Non-Interventional Study Protocol
C1231006

Observational, Real-World Study of INFLECTRA in Patients With Inflammatory Bowel Disease (IBD) in the United States and Canada

Statistical Analysis Plan
(SAP)

Version: 2.0

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Changes made in the description of the study design section.

2. INTRODUCTION

REMICADE® (infliximab) is monoclonal antibody in a class of drugs referred to as anti-tumor necrosis factor alpha (TNF-α). It was initially approved in the United States in August 1998 for the treatment of Crohn's disease (CD),[1] in November 1999 for the treatment of rheumatoid arthritis (RA),[2] and September 2005 for the treatment of ulcerative colitis (UC).[3] In 2011, Remicade was approved for use in pediatric forms of Crohn's disease and ulcerative colitis. It is also approved for treatment of ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis[3]

In September 2013 CT-P13 (infliximab-dyyb), the first biosimilar in the class of TNF-α therapies, was approved in Europe, and marketed as REMSIMA® and INFLECTRA.® The biosimilar was approved for use based on clinical trials conducted in Rheumatoid Arthritis and Ankylosing Spondylitis. This approval was extended to all of the other indications for which the originator product, REMICADE® (infliximab) was approved, based on the concept of extrapolation[4] The European Medicines Agency concluded that extrapolation of clinical efficacy and safety profile data to other indications of the originator product, not specifically studied during the clinical development of the biosimilar was possible based on the overall evidence of comparability provided from the comparability exercise and included adequate justification that the products did not differ in a clinically meaningful manner. In response to concern from gastroenterologists on the lack of clinical data supporting the utilization of INFLECTRA in patients with inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]),[5] researchers in Europe and Asia initiated prospective and retrospective studies to collect real world data on the use of INFLECTRA in patients with inflammatory bowel disease (IBD).[6-12] The published results of these studies reported no significant difference in the safety and efficacy between the originator and the biosimilar.

In Hungary, Gecse et al[7] conducted a prospective, nationwide, multicenter observational cohort study of 210 consecutively enrolled patients with IBD (n=126 UC, n=84 UC) initiating treatment with INFLECTRA. At week 14, 81.4% of CD and 77.6% of UC patients showed a clinical response and 53.6% of CD and 58.6% of UC patients were in clinical remission. Clinical remission rates at week 14 were significantly higher in CD and UC patients who were infliximab naïve, compared with those with previous exposure to the Remicade [$p < 0.05$]. Adverse events were reported in 17.1% of all patients through week 30. Infusion reactions and infectious adverse events occurred in 6.7% and 5.7% of all patients, respectively.

In the Netherlands, Smits et al[11] conducted a prospective observational cohort study of 83 patients with IBD (57 CD, 24 UC, 2 IBD-Undefined). The median change in disease activity (Harvey-Bradshaw Index) was 0 for CD and 0 for UC/IBD-U. Median CRP and FCP levels did not change significantly during follow-up. The median infliximab trough level increased from 3.5 μg/ml [range 0–18] to 4.2 μg/ml [range 0–21] at week 16 [p = 0.010]. Two patients developed a new detectable anti-drug antibody (ADA) response during follow-up and 5 patients discontinued INFLECTRA. No serious adverse events occurred.

In Norway, Jorgensen et al.[13] conducted randomized, non-inferiority, double-blind phase 4 trial with 52 weeks of follow up (NOR-SWITCH). Patients who enrolled in the study were randomized to remain on infliximab or switch CT-P13. A total of 482 patients enrolled (241 to infliximab, 241 to CT-P13). Patients had a mix of autoimmune diseases (32% Crohn's disease, 19% ulcerative colitis, 16% ankylosing spondylitis, 16% rheumatoid arthritis, 7% chronic plaque psoriasis 6% psoriatic arthritis). Disease worsening occurred in 26% of the infliximab group, and 30% in the CT-P13 group (per-protocol set; adjusted treatment difference −4·4%, 95% CI −12·7 to 3·9). The frequency of adverse events was similar between groups (for serious adverse events, 24 (10%) for infliximab originator vs 21 [9%] for CT-P13. The NOR-SWITCH trial showed that switching from infliximab to CT-P13 was not inferior to continued treatment with infliximab.

