STATISTICAL ANALYSIS PLAN

Amendment 5

Study: C87075

Product: Certolizumab pegol

A Non-Interventional Long-term Post-Marketing Registry of Patients Treated with Certolizumab pegol (Cimzia®) for Crohn's Disease

SAP/Amendment Number	Date
Final SAP	03Aug2009
SAP Amendment 1	25Sep2014
SAP Amendment 2	30Jun2016
SAP Amendment 3	26Apr2019
SAP Amendment 4	26Mar2020
SAP Amendment 5	01Sep2020

Confidentiality Statement

Confidential

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LIST OF ABBREVIATIONS

AE	Adverse Event
Anti-TNF	Anti-tumor Necrosis Factor
CD	Crohn's Disease
DAG	Directed Acyclic Graph
eCRF	Electronic Case Report Form
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
HBI	Harvey-Bradshaw Index
HLGT	High-Level Group Term
HLT	High-Level Term
ICON	Informed Consent
KS	Kolmogorov-Smirnov
MH	Mantel-Haenszel
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious Adverse Event
SOC	System Organ Class
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under UCB, Inc. Protocol C87075.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol amendment 5 dated 08Sep2017 and annotated eCRF. Any further changes to the protocol or eCRF may necessitate updates to the SAP.

Following the Food and Drug Administration (FDA) approval of certolizumab pegol (Cimzia®) for Crohn's disease (CD), UCB has committed to collect additional long-term, post-marketing safety data on patients exposed to the product in a real-life setting. To achieve this goal, a pharmacoepidemiologic study entitled SECURE was designed. The study began in January 2009 with the goal of collecting prospective data on 2000 patients prescribed Cimzia and a 2000 patient comparator group prescribed other treatments (including biologics) for CD. At study start, this study anticipated to continue monitoring all enrolled patients for approximately 10 years after enrollment.

The protocol has been amended (Amendment 5) to close enrollment and revise the patient follow-up to 8 years following agreement with the FDA. The decision was based on the results of a 2017 interim analysis that indicated no new safety issues had emerged from the currently known safety profile of Cimzia. Patients who already enrolled in C87075 at the time of stopping enrollment will continue to be followed.

As agreed with FDA in Type C written responses dated 31 July 2020, the SECURE registry study can now be closed. Within the response letter, FDA provided comments and recommendations on the SECURE SAP Amendment 4. The SAP Amendment 5 is updated with consideration to the Agency's feedback.

2 PROTOCOL SUMMARY

2.1 Study objective(s)

2.1.1 Primary objective(s)

The objective of this registry is to measure the safety outcomes among Cimzia patients compared to those that occur while on a different CD treatment regimen.

All SAEs and AEs of interest will be collected and summarized (see Section 8.2.3). All these events represent serious risks known to the class of tumor necrosis factor (TNF) blocking agents. During the clinical development program for CD and rheumatoid arthritis consisting of over 6,000 patients, reported events were consistent with the class.

All analyses are descriptive. No formal hypothesis testing will be conducted.

2.2 Study variable(s)

2.2.1 Primary variable(s)

The primary outcome of this observational study is malignancy (malignant tumors and malignant or unspecified tumors). Additionally, the following safety events will be presented using incidence and event rates, and time-to-event statistics:

- Serious infections
- Opportunistic infections
- Serious cardiovascular events (also called major adverse cardiac events, or MACE)
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions

Although not officially AEs of interest, the following events will also be summarized as described in the AEs of Interest – Cimzia Program 2018-06-18 guidance document.

- Hepatic Events
- Hypersensitivity reactions and anaphylactic reactions

Separate from the AEs of interest document, malignant lymphomas, non-melanoma skin cancer, and autoimmune disorders will also be summarized.

2.2.2 Secondary variable(s)

Secondary endpoints include the following:

- Changes in HBI rating scale from baseline to each post-Baseline assessment
- Changes in physician's assessment of disease from baseline to each post-Baseline assessment
- Changes in the patient's disease assessment of disease from Baseline to each post-Baseline assessment

2.3 Study design and conduct

Following protocol amendment 5, this long-term observational study in the USA stopped enrollment with approximately 3045 patients enrolled since study start. From the original study design, approximately half of enrolled patients will be receiving Cimzia for ≤12 months or about to receive Cimzia at the time of enrollment. The study will be conducted in all regions in the USA at approximately 280 enrolling investigative sites (community based and academic practice).

Recruitment of Cimzia-treated and comparator patients will be monitored and controlled as needed, and to ensure balanced enrollment over time between both cohorts, recruitment will be matched for disease severity (mild/moderate/severe), age categories and gender.

Patients will be followed for approximately 8 years (reduced from 10 years in protocol amendment 5) during normal physician visits and through direct patient follow-up in the form of web, mail surveys and/or phone follow-up calls. All patients will receive and use their medications according to their normal course of medical treatment per physician clinical judgment.

Follow-up data on the patients will be reported by physicians approximately every six months following enrollment while direct patient follow-up data will be collected quarterly via internet, mail or telephone.

Quarterly progress reports will be generated and sent to the FDA during the patient enrollment period. Subsequently, more detailed yearly informal interim analyses may be conducted to provide updates for regularly scheduled steering committee meetings or to the FDA on the information collected in this study. As agreed with FDA, the study is ending on 28 August 2020, and a single final study report will be submitted in 2021.

2.3.1 Patient Inclusion/Exclusion Criteria

Patients who meet all of the following criteria will be eligible for inclusion into the SECURE Registry:

- Patient (or his/her legally acceptable representative) is able to provide written informed consent to permit collection of data.
- Patient must be 18 years of age or older.
- Patient must have medically documented CD.
- The decision to prescribe Cimzia or other medications has been made by the physician independently of the decision to include the patient in the study.
- Patients participating in randomized, blinded clinical trials for CD or other conditions are not eligible for inclusion into the SECURE registry. Involvement in other registries, where patients follow routine clinical practice, is permitted, however.
- The rules for handling erroneous patient entries are laid out in a separate Analysis Data Reviewers Guide.

Cimzia-treated patients

For a patient to qualify as being treated with Cimzia, they must meet one of the following criteria:

- Patient is receiving treatment with Cimzia for the first time. Patient must receive Cimzia treatment within 2 months of enrollment into the registry.
- Patient is currently receiving treatment with Cimzia for ≤12 months. Patients must also receive a Cimzia dose within 2 months following enrollment into the registry.

Comparator patients

Patients enrolled in the comparator group are eligible to participate in the registry if one of the following criteria is fulfilled:

- Patient is switching CD treatments or beginning CD treatment for the first time. Previous Cimzia treatment is prohibited in the comparator group. Patient must receive new CD treatment within 2 months of enrollment into the registry.

- Patient is currently receiving other biologic treatment (excluding Cimzia) for ≤12 months. Patient must receive other biologic treatment within 2 months following enrollment into the registry.
- Patient is currently receiving immunosuppressant therapy for ≤12 months. Patient must receive immunosuppressant therapy within 2 months following enrollment into the registry.
- Patient is currently receiving systemic steroid therapy for ≤12 months. Patient must receive systemic steroid therapy within 2 months following enrollment into the registry.

2.3.2 Schedule of Assessments

No visits are required as part of this protocol. All visits will be scheduled and conducted per standard of care.

Enrolling physicians will complete the baseline data for each patient after enrollment into the study. Although patient care will follow the physician's clinical judgment, it is anticipated that the enrolling physician will see and, therefore, report follow-up data on the patients approximately every 6 months after enrollment (months 6, 12, 18,…). Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the physician every 12 months at a minimum per usual practice. All data, as described in the protocol are to be collected as available during the telephone contacts.

In an effort to minimize missing data and unreported events patients will directly report data in parallel to the enrolling physician reported data. Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system, by mail or phone as requested by the patient. If a patient does not provide the information via the web, mail or phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review. If 8 consecutive quarterly patient surveys have not been at least partially completed, further attempts at patient contact are not required and the patient is considered lost to follow-up at their last known date.

	Study Entry (Baseline)	Physician-Reported Follow-up[b]	Direct Patient Follow-up
	ENROLLMENT	**EVERY 6 MONTHS**	**EVERY 3 MONTHS**
Written informed consent	X		
Assessment of inclusion/exclusion criteria	X		
Demography	X		
Crohn's disease history	X		
Medical and surgical history	X		
Family history	X		
Reason for initiating Cimzia or other medication	X		
Planned Cimzia or other medication treatment period	X	X	
CD treatment medication changes and reason		X	X
Concomitant medications	X	X	X
All SAEs and AEs of interest since time of last completed follow-up[a]		X	
Major changes in health status since last completed follow-up			X
Physician's assessment of disease severity	X	X	
Physician's HBI[c] (see APPENDIX A)	X	X[e]	
Patient's Modified HBI[d]	X		X
Patient's assessment of disease severity	X		X
Reasons for discontinuation from registry (early termination or end of Year 8)		X	

AE=adverse event; CD=Crohn's disease; HBI=Harvey-Bradshaw Index; SAE=serious adverse event

[a]All SAEs and AEs of interest are to be reported through the registry.

