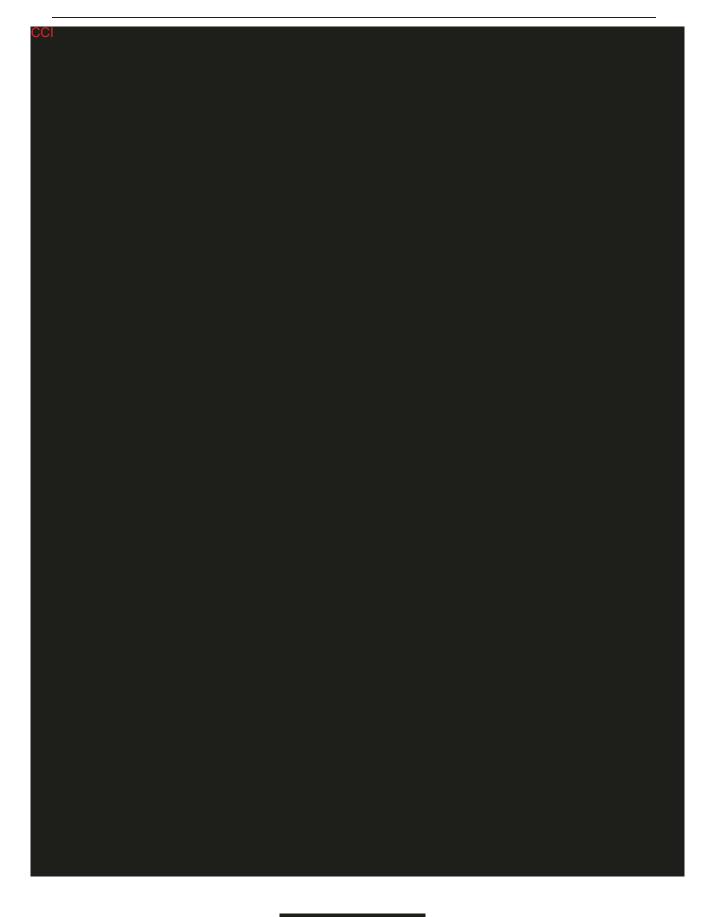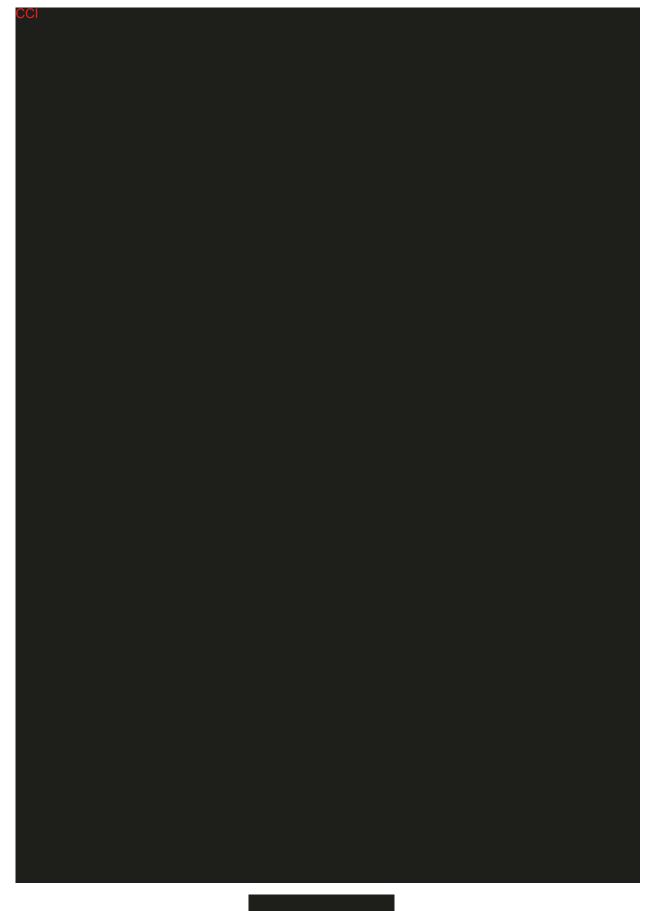
CCI

CCI

CCI

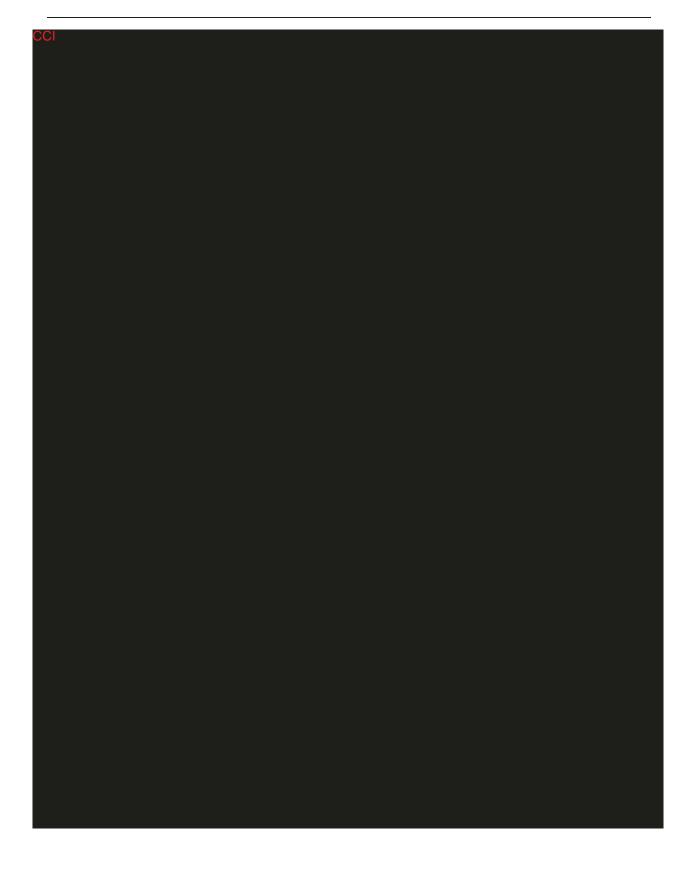CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

## 9.4. DEFINITION OF PROTOCOL DEVIATIONS THAT RELATE TO STATISTICAL ANALYSES/POPULATIONS

The following describes any protocol deviations that relate to the statistical analyses or populations:

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 below.

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

Deviations Assessed Prior to Randomization:

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

Deviations Assessed Post-Randomization:

Only protocol deviations that are thought to affect the efficacy of study drug 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 affected in the cases of these specific classes of protocol deviations assessed post randomization:

- Subjects who receive excluded concomitant medications;

- Subjects who interrupt therapy for longer than allowed;

- Subjects who were randomized but took incorrect treatment;

- CCI

- Subjects whose background medications are changed in violation of protocol, including subjects who use rescue medication in violation of protocol.

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

CCI

CCI

CCI

CCI

CCI