In April 2016, INFLECTRA, was approved by the FDA for the following indications:[14]

- *adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy;*
- *adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;*
- *patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;*
- *patients with active ankylosing spondylitis (arthritis of the spine);*
- *patients with active psoriatic arthritis;*
- *adult patients with chronic severe plaque psoriasis.*

To date, there has been no real world data published on the use of INFLECTRA in the US population.

2.1. Study Design

This is a prospective, observational, multicenter study conducted in patients with UC and CD. The study plans to recruit 300 subjects in the United States and Canada initiating or switching to treatment with INFLECTRA over an 8-month period (Figure 1). The decision to start INFLECTRA will be entirely a clinical decision made by the participating physician irrespective of this study. The study will evaluate direct medical costs, indirect costs, disease activity, remission status, relapse status, treatment patterns, treatment satisfaction, and healthcare resource utilization. There are no mandated study visits, as patients will follow local standard of care. Patients will be assessed at regular intervals that coincide with regularly scheduled appointments, for 52 weeks after initiating treatment with INFLECTRA.

The primary objective for this study is descriptive in nature. As such, precision estimates (PEs) have been provided at the 95% confidence level, in lieu of power calculations. While as a descriptive study in which there is no comparison between countries or other subgroups planned, it is important to consider the precision and face validity of estimates in smaller populations. A common rule of thumb is that a sample size of at least 30 is large enough in order for the central limit theorem (in which the mean of the sample is representative of the true mean of the population) to apply.[15] The table below (Table 1) provides precision estimates for analyses conducted across all patients. For any categorical outcome (for example, proportion of patients on INFLECTRA at 12 months), these represent the 'margin of error' around the numbers reported. For example, if 90% of people report using INFLECTRA at 12 months, where the sample size is 139, the actual percent will be between 85.0% and 95%. We anticipate this to be sufficient precision to meet study needs.

Furthermore, after multiple rounds of review with key opinion leaders during the study design phase, it was determined that while the minimum number of patients needed would be approximately 139, a sample size closer to 300 patients would be needed to satisfy clinicians.

Table 1. Precision Estimates for 95% Confidence Intervals of Categorical Variables

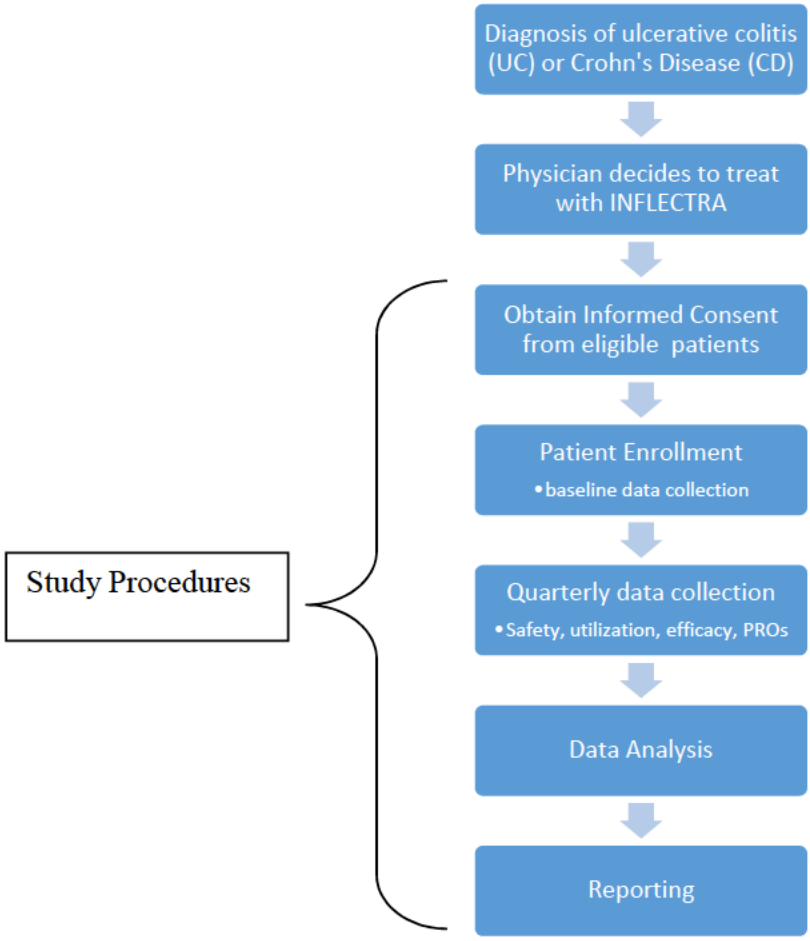
	Sample Size for Precision of:			
Percent of patients with a given risk factor	±1%	±2.5%	±5%	±10%
90%/10% responding to categorical variable	3458	554	139	35
70%/30% responding to categorical variable	8068	1291	323	81
50%50% responding to categorical variable	9604	1537	385	97