[b] Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the physician every 12 months at a minimum per usual practice. No study visits are required as part of this protocol; treating physicians are to manage patients based on clinical judgment and standard of care.

[c.] This may also be completed by qualified site personnel as designated by the physician.

[d] The Modified HBI does not include the abdominal mass question.

[e] The Modified HBI is completed during the physician telephone contact instead of the full HBI.

2.4 Determination of sample size

Assuming an 8% annual drop-out rate (1) (withdrawal, lost-to-follow-up or death), approximately 25,000 (12,500 per arm) total patient years (p-y) post-enrollment is expected in this registry. With a two-sided significance level of 0.05, the study is designed to have at least 80% power to detect incidence rate ratios (calculated based on observed rates in the control group) of 1.5 for serious infections, 3.3 for lymphoma, and 1.56 for solid malignancies after 10 years. Event rate estimates for this study were calculated using corresponding event rates observed in a CD anti-TNFα registry study control group (1, 2).

Prior to Amendment 5, the study planned for a total of 4000 patients (2000 patients per arm). A total of 3045 patients (1371 in the Cimzia Cohort and 1674 in the Comparison Cohort) were enrolled as of Mar 2017. The total duration of participation (treatment and follow-up) of 8 years is planned for each patient. At the time of the final analysis, 3076 patients were enrolled in the study.

Prior to Amendment 5, the study planned for a total of 4000 patients (2000 patients per arm). A total of 3045 patients (1371 in the Cimzia Cohort and 1674 in the Comparison Cohort) were enrolled as of Mar 2017. The total duration of participation (treatment and follow-up) of 8 years is planned for each patient. At the time of the final analysis, 3076 patients were enrolled in the study.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Descriptive statistics will be displayed to provide an overview of the study results. Categorical variables will be summarized by using the number of patients and percentages. The denominator for percentages will be based on the number of patients appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. Continuous variables will be summarized by using descriptive statistics (n, mean, standard deviation [SD], median, 25th and 75th percentile, and minimum and maximum). All tests will be two-tailed with a Type I error of α=0.05. No adjustments for multiple comparisons will be made as all statistical testing will be considered descriptive in nature. All confidence intervals presented will be two-sided. Observed data will be presented to the same number of decimal places as collected. Minimum and maximum will be presented to the same number. Mean, median, coefficient of variance (CV [%]), and any percentiles of interest to 1 extra decimal place and standard deviation to 2 extra decimal places. All of the derivations, summaries, and analyses will be performed by using SAS® Version 9.1.3 or higher. All tables and listings will use Courier New font size 9. Data listings will include all the data collected for all patients in the Enrolled Set (ES). Following FDA approval to close enrollment and reduce the follow-up from 10 years to 8 years, tables will only contain data up to 8 years. Data already collected past year 8 will be listed. A separate Analysis Data Reviewers guide provides guidance for the interpretation of the Analysis Data of C87075. In addition it describes the methods and rules used to reconcile data issues that could not be queried at the sites.

3.2 General study level definitions

Any reference to comparator medication is referring to the 3 medication classes in the eligibility criteria (Corticosteroids, Immunosuppressants or treatment with biologics other than Cimzia) only.

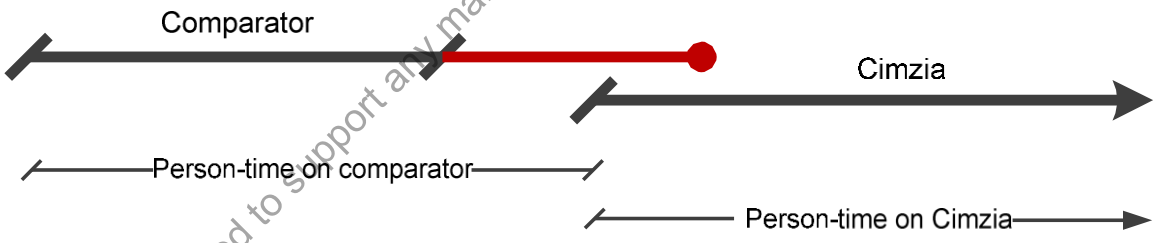
3.2.1 Exposure

Cancer progresses in several stages before reaching a detectable, malignant state. While this latency period may differ by cancer type, it is generally believed to occur over a long period of time (3). Thus, a treatment-related event may not be seen until years after the initial exposure. In contrast, acute events typically have very short latency periods; therefore, it is unlikely that a treatment-related event will occur after exposure to the product has ended. For the primary endpoint analysis, 2 different methods of person time calculations will be used, one for malignancy events (Section 3.2.1.1) and one for acute events (Section 3.2.1.2).

3.2.1.1 Person-time at risk calculations for malignancy

Due to the long latency of malignancy, gaps in exposure between treatments will be attributed to the most recent, previous treatment. Gaps in exposure before first known treatment will not be factored into person-time calculations for these events. Any patient exposed to Cimzia during the study will only contribute person-time to the Cimzia cohort from that point onward (Figure 1). As an example, if a malignancy should occur any time after Cimzia exposure (including when Cimzia was known to be used prior to enrollment), it will be attributed to Cimzia. If a malignancy occurred in a patient prior to Cimzia exposure or in a patient with no Cimzia exposure, then it would be attributed to comparator. Thus, a patient may have exposure to multiple comparator drugs, but any malignancies diagnosed after treatment with Cimzia would be systematically attributed to Cimzia, even after ending or switching from Cimzia.

Figure 1: Example person-time at risk for malignancy events



Exposure person-time at risk will be calculated for each CD treatment using the following equation:

$$\text{Last Date} - \text{First Date} + 1$$

where all person-time is contributed to Cimzia after first Cimzia dose is administered.

First date is defined as the latest enrollment date or first CD treatment date after enrollment (whichever is later) or first Cimzia dose date if switching from a comparator treatment after enrollment. Last date is defined as the earliest of the following:

- Date of safety event of interest (for incidence rate calculations only)

- Date of discontinuation, withdrawal, or data cutoff

See Section 11.1, appendix 1 for more examples of treatment allocation scenarios for malignancies.

3.2.1.2 Person-time at risk calculations for acute events

Exposure person-time at risk will be calculated for each CD treatment using the following equation:

$$\text{Last Date} - \text{First Date} + 1$$

First date is defined as the latest enrollment date or first CD treatment date after enrollment (whichever is later) or the first dose of new treatment if switching treatments. Last date is defined as the earliest of the following:

- Date of safety event of interest (for incidence rate calculations only)
- Last dose date + treatment class-specific half-life exposure for product
- Date of discontinuation, withdrawal, or data cutoff

Any gaps in exposure, as illustrated in the figure below, will be included in the gap treatment group person-time at risk calculations for acute events. Any overlap in treatment groups will be included in the overlap group person-time at risk calculations for acute events.

Figure 2: Example person-time at risk for acute events

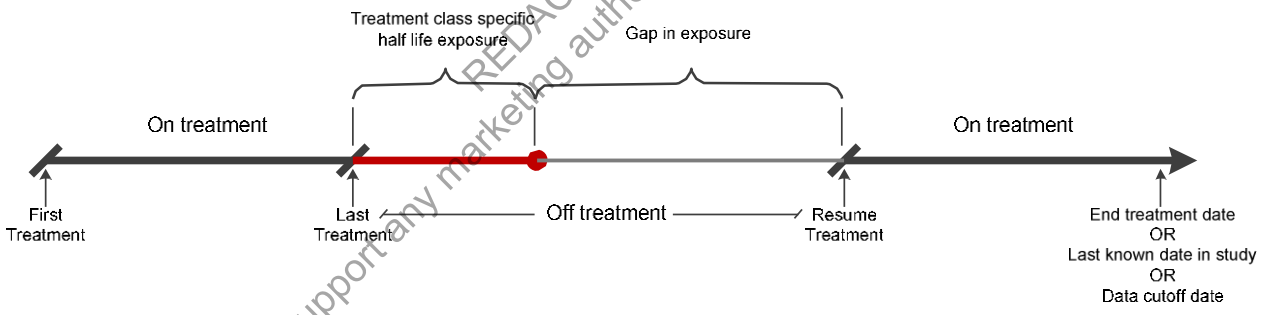


Figure 2 presents an example of a patient's exposure history. For this example, exposure person-time at risk would be calculated as follows:

Exposure person-time = (Last treatment date + Treatment class-specific half-life) – First treatment date + 1) + (earliest of End treatment date + treatment class-specific half-life exposure, last date in study, data cutoff date) – Resume treatment date + 1).