The enrollment of new patients was stopped before reaching the minimum sample size (N = 139) determined to be necessary. The primary reason for discontinuing recruitment was lack of formulary availability/insurance coverage of infliximab-dyyb during patient enrollment. Due to the lack of uptake of biosimilars/Inflectra in the US, fewer study sites than planned were able to identify and recruit patients because infliximab-dyyb was not on their formulary or patient insurance would not cover infliximab-dyyb. To resolve this issue, the patient enrollment timeframe was extended one year beyond the planned enrollment time, and even with this extension, the study only reached 118 patients. The final analytical sample included

115 patients after excluding 1 patient due to not meeting inclusion criteria and 2 additional patients because they did not receive infliximab-dyyb due to being given RP infliximab at their infusion center/pharmacy.

Clinical information will be recorded in the patient's chart during each treatment/clinical visit. Data entry into the EDC system will occur quarterly, along with the administration of PROs. Patients who discontinue treatment before the end of the study will be followed for the full duration of the study. Data collected on patients with CD and UC may be analyzed separately.

Figure 1. Study Design



Study procedures

In this study, recruited physicians and/or their assigned staff will be responsible for patient identification, qualification and selection, patient interview, exam recording, data abstraction and completion of the patient case report form (CRF), which is described in greater detail below.

During the baseline visit, the following procedures will be carried out:

- *Verification of eligibility criteria;*
- *Record demographic data, medical history, and prior disease specific concomitant medications (minimum of 12 months, unless newly diagnosed);*
- *Record consumption of cigarettes/nicotine products;*
- *Administration of baseline questionnaires;*
- *Completion of clinical assessments;*
- *Document adverse events (AE) and serious adverse events (SAEs), if applicable;*
- *Patient summary and disposition.*

If any abnormalities are detected during the assessments, the medical practitioner will communicate the results to the patient. The medical practitioner will manage and treat the detected abnormality as per routine clinical practice. Sponsor will not fund any additional diagnostic procedures or treatment related to the detected abnormalities.

There are no protocol required medical procedures for this study. Lab tests are not required, but if recent test results are available, they should be provided in the CRF. While there are no required study visits, there are multiple patient reported questionnaires, depending on indication that should be completed at various time points (approximately) during the study (Table 2).

Table 2. Planned Schedule of Events

Procedure	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4	Unscheduled visit
	Day 0 (±14 days)	Day 90 (±30 days)	Day 180 (±30 days)	Day 365 (±30 days)	N/A
Informed Consent	X				
Patient Baseline Characteristics	X				
Disease History	X				
Safety Information	X	X	X	X	X
Disease-related Resource Use	X	X	X	X	
Clinical Outcomes	X	X	X	X	
Treatment Details	X	X	X	X	
Physician Information	X				