See Section 11.1, appendix 1 for more examples of treatment allocation scenarios for acute events.

3.2.1.3 Determination of Event Rate Numerator

The number of events will be determined for Cimzia and for all other CD treatments considered comparator treatments based on the date of the last dose received before event onset and treatment class-specific half-life exposure of the medication. The exposure half-lives used for rate calculations for each treatment class are as follows:

- Corticosteroids: 7 days
- Immunosuppressants: 28 days
- Biologic agents (including Cimzia): 70 days

3.2.2 Physician reported Harvey-Bradshaw Index

The physician reported Harvey-Bradshaw Index (HBI) is composed of 5 parameters:

1. General well-being (0=Very well, 1=Slightly below Par, 2=Poor, 3=Very poor, 4=Terrible)
2. Abdominal pain (0=None, 1=Mild, 2=Moderate, 3=Severe)
3. Number of liquid stools per day
4. Abdominal mass (0=None, 1=Dubious, 2=Definite, 3=Definite and tender)
5. Complications (1 per item: Arthralgia, Uveitis, Erythema nodosum, Aphthous ulcers, Pyoderma gangrenosum, Anal fissure, New fistula, and Abscess)

Note for #3 that if a patient is using a colostomy bag, the number of times per day the bag is emptied is counted instead.

The use of eCRFs in this registry will allow the total score to be computed and, therefore, not require the investigators to record the total HBI score. If any of the first 4 parameters are missing, then the total HBI score will be set to missing. Otherwise, the total will be the sum of available data.

In cases where HBI is collected multiple times in the same visit a worst case approach will be taken.

HBI response, determined based on physician reported HBI total scores, is defined as a drop of at least 3 points from baseline HBI total score.

HBI remission, determined based on physician reported HBI total scores, is defined as an absolute score of 4 points or less.

3.2.3 Patient reported Harvey-Bradshaw Index

The patient reported Harvey-Bradshaw Index (HBI) is composed of 4 parameters:

1. General well-being (0=Very well, 1=Slightly below Par, 2=Poor, 3=Very poor, 4=Terrible)
2. Abdominal pain (0=None, 1=Mild, 2=Moderate, 3=Severe)
3. Number of liquid stools per day
4. Complications [1 per item: Joint pain (Arthralgia), Eye inflammation (Uveitis), Red nodules on skin (Erythema Nodosum), Canker sores (Aphthous ulcers), Skin wound/ulcers (Pyoderma Gangrenosum), Tear in skin of anal area (Anal fissure), Fluid or pus drainage from anal area (New fistula), and Abscess

Note for #3 that if a patient is using a colostomy bag, the number of times per day the bag is emptied is counted instead.

The use of eCRFs in this registry will allow the total score to be computed and, therefore, not

require the patients to compute the total HBI score. If any of the first 3 parameters are missing, then the total HBI score will be set to missing. Otherwise, the total will be the sum of available data.

In cases where HBI is collected multiple times in the same visit a worst case approach will be taken.

HBI response, determined based on patient reported HBI total scores, is defined as a drop of at least 3 points from baseline HBI total score.

HBI remission, determined based on patient reported HBI total scores, is defined as an absolute score of 4 points or less.

HBI response, determined based on patient reported HBI total scores, is defined as a drop of at least 3 points from baseline HBI total score.

HBI remission, determined based on patient reported HBI total scores, is defined as an absolute score of 4 points or less.

3.3 Definition of Baseline values

In general Baseline values will be determined from the study entry visit (enrollment visit, screening visit, and Baseline visit used interchangeably).

3.4 Protocol deviations

An important deviation is defined as a deviation from the protocol which could potentially have a meaningful impact on the primary outcome of this study, and are defined as follows:

1. Patient did not sign informed consent.
2. Patient did not have medically documented CD.
3. Patient under 18 years (from protocol amendment 3 onwards)
4. Patient participates in a randomized & blinded clinical trial.
5. Cimzia Cohort patient does not receive Cimzia within 2 months after enrollment (Window of 7 days is allowed).
6. Comparison Cohort patient receives Cimzia prior to enrollment.
7. Comparison Cohort patient does not receive comparator treatment within 2 months after enrollment (Window of 7 days is allowed).
8. Patient is enrolled at more than one site.
9. Any other deviation that the study team determines to be an important deviation over the course of the study.

3.5 Analysis sets

3.5.1 Enrolled Set

All Analyses will be performed on the Enrolled Set, defined as all patients enrolled and with an informed consent. Subjects that were enrolled at more than one site were excluded from the Enrolled Set (See Analysis Data Reviewers Guide for details).

3.5.2 Full Analysis Set

All analyses will be conducted on the Full Analysis Set, defined as all patients enrolled in this non-interventional study that meet eligibility requirements. All data captured from enrollment to last completed follow-up (physician or direct-to-patient) will be included.

3.5.3 Propensity Score Set

A subset of the Enrolled Set, the Propensity Score Set will be created using the rules in Section 8.1.2 in order to create a population with treatment cohorts with similar Baseline variables.

3.6 Treatment assignment and treatment groups

Given that patients will be followed for 8 years, it is anticipated that patients will switch CD medications while enrolled in the registry. Therefore, a patient's treatment at registry enrollment will most likely not reflect their exposure throughout the study. Three comparisons may be used to reflect these treatment changes over time and provide context for events reported to the registry. See Section 8.1.4 for details.

Treatment start is the recording period (ie, the informed consent date). Only study emergent adverse events will be reported. Study emergent begins at the informed consent through the end of the study.

Treatment by enrollment cohort will consist of two groups:

- Cimzia
- Comparator

  where comparator includes:
  - Corticosteroids
  - Immunosuppressants
  - Other biologics (e.g. anti-TNFs) other than Cimzia

Enrollment cohort is recorded and will be assumed regardless of the presence of prior or imputed CD medication referring to the other treatment group. These are the default treatment groups.

Some summaries will be repeated by actual treatment at Baseline to examine differences between treatment by enrollment cohort. Actual treatment at Baseline will be summarized in three groups:

- Cimzia at BL
- No Cimzia at BL
- Gap (absence of Cimzia and comparator)

Actual treatment will be used for adverse event tables unless specified otherwise. If a patient received Cimzia up to 70 days prior to baseline (half-life of CZP), the patient is a member of the treatment group "Cimzia at BL". For the calculation of the Hazard Ratio, the group 'Cimzia at BL' is compared against the combined group "No Cimzia at BL" and "Gap".

For malignancies, person-time and events will be categorized into 2 groups:

- Cimzia
- Comparator

where a patient is systematically attributed to Cimzia from their first dose of Cimzia until the end of the study, even after ending or switching from Cimzia.

For acute events, person-time and events will be categorized into 5 groups:

- Cimzia
- Comparator
- Overlap (Cimzia and comparator)
- Gap (absence of Cimzia and comparator)
- Any Cimzia (Cimzia and Overlap)

Example treatment allocations for malignancies and acute events are in Section 11.1, appendix 1.

3.7 Coding dictionaries

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0.

Medications will be coded using the most recent World Health Organization Drug Reference List (WHODD) Version (MAR/2018).

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Conventional multiple regression analysis and propensity score analysis will include (but are not limited to) the following Baseline characteristics in the initial run of the model. Characteristics that are continuous will remain as such. Categorical variables will use the values in parentheses:

- Age
- Gender (Male, Female)
- Race (American Indian/Alaskan native, Asian, Black, Native Hawaiian/Pacific Islander, White, Other/Mixed)
- Smoking status (Never, Current, Former)
- Other biologic treatment use in the year prior to Baseline (Yes, No)
- Immunosuppressant use in the year prior to Baseline (Yes, No)
- Corticosteroid use in the year prior to Baseline (Yes, No)
- Disease extent (Ileum, Colon, Illeocolon, Upper GI, Ileum + upper GI, Colon + upper GI, Illeocolon + upper GI, Other)
- Diagnosed with fistulas (Yes, No)
- Duration of disease
- Physician assessment of disease severity (Remission, Mild-moderate, Moderate-severe, Severe)
- Number of Crohn's related hospitalizations in the year prior to Baseline
- Number of surgical resections in the year prior to Baseline
- Calendar year of enrollment

4.2 Handling of dropouts or missing data

For HBI scores, all missing values will remain as missing. No attempt will be made to impute missing values. Only observed values will be used in data analyses and presentations.

For both the physician and patient reported HBI, the use of eCRFs will allow the total score to be computed and therefore not require the recording of the total HBI score. However, for the physician reported HBI, if any of the first 4 parameters are missing, then the total HBI score will be set to missing. For the patient reported HBI, if any of the first 3 parameters are missing, then the total HBI score will be set to missing.

Missing safety data, in general, will not be imputed. However, if relationship to CD treatment is missing for an AE, the event will be categorized as having a reasonable possibility of being caused by the treatment for the summary of AEs by relationship.

Concomitant medications will be imputed as described below in accordance with the GSS global conventions document version 1.1.

The following rules are applied to impute partial start and stop dates for medications.

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of informed consent is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of informed consent is the same as the month and year of the start date, then use the date of informed consent.
- If only the year is specified, and the year of informed consent is not the same as the year of the start date, then use January 1 of the year of the start date.
- If only the year is specified, and the year of informed consent is the same as the year of the start date, then use the date of informed consent.
- If the start date is completely unknown, and the stop date is unknown or not prior to the date of informed consent, then use the date of informed consent.

Imputation of Partial Stop Dates

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date.

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant.

4.3 Interim analyses and data monitoring

Data captured for the study will be analyzed periodically, and at the end of the study. Supplemental data analyses may be performed throughout the study in addition to the periodic and final analyses.

Quarterly progress reports will be sent to the FDA during the patient recruitment period. Further, more detailed informal interim analyses will be conducted yearly during the follow-up portion of the study in order to provide the steering committee and FDA regular updates.

Supplemental data analyses may be performed throughout the study in addition to the periodic and final analyses.

4.4 Multiple comparisons/multiplicity

No adjustments for multiple comparisons will be made as all statistical testing will be considered descriptive in nature.

4.5 Examination of subgroups

The primary analysis for acute events will be stratified on incidence/prevalence use (yes/no).

The impact of data from the high accruing study site #849 on key outcomes will be assessed (Clinical site closed due to significant noncompliance; reported to FDA's Division of Scientific Investigations in letter dated 29 April 2020).

If sufficient power exists, further stratification based on duration of prevalent use (e.g., 1-5 months, 6+ months, etc.) may be performed. This is described in more detail in Section 8.1.5.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number and percentage of patients who enrolled and the number and percentage of patients who completed the study will be presented, together with the number and percentage of patients who withdrew from the study prematurely and a breakdown of the corresponding reasons for discontinuation will be produced by enrollment cohort and actual treatment at Baseline.

A Cox proportional hazards model utilizing Kaplan-Meier methods for time to discontinuation by year 1, year 2, … , year 8, will be performed by enrollment cohort and actual treatment at Baseline. Discontinuation status, discontinuation time (median, 25th and 75th quartiles and corresponding two-sided 95% confidence intervals), and a hazard ratio and exploratory p-value from a log-rank test at α=0.05 overall significance level will be included for the analysis of each year.

A Cox proportional hazards model utilizing Kaplan-Meier methods for time to discontinuation by year 1, year 2, … , year 8, will be performed by enrollment cohort and actual treatment at Baseline. Discontinuation status, discontinuation time (median, 25th and 75th quartiles and corresponding two-sided 95% confidence intervals), and a hazard ratio and exploratory p-value from a log-rank test at α=0.05 overall significance level will be included for the analysis of each year.

A summary of expected and actual patient retention by enrollment cohort and actual treatment at Baseline will include total patient-years and the number of patients followed for at least 1 year, at least 2 years, … , at least 8 years.

Time to discontinuation will be analyzed using two different censoring rules (A and B). According to censoring rule A, the time for patients in the Cimzia cohort will be censored when they switch to Comparator treatment and the time for patients in the Comparator cohort will be censored when they switch to Cimzia treatment. According to censoring rules B, time for all patients will be censored when they switch from one biologic treatment to another biologic treatment.

A table summarizing the number and percentage of patients enrolled at each site by enrollment cohort will be presented.

5.2 Protocol deviations

A table summarizing the number and percentage of patients who had any important protocol deviations by enrollment cohort will be presented. A listing of all patients who had any important protocol deviations during the study will be provided. See Section 3.4 for important protocol deviation definitions.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and other baseline characteristics

Demographic and baseline characteristics include age, gender, race, ethnicity, height, weight, socioeconomic status (employment status and annual income) and smoking status and will be summarized by enrollment cohort and actual treatment at Baseline. Age will be calculated based on the date of informed consent. If data are available, the demographic analysis will include a summary for physical examination findings and vital sign values.

Listings of demographics and baseline characteristics will be provided.

6.2 Medical history

The number and percentage of patients who had medical history conditions of interest will be summarized by enrollment cohort and actual treatment at Baseline. Family medical history for anyone in each patient's immediate family (defined as the patient's biological parents and siblings) who had medical history conditions of interest will be summarized by enrollment cohort and actual treatment at Baseline. In addition, the number and percentage of patients with CD history will be summarized by enrollment cohort and actual treatment at Baseline.

Listings of medical history, family medical history, CD history, and CD medication history will be provided.

6.3 Concomitant medications

Medications received concomitantly with Cimzia or any non-Cimzia CD medication, categorized at each analysis by drug class, and by the most recently available version of the WHO Drug preferred term, will be summarized for the Enrolled Set and using actual treatment based on the acute event rules. The number and percentage of patients using each medication will be displayed. The number and percentage of patients for each level of the covariates listed in Section 4.1 will be presented. Concomitant medications will be defined as medications that started on or after the date of enrollment.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable.

8 PRIMARY ANALYSES

The primary outcome of this observational study is malignancy (malignant tumors and malignant or unspecified tumors). However, in addition, the following list of AEs of interest will be

summarized using cumulative incidence (proportion) and incidence rate (events per 100 patient-years). These AEs are described in section 8.2.3 and defined in detail in the AE of interest – Cimzia Program 2018-01-05 document.

- Serious infections
- Opportunistic infections
- Serious cardiovascular events (also called major adverse cardiac events, or MACE)
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions

Although not officially AEs of interest, the following events will also be summarized as described in the AEs of Interest – Cimzia Program 2018-01-05 guidance document.

- Hepatic Events
- Hypersensitivity reactions and anaphylactic reactions

Separate from the AEs of interest document, malignant lymphomas, non-melanoma skin cancer, and autoimmune disorders will also be summarized.

8.1 Statistical analysis of the primary endpoints

The primary analysis of this study is descriptive and no formal hypothesis testing will be conducted. For the primary analysis, adverse event rates will be calculated by dividing the number of reported safety events by the patient-years at risk. Cimzia-specific rates will be calculated and compared to all other CD treatment rates.

Propensity scores will be used to assess the comparability of patients who are receiving Cimzia at baseline to those who are receiving another CD medication. Appropriate analytical methodologies will be used to investigate the effect of time varying confounders.

Time-to-event analyses for each Adverse Event of Interest will be conducted using Cox proportional hazard modeling and Kaplan-Meier curves.

Analyses of specific outcomes may be conducted if appropriate.

8.1.1 Malignancy events

The following analyses will be conducted to better elucidate treatment patterns and treatment attribution in malignancy events:

- The number of malignancy events and number of patients experiencing malignancy events will be tabulated by the number of CD treatments received during the study up to and including the onset date of malignancy. Also, the mean number of treatments

received per patient in the Cimzia and comparator groups (based on baseline assignment) will be calculated, as well as for both groups combined.

- The number of malignancy events and number of patients experiencing malignancy events will be tabulated by treatment patterns for biologics observed in the study. The name and order of the biologic treatment will be specified in the summary table (eg, "A-B" implies that patients received two different biologics, "A" followed by "B"; "C" implies that patients received biologic "C" throughout the study; "A-C-D" implies that patients received three different biologics, in the order of "A", "C", then "D", etc.).
- The number of malignancy events and the number of patients experiencing malignancy events will be tabulated by the type of CD therapy received (monotherapy versus combination therapy). If a patient received combination therapy (TNF-α antagonist plus immunosuppressant) at least once during the study, then this patient will be included in the combination therapy category.

8.1.2 Propensity score analysis

Propensity scores will be calculated for each patient using all collected, potentially confounding variables (analogous to Section 4.1). These variables include (but are not limited to) the following Baseline characteristics:

- Age
- Gender
- Race
- Smoking status
- Other biologic treatment use in the year prior to Baseline
- Immunosuppressant use in the year prior to Baseline
- Corticosteroid use in the year prior to Baseline
- Disease extent
- Diagnosed with fistulas
- Duration of disease
- Physician assessment of disease severity
- Number of Crohn's related hospitalizations in the year prior to Baseline
- Number of surgical resections in the year prior to Baseline
- Calendar year of enrollment

8.1.2.1 Propensity score estimation

The propensity score represents the probability that a specific patient receives Cimzia conditional on a set of known baseline confounding factors (4). A logistic regression model, with treatment cohort as the dependent variable, will be employed to estimate the conditional distribution of the treatment given the covariates. The predictors in this model are pre-treatment variables believed to be related to the study outcome of interest and are listed in Section 8.1.2 These variables were

selected a priori using a directed acyclic graph (DAG). This approach has the advantage of improving the statistical efficiency of a model. It also minimizes the introduction of bias which may result from more traditional confounder identification and adjustment approaches (5).

8.1.2.2 Overlap and Region of Common Support

Once the propensity scores are estimated, it is essential to investigate the validity or performance of these scores by verifying that sufficient overlap or common support of these scores exists between treatment cohorts. It is possible that some of the strata may contain only patients from either the Cimzia cohort or from the comparator cohort, which could lead to invalid comparisons. A necessary condition is that patients with the same covariate values have a positive probability of being assigned to either Cimzia or comparator, but with no perfect predictability (i.e. without a 0 or 1 probability). Thus, to ensure adequate performance of the propensity score, a common support region or a sufficient overlap of the distribution of the variables in Cimzia and comparator cohorts are needed. The common support region ensures that any combination of Baseline prognostic factors in the Cimzia cohort would also be observed in the comparator cohort. To evaluate adequate overlap of the propensity scores, several methods will be examined:

- Graphical method: A visual inspection of the density distribution of the propensity scores in both Cimzia and comparator cohorts will be performed (6). The extent of overlap should be evident from simple histograms or density distribution plots of the propensity scores from Cimzia and comparator cohorts. If the graphical representation shows a large disparity in propensity scores between the two cohorts, then covariates which are strong predictors of treatment will be examined to determine their confounding effects.
- Minima-Maxima Rule: The lower bound of the propensity scores will be determined as the larger of the minima of the scores in the 2 treatment groups while the upper bound will be computed as the smaller of the maxima. As an example, if Cimzia and the comparator propensity scores range from 0.01 to 0.8 and from 0.03 to 0.8, respectively, then the common region will be defined as [0.03, 0.8].
- Caliper method (matching): In order to obtain the largest sample possible from the entire patient enrollment, the size of the caliper will be set to a quarter of a standard deviation of the logit of the propensity score used as recommended by Rosenbaum and Rubin[7].

Once an appropriate common support region is found, only non-discarded patients will be used in further propensity score analyses aimed at estimating treatment effects. Demographic and baseline characteristics of patients disregarded will be compared to those remaining in the analysis, and any difference detected between these two groups of patients will be taken into account in the interpretation of estimated treatment effects. Moreover, if these two groups of patients are found to be different with regards to baseline prognostic factors, the predicted probabilities generated from the propensity score model will be re-estimated on the reduced dataset determined by the common support region(8).

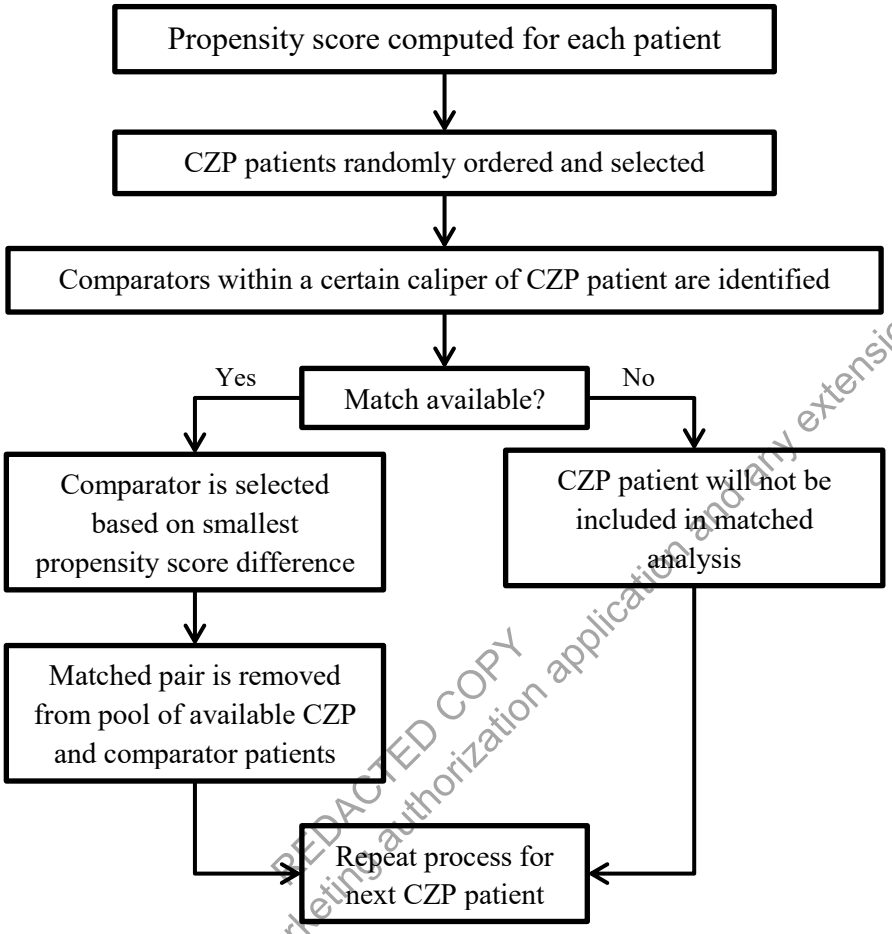
8.1.2.3 Propensity score matching

Propensity score matching will be used to construct a sample of patients which have similar covariate distributions between the Cimzia and comparator cohorts. A common sampling method known as the Mahalanobis metric matching with calipers will be implemented which will better balance the covariates between the cohorts. This method is

considered to be superior to other propensity score matching methods[9,10].

The matching algorithm will proceed as follows. Propensity scores will be computed for each patient in the database using a logistic regression model with covariates as listed in Section 8.1.2 Cimzia patients will be randomly ordered, and the first Cimzia patient is selected. Comparator patients whose propensity score is within a given caliper are identified as an initial matched candidate to the Cimzia patient. Cimzia and comparator patients will be matched in a 1:1 ratio based on the smallest distance between propensity scores. If there is no comparator patient match, then this round of matching stops and the process continues with the next Cimzia patient. If there is only one match, then this match is considered final and the matched pair is removed from the pool and the process continues with the next Cimzia patient. If there are more than 2 comparator matches using a 1:1 ratio, then the Mahalanobis distances are recalculated based on a smaller set of key covariates and propensity score between the given Cimzia patient and those initially selected from the comparator cohort. The patient with the smallest distance from the given Cimzia patient is selected as the final matched candidate. The matched pair is then removed from the pool and the process repeats for the next Cimzia subject. All remaining comparator patients are available for the remaining matching rounds. The matching process continues until all Cimzia patients in the pool are exhausted.

Diagram of the matching algorithm



To maximize the comparability of treatment cohorts, an iterative data-driven approach such as the one described by Rosenbaum and Rubin[11] will be adopted to develop the propensity score model. Terms in the model will include main effects, interactions, and nth-order (n<5) polynomials. A buildup approach, starting with a simpler model, will be implemented. Comparability of treatment cohorts will be assessed after each iteration. If residual systemic differences are identified, the model will be re-parameterized until covariate balance is achieved or maintained within reasonable limits. If some differences persist, the variables in question will be controlled for in the regression model that assesses the effect of treatment cohorts on the risk of serious infections.

8.1.2.4 Assessing the Quality of the Balance

The overarching aim of the propensity score model is to balance the treatment cohorts on the measured covariates so that an unbiased treatment effect can be determined. One way to evaluate whether this goal has been achieved is to compare the distribution of the baseline covariates between the two treatment cohorts.

The standardized bias will be used as described in Yang and Dalton[14] to assess the distance in marginal distributions of the covariates. For each covariate X it is defined as

the difference of the sample means before and after matching. For continuous variables the standardized bias before matching is given by:

$$Standardized\ Bias = \frac{(\bar{X}_1 - \bar{X}_2)}{\sqrt{0.5[V_1(X) + V_2(X)]}}$$

where X_1 (V_1) is the mean (variance) in the treatment group and X_2 (V_2) is the mean (variance) for the control group. The standardized bias will be calculated before and after matching.

For categorical variables with two levels, the standardized bias will be given by:

$$Standardized\ Bias = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{0.5[\hat{p}_1(1-\hat{p}_1) + \hat{p}_2(1-\hat{p}_2)]}}$$

where $\hat{p}_2$ and $\hat{p}_2$ denote the proportion or mean of the binary variable in the treatment and control group respectively. The standardized bias will be calculated before and after matching.

For categorical variables with more than two levels, a multivariate approach will be taken such that

$$T = (\hat{p}_{12}, \hat{p}_{13}, \ldots \hat{p}_{1K})'$$
$$C = (\hat{p}_{22}, \hat{p}_{23}, \ldots \hat{p}_{2K})'$$

where $\hat{p}_{jk}$ = Pr(category k | treatment group j) for j=1 or 2 and k=1 to K.

The standardized difference is given by:

$$Standardized\ Bias = \sqrt{(T-C)'S^{-1}(T-C)}$$

Where S is the covariance matrix defined as:

$$S = [S_{kl}] = \begin{cases} \dfrac{\hat{p}_{1k}(1-\hat{p}_{1k}) + \hat{p}_{2k}(1-\hat{p}_{2k})}{2}, k = l \\ \dfrac{\hat{p}_{1k}\hat{p}_{1l} + \hat{p}_{2k}\hat{p}_{2l}}{2}, k \neq l \end{cases}$$

Imbalance of covariates is defined as an absolute Standardized Bias greater than 0.2[15].

Furthermore, differences in propensity scores for each matched pair (CZP minus comparator) will be calculated and presented as the number and percent of positive and negative differences.

If there is evidence of covariate imbalance after adjustment for PS quintiles, the propensity score model specification will be refined according to the iterative algorithm outlined in Section 8.1.2.2. The iterative process ends when the bias associated with observable baseline characteristics is either removed or reduced to a reasonable level. In the final analysis of the effect of treatment cohorts, a regression adjustment will be made for any covariate with residual imbalance after propensity score matching (Section 8.1.2.3).

8.1.3 Time-to-event analysis

Time-to-event analyses will be conducted for each Adverse Event of Interest.

Please refer to Section 3.6 for the assignment of treatment groups and to Section 3.2.1 for details on exposure times.

Cimzia vs. Comparator (acute event rules)

Per patient and Adverse Event of Interest, exposure time until the first occurrence of the AE is considered. Prior to the AE, at any given time after treatment start, the patient can be exposed to either of: Cimzia, Comparator, Overlap, or Gap (one at a time but with switches between them). Thus, up to the first occurrence of the AE, 4 exposure times are recorded, one for each treatment. The first occurrence of the AE is counted as event for the actual treatment where it occurred (i.e. exactly one of Cimzia, Comparator, Overlap, or Gap), and exposure time is censored for the remaining 3 treatments. If no AE of interest occurred, time will be censored at the end of exposure for all treatments. The comparison of interest is Cimzia vs. Comparator.

Any Cimzia vs. Comparator (acute event rules)

Per patient and Adverse Event of Interest, exposure time until the first occurrence of the AE is considered. Prior to the AE, at any given time after treatment start, the patient can be exposed to either of: Any Cimzia (i.e. Cimzia monotherapy or Overlap), Comparator, or Gap (one at a time but with switches between them), Thus, up to the first occurrence of the AE, 3 exposure times are recorded, one for each treatment. The first occurrence of the AE is counted as event for the actual treatment where it occurred (i.e. exactly one of any Cimzia, Comparator, or Gap), and exposure time is censored for the remaining 2 treatments. If no AE of interest occurred, time will be censored at the end of exposure for all treatments. The comparison of interest is Any Cimzia vs. Comparator.

Cimzia vs. Comparator (malignancy rules)

Per patient and Adverse Event of Interest, exposure time up to the first occurrence of the AE is considered. The attribution of the AE to Cimzia or Comparator follows the exposure rules as described in Section 3.2.1.1, i.e., if the patient was exposed to Cimzia, prior to the AE, the event will be systematically attributed to Cimzia, irrespective of actual treatment. If the patient was not exposed to Cimzia prior to the AE, it will be attributed to Comparator. Exposure to Comparator prior to a first treatment switch to Cimzia will be attributed to Comparator. As detailed in Section 3.2.1.1, Exposure time is measured from first exposure to Cimzia (or Comparator), irrespective of treatment gaps. If no AE of interest occurred, time will be censored at the end of exposure.

All time-to-event analyses are exploratory and not confirmatory. No formal hypothesis testing will be conducted. P-values are for descriptive purposes only.

The number and percentage of patients with AEs of interest, as well as those censored, will be displayed. Time-to-AEs of interest will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median and 25th and 75th percentile event times, with corresponding 2-sided 95% confidence intervals as well as the range of event times will be provided by treatment group. The estimated hazard ratio, 2-sided 95% confidence interval and exploratory p-value will be provided.

8.1.4 Incidence and event rate calculation

In general, for each, the cumulative incidence, incidence rate and corresponding 95% confidence interval will be presented. For the incidence rate, the numerator will be the total number of patients experiencing the AE of interest for the first time in the study (if a patient switches treatment and has an AE of interest it will be considered a recurrence if the AE occurred while on a previous treatment). The denominator will be in 100 patient-years. That is, the denominator will be the total summation of individual patient-years at risk up the first occurrence of the AE of interest for subjects with that AE, and the total patient-years at risk for those subjects not experiencing that AE, divided by 100. Two-sided 95% confidence intervals for the incidence rates are calculated [using the GAMINV function in SAS] to determine the upper and lower limits for the number of events for each AE of interest, which is assumed to follow a Poisson distribution, divided by the total patient-years of exposure multiplied by 100. [Note that the method to be used follows a SAS implementation using the GAMINV function and is described in detail on bottom, right hand side of p. 2 and the code in the box on the left hand side of p. 3 in the SUGI paper http://www2.sas.com/proceedings/sugi26/p241-26.pdf].

A Poisson AE of interest regression analysis, accounting for within-patient correlations, implemented with the GENMOD procedure in SAS, is used to test for the differences in incidence rates between actual treatment cohorts at the two-sided α=0.05 level. Potential code for these models is:

```
PROC GENMOD data = XXXXX;

CLASS COHORT;

MODEL  AEOFINT = COHORT / D = POISSON OFFSET = LPRSNYRS;

 RUN;
```

Where AEOFINT is the number of events for a particular AE of interest, LPRSNYRS is the log of the total number of patient-years, and COHORT represents the actual treatment cohorts. Type III analysis will be used to get the cohort effects conditional on all covariates listed above in Section 4.1.

For event rates, the numerator will be the number of AEs of interest, including repeat occurrences in individual subjects. The denominator will be the total exposure in 100 patient-years, without censoring the exposure to the first event. That is, the total summation of individual patient-years divided by 100. No confidence intervals will be computed for event rates.

8.1.5 Secondary analyses of the primary endpoints

In addition to the propensity score analysis, comparisons between Cimzia event rates and all other CD treatment rates for comparator products will be examined using rate ratios and corresponding 95% CIs from conventional multivariate regression analyses. The same vector of

covariates that are included in the propensity score analysis will be also used as confounders in the conventional multivariate regression analyses. This will allow for an assessment of the robustness of study findings. Note that the interpretation of any rate ratios using conventional modeling may be hindered if there are substantial differences in the characteristics of patients between the Cimzia and comparator cohorts.

Rate ratios comparing Cimzia event rates to other frequently used CD treatments or treatment classes will also be calculated as appropriate.

The primary analysis for acute events will be stratified on incidence/prevalence use (yes/no), where incidence use is defined as only those patients who initiated treatment upon study enrollment and prevalent use is defined as those patients who were receiving treatment prior to enrollment. If sufficient power exists, further stratification based on duration of prevalent use (eg, 1-5 months, 6+ months, etc.) may be performed.

8.2 Statistical analysis of the secondary endpoints

A patient reported HBI, completed by each patient, is included as part of the patient disease assessment. Total HBI score will be summarized by enrollment cohort and actual treatment at Baseline for each time point the assessment was collected. Change from baseline for each post-baseline assessment will also be summarized by enrollment cohort and actual treatment at Baseline.

Summary statistics will be provided for the physician assessment of disease severity by enrollment cohort and actual treatment at Baseline for each time point the assessment was collected as well as for the change from baseline for each post-baseline assessment and actual treatment at Baseline.

Summary statistics will be provided for the patient assessment of disease severity by enrollment cohort and actual treatment at Baseline for each time point the assessment was collected as well as for the change from baseline for each post-baseline assessment. The number and percentage of patients in each patient reported disease severity category (remission, mild-moderate, moderate-severe, severe) will also be presented by enrollment cohort and actual treatment at Baseline for each time point.

The physician reported total HBI score will be summarized by enrollment cohort and actual treatment at Baseline for each time point the assessment was collected. Change from baseline for each post-baseline assessment will also be summarized by enrollment cohort and actual treatment at Baseline.

The number and percentage of patients in HBI remission and HBI response, based on the physician reported HBI total score will be presented at each visit for remission and at each post baseline visit for response. The number of patients at each visit will be used as the denominator for percentage of HBI remission. The number of patients with baseline at each post baseline visit will be used as the denominator for percentage of HBI response. Analyses using actual treatment at Baseline will remove the subject from the summaries after they have switched treatment.

A listing will be provided with the physician reported individual HBI items, HBI remission, and HBI response as well as the total score and assessment of disease severity.

8.2.1 Extent of exposure

Length of exposure (weeks), length of exposure category (weeks) and total years of exposure will be presented. This summary will be repeated for each of the exposure definitions presented in Section 3.2.1.

In order to summarize treatments received by both cohorts (ie, treatment switch patterns), descriptive statistics by cohort will be presented for the number of events, the number of exposure patients, and for person-time calculations.

A stratified analysis by cumulative Cimzia exposure may also be performed for malignancy events to identify potential patterns in long-term use of Cimzia.

8.2.2 Adverse Events

Any event reported by the investigator or found in the drug safety database excerpt is considered an adverse event. Investigator and drug safety AEs have been reconciled by the study physician to avoid over reporting.

When an AE is considered serious in either source, it is treated as serious in the analysis and the related coding data is used.

Events reported in the patient survey are not considered confirmed AEs and are excluded from the analysis.

AE tabulations will be done using malignancy rules (for malignancies) separately using acute event rules (all AEs) unless otherwise specified.

A summary of study-emergent AEs, including the number of events reported, the number and percentage of patients reporting at least one AE, the number and percentage of patients reporting at least one AE of Interest, the number and percentage of patients with at least one serious AE (SAE), and the number and percentage of deaths will be presented. In addition, the number and percentage of patients reporting at least one study-emergent treatment-related AE, the number and percentage of patients reporting at least one study-emergent treatment-related AE of Interest, and the number and percentage of patients with at least one study-emergent treatment-related SAE will also be reported. AE summaries will be produced on the enrolled cohort as well as the malignancy/acute event rules.

Study-emergent AEs are those which first occur or increase in relationship to treatment after the first dose of any CD drug following enrollment.

A breakdown of the number and percentage of patients reporting each AE as well as the number of AEs, categorized by SOC, HLT, and PT coded according to MedDRA, will be presented. Note that patients are only counted once within each SOC, HLT, or PT. Uncoded AEs will be summarized in unknown SOC, HLT and PT. This will be produced for the enrolled cohort as well as both the malignancy and acute event rules.

A further tabulation of these data, broken down by relationship to treatment, will be presented. Patients with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that SOC, HLT or PT. Relationship to treatment is categorized as related or not related as collected on the eCRF.

A breakdown of the number and percentage of patients reporting each AE as well as the number of AEs, categorized by SOC, HLT, and PT coded according to MedDRA, will be presented, including only patients in the Enrolled Set with multiple occurrences of any AE.

All AEs will be coded using the most recently available version of MedDRA available at each analysis (and version 20.0 for interim analysis 2) and all AEs collected on the eCRF will be included in a listing (except patient survey data). SOC, HLT and PT terms will be presented by decreasing frequency.

8.2.3 Adverse Events of Interest

The AEs of interest and the approach for summarizing them is briefly described below. Further information is provided in the guidance document (AEs of Interest – Cimzia Program 2018-01-05).

- Serious infections, including opportunistic infections. Serious infections will be summarized using the Serious TEAE table. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.
- Malignancies, including lymphoma. These will be presented in 2 tables using the Standardized MedDRA Query (SMQ) criteria "Malignant or unspecified tumours" and "Malignant tumours" respectively.
- Serious cardiovascular events (also called major adverse cardiac events or MACE). These will be presented in a table including all serious TEAEs with the SMQs of "Haemorrhagic central nervous system vascular conditions", "Conditions associated with central nervous system haemorrhages and cerebrovascular accidents", and "Ischaemic central nervous system vascular conditions" with the exception of events coding to a PT of "Transient ischaemic attack", including all serious TEAEs with the HLT of "Ischaemic coronary artery disorders" except events coding to PTs of "Chest Pain" or "Chest discomfort" and including all serious TEAEs with HLTs of "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders".
- Congestive heart failure. These will be manually identified by the study physician from the TEAE table.
- Demyelinating-like disorders will be presented in table which is based on the SMQ = "Demyelination". The SMQ search should include all TEAEs which code to a PT included in Scope=Narrow group within the SMQ. TEAEs which code to a PT included in the Scope=Broad group within the SMQ should be excluded from the search.
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = "Haematopoietic cytopenias" in the subset of Serious TEAEs.
- Serious bleeding events. These will be presented in a table using the criteria SMQ = "Haemorrhage terms (excl laboratory terms)" in the subset of Serious TEAEs.
- Lupus and lupus-like illness. These will be manually identified by the study physician from the TEAE table.

- Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from Serious TEAE table.

Although not officially AEs of interest, the following events will also be summarized as described in the AEs of Interest – Cimzia Program 2018-01-05 guidance document.

- Hepatic events. These will consist of a subset of all TEAEs, identified using the following 5 SMQs: Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions; Hepatitis, noninfectious; Liver-related investigations, signs and symptoms; and Liver-related coagulation and bleeding disturbances.
- Hypersensitivity reactions and anaphylactic reactions. Hypersensitivity reactions will be summarized as any TEAEs occurring on the same day or the day after injection was received, which code to the following preferred terms: Administration site hypersensitivity, Documented hypersensitivity to administered product, Drug hypersensitivity, Hypersensitivity, Hypersensitivity vasculitis, Infusion site hypersensitivity, Injection site hypersensitivity, Medical device site, hypersensitivity, Type II hypersensitivity or Type IV hypersensitivity reaction. Anaphylactic reactions will be defined using an algorithmic approach as described in the "AEs of Interest – Cimzia Program 2018-01-05" guidance document.
- Specific to study and not from the "AEs of Interest – Cimzia Program 2018-01-05" guidance document, we will also look at Malignant Lymphomas using the Narrow PTs from the "Malignant Lymphomas" SMQ, and into Autoimmune disorders and Lupus/Lupus-Like syndromes.
- Specific to study and not from the "AEs of Interest – Cimzia Program 2018-01-05" guidance document, we will also look at cases of non-melanoma Skin Cancer. These will be manually identified by the study physician from the TEAE table.

Table 8.1: Overview of malignancy events and acute events in this study

Overview of Events	
Event	**Event Type** (Malignancies are in addition analyzed following acute rules)
Malignant or unspecified tumor	Malignancy
Malignant tumor	Malignancy
Non melanoma skin cancer	Malignancy
Malignant Lymphoma	Malignancy
Serious infection	Acute
Opportunistic infection	Acute
Serious cardiac event	Acute
Congestive heart failure	Acute
Demyelinating-like disorder	Acute
Aplastic Anemia	Acute
Serious bleeding	Acute
Lupus and Lupus-like illness	Acute

Serious skin reaction	Acute
Hepatic event	Acute
Hyper/Anaphylactic reaction	Acute
Autoimmune Disorder	Acute

8.2.4 Serious Adverse Events and Deaths

SAEs, and SAEs by relationship will be presented as described for AEs in Section 8.2.2.

A listing of patients who experienced SAEs will also be provided. A separate listing of deaths will be included.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

10 REFERENCES

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11 APPENDICES

11.1 Appendix 1 – Treatment Allocation of Malignancies and Acute Adverse Events

Assumptions:

- Treatment periods described in the dosing column have the drug half-life added to the end of each treatment.
- Overlap is when comparator and Cimzia treatment periods overlap. The overlap can occur during the extended treatment for the drug half-life.
- Abbreviations; IC=Informed Consent Date, EoS= End of Study Date
- Gap and Overlap are not possible treatment groups for Malignancy Time at Risk as per SAP section 3.2.1.1 "Person-time at risk calculations for malignancy". Overlap would be considered Cimzia and Gap would be assigned to the prior treatment.
- The dosing prior to IC only has an impact on malignancy time at risk. If a subject has no Cimzia dosing prior to IC it is considered to have had Comparator dosing prior to IC regardless of what is recorded in the dosing information.

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
1a	No Cimzia	Comparator > Cimzia > Comparator	None	N/A	Start of Cimzia to EoS	IC to Start of Cimzia	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to EoS)	None	None
1b	Cimzia	Comparator > Cimzia > Comparator	None	N/A	IC to EoS	None	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to EoS)	None	None

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
2a	No Cimzia	Comparator > Cimzia > Comparator	Malignancy during second period of Comparator	Cimzia	Start of Cimzia to Malignancy Start Date	IC to Start of Cimzia	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to EoS)	None	None
2b	Cimzia	Comparator > Cimzia > Comparator	Malignancy during second period of Comparator	Cimzia	IC to Malignancy Start Date	None	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to EoS)	None	None
3a	No Cimzia	Comparator > Cimzia > Comparator	Malignancy during first period of Comparator	Comparator	None	IC to Malignancy Start Date	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to EoS)	None	None
3b	Cimzia	Comparator > Cimzia > Comparator	Malignancy during first period of Comparator	Cimzia	IC to Malignancy Start Date	None	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to EoS)	None	None

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
4a	No Cimzia	Comparator > Cimzia > Comparator	Other AE during second period of Comparator	Comparator	Start of Cimzia to EoS	IC to Start of Cimzia	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to Other AE start date)	None	None
4b	Cimzia	Comparator > Cimzia > Comparator	Other AE during second period of Comparator	Comparator	IC to EoS	None	Start of Cimzia to Start of Second Period of Comparator	(IC to Start of Cimzia) plus (Start of Second Period of Comparator to Other AE start date)	None	None
5a	No Cimzia	Comparator > Overlap > Cimzia	Malignancy during Overlap	Cimzia	Start of Overlap to Malignancy Start Date	IC to Start of Overlap	Start of Cimzia to EoS	IC to Start of Overlap	None	Start of Overlap to Start of Cimzia
5b	Cimzia	Comparator > Overlap > Cimzia	Malignancy during Overlap	Cimzia	IC to Malignancy Start Date	None	Start of Cimzia to EoS	IC to Start of Overlap	None	Start of Overlap to Start of Cimzia

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
6a	No Cimzia	Comparator > Overlap > Cimzia	Other AE during Overlap	Overlap	Start of Overlap to EoS	IC to Start of Overlap	None	IC to Start of Overlap	None	Start of Overlap to Other AE start date
6b	Cimzia	Comparator > Overlap > Cimzia	Other AE during Overlap	Overlap	IC to EoS	None	None	IC to Start of Overlap	None	Start of Overlap to Other AE start date
7a	No Cimzia	Comparator > Overlap > Cimzia	None	N/A	Start of Overlap to EoS	IC to Start of Overlap	Start of Cimzia to EoS	IC to Start of Overlap	None	Start of Overlap to Start of Cimzia
7b	Cimzia	Comparator > Overlap > Cimzia	None	N/A	IC to EoS	None	Start of Cimzia to EoS	IC to Start of Overlap	None	Start of Overlap to Start of Cimzia
8a	Cimzia	Comparator > Gap > Cimzia	Malignancy during Cimzia	Cimzia	IC to Malignancy Start Date	None	Start of Cimzia to EoS	IC to End of Comparator	Start of Gap to End of Gap	None
8b	No Cimzia	Comparator > Gap > Cimzia	Malignancy during Cimzia	Cimzia	Start of Cimzia to Malignancy Start Date	IC to End of Gap	Start of Cimzia to EoS	IC to End of Comparator	Start of Gap to End of Gap	None

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
9	No Cimzia or Cimzia	Cimzia > Gap > Comparator	Malignancy during Comparator	Cimzia	Start of Cimzia to Malignancy Start Date	None	Start of Cimzia to End of Cimzia	Start of Comparator to End of Comparator	Start of Gap to End of Gap	None
10	No Cimzia or Cimzia	Cimzia > Gap > Comparator	Malignancy during Gap	Cimzia	Start of Cimzia to Malignancy Start Date	None	Start of Cimzia to End of Cimzia	Start of Comparator to EoS	Start of Gap to End of Gap	None
11	No Cimzia or Cimzia	Cimzia > Gap > Comparator	Other AE during Gap	Gap	Start of Cimzia to EoS	None	Start of Cimzia to End of Cimzia	None	Start of Gap to Other AE start date	None
12	No Cimzia or Cimzia	Cimzia > Gap > Comparator	None	N/A	Start of Cimzia to EoS	None	Start of Cimzia to End of Cimzia	Start of Comparator to End of Comparator	Start of Gap to End of Gap	None
13	No Cimzia or Cimzia	Cimzia > Comparator	Malignancy during Comparator and Other AE during Comparator	Malignancy (Cimzia), Other AE (Comparator)	Start of Cimzia to Malignancy Start Date	None	Start of Cimzia to End of Cimzia	Start of Comparator to Other AE start date	None	None

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
14a	No Cimzia	Comparator > Gap > Cimzia	Malignancy during Gap	Comparator	None	Start of Comparator to Malignancy Start Date	Start of Cimzia to End of Cimzia	Start of Comparator to End of Comparator	Start of Gap to End of Gap	None
14b	Cimzia	Comparator > Gap > Cimzia	Malignancy during Gap	Cimzia	IC to Malignancy Start Date	None	Start of Cimzia to End of Cimzia	Start of Comparator to End of Comparator	Start of Gap to End of Gap	None
15a	No Cimzia	Comparator > Gap > Cimzia	First Malignancy during Gap and Second Malignancy during Cimzia	Comparator	None	Start of Comparator to First Malignancy Start Date	Start of Cimzia to End of Cimzia	Start of Comparator to End of Comparator	Start of Gap to End of Gap	None
15b	Cimzia	Comparator > Gap > Cimzia	First Malignancy during Gap and Second Malignancy during Cimzia	Cimzia	IC to Malignancy Start Date	None	Start of Cimzia to End of Cimzia	Start of Comparator to End of Comparator	Start of Gap to End of Gap	None
16a	No Cimzia	Gap > Cimzia	Malignancy during Gap	Comparator	None	IC to Malignancy Start Date	Start of Cimzia to End of Cimzia	None	IC to End of Gap	None

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
16b	Cimzia	Gap > Cimzia	Malignancy during Gap	Cimzia	IC to Malignancy Start Date	None	Start of Cimzia to End of Cimzia	None	IC to End of Gap	None
17a	No Cimizia	Gap > Comparator	Malignancy during Gap	Comparator	None	IC to Malignancy Start Date	None	Start of Comparator to End of Comparator	IC to End of Gap	None
17b	Cimzia	Gap > Comparator	Malignancy during Gap	Cimzia	IC to Malignancy Start Date	None	None	Start of Comparator to End of Comparator	IC to End of Gap	None
18a	No Cimzia	Gap > Cimzia	Other AE during Gap	Gap	Start of Cimzia to EoS	IC to Start of Cimzia	None	None	IC to Other AE start date	None
18b	Cimzia	Gap > Cimzia	Other AE during Gap	Gap	IC to EoS	None	None	None	IC to Other AE start date	None
19a	No Cimzia	Gap only i.e. no evidence of Comparator or Cimzia dosing	Malignancy during Gap	Comparator	None	IC to Malignancy Start Date	None	None	IC to EoS	None

#	Dosing prior to IC	Dosing during study (IC onwards)	Adverse Event	Treatment AE assigned to	Malignancy Time at Risk		Other AE Time at Risk			
					Cimzia	Comparator	Cimzia	Comparator	Gap	Overlap
19b	Cimzia	Gap only i.e. no evidence of Comparator or Cimzia dosing	Malignancy during Gap	Cimzia	IC to Malignancy Start Date	None	None	None	IC to EoS	None
20a	No Cimzia	Gap only i.e. no evidence of Comparator or Cimzia dosing	Other AE during Gap	Gap	None	IC to EoS	None	None	IC to Start of Other AE start date	None
20b	Cimzia	Gap only i.e. no evidence of Comparator or Cimzia dosing	Other AE during Gap	Gap	IC to EoS	None	None	None	IC to Start of Other AE start date	None

12 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

12.1 AMENDMENT 1

Rationale for the amendment

Amendment 1 of the SAP converts the original SAP dated 03Aug2009 from the PRA SAP template to the UCB SAP template, and includes new analyses as defined in amendment 3 of the protocol. In addition, the original TFL shells from 2009 have been converted from the PRA standard templates to UCB standard templates, and new shells have been included for the new analyses as defined in amendment 3 of the protocol.

12.2 AMENDMENT 2

Rationale for the amendment

Amendment 2 of the SAP adds new FDA analyses as requested in 13Dec2014 response letter. The SAP was also updated to the latest UCB SAP template.

12.3 AMENDMENT 3

Rationale for the amendment

Amendment 3 of the SAP is an update to account for the FDA feedback to stop enrollment and reduce the follow-up of patients from 10 years to 8 years. Additionally, several analyses were added in hopes to provide better interpretation of the data including updating the SMQs for MedDRA.

12.4 AMENDMENT 4

Rationale for the amendment

Amendment 4 of the SAP, from March 26, 2020, provides

1.) Specifications about the handling of erroneous patients entries. The rules for the handling of erroneous data are detailed in the Analysis Data Reviewers Guide, referenced in this SAP.

2.) A clarification of the censoring rules for time-to-event analyses, including sensitivity assessment.

3.) An update of important protocol deviations.

12.5 AMENDMENT 5

Rationale for the amendment

Amendment 5 of the SAP, dated September 1, 2020, provides an update to the censoring rules for the time-to-event analyses of Adverse Events of Interest. This now considers actual exposure until the occurrence of an Adverse Event of Interest, and makes the time at risk consistent with that of the exposure adjusted incidence analyses. There is also an update to state that analyses will be based on the FAS, and additionally on the ES.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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