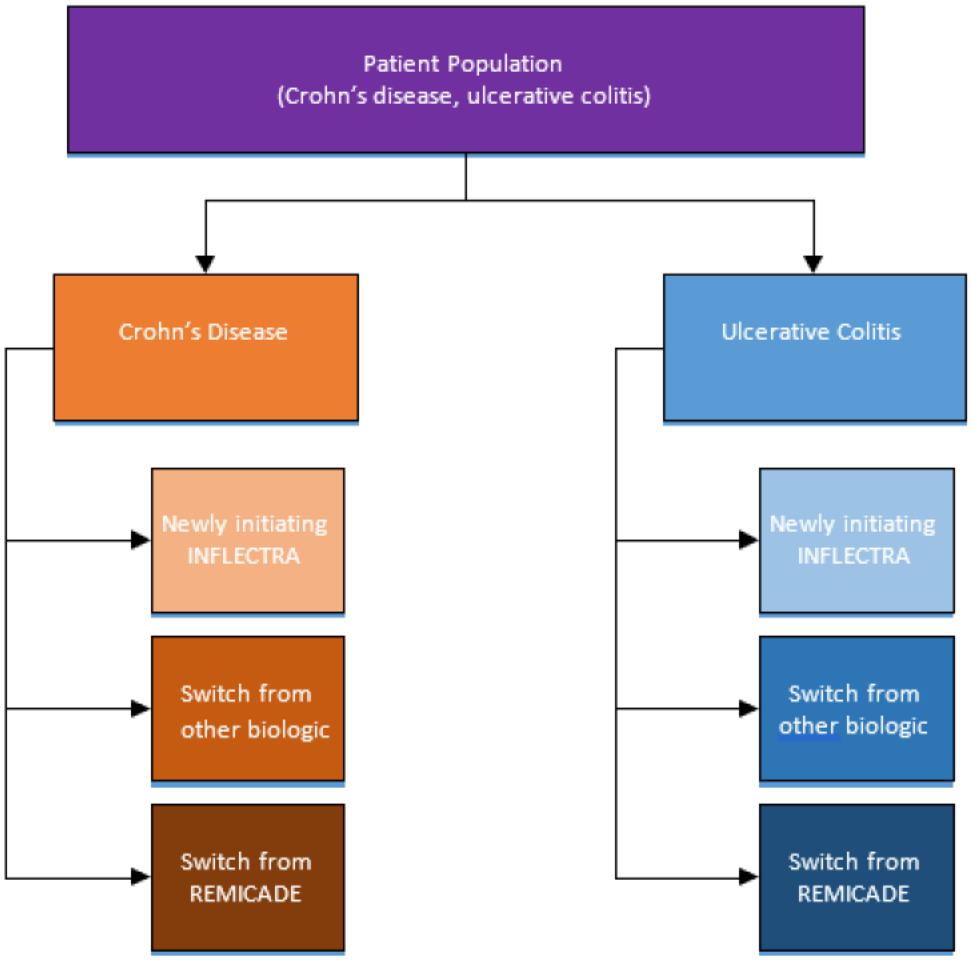
Note: Patients typically receive infusions every 8 weeks, hence this study provides a 60-day window assuming the visit might occur within this window. All visits will be as per the participating physicians clinical care routine, and no visits are mandated by this study.

Study population

This is an observational study; therefore, the decision to treat a patient with INFLECTRA must be made prior to a decision to enroll them in this study. Patients are eligible to participate if they have (Figure 2):

- *Initiated therapy with INFLECTRA as their first biologic;*
- *Switched to INFLECTRA while in remission on a stable dose of REMICADE; or,*
- *Switched to INFLECTRA from another biologic, due to non-responsiveness, intolerance, or other reasons.*

Figure 2. Distribution of Eligible Patients



Inclusion criteria

Patients must meet all of the following criteria to be eligible for inclusion in the study:

- *Patients with confirmed diagnosis of UC or CD.*
- *Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.*
- *Patient eligible to receive INFLECTRA for the treatment of their disease per approved drug label (patients with fistula, or stoma are eligible).*

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- *Patient age less than 18 years at the time of consent.*
- *Patient previously failed treatment with REMICADE or INFLECTRA/CT-P13.*
- *Any reported contraindications for INFLECTRA/CT-P13 or REMICADE.*
- *Known hypersensitivity (including severe, acute infusion reactions) to infliximab, its excipients or other murine proteins, at the time of enrolment.*
- *Patients with communication difficulties in reading or understanding the study consent or questionnaires.*

Data source

Patient interviews and data collection will be performed by site physicians and/or their assigned staff. Recruited physicians and/or their assigned staff will be responsible for patient identification, qualification and selection, patient interview, exam taking, data abstraction, and completion of the patient CRF.

Physicians and/or site staff will be instructed to assign a unique identifier for each patient enrolled in the study to facilitate follow-up on data queries and for data validation. Patient data will be de-identified and will be reported in aggregate. Patient clinical data should be abstracted from the patient's medical chart, or in the case of the patient reported outcome measures, from the assessment tools themselves, which will serve as the source document. No other source documents will be provided.

Clinical data will be collected in electronic form by the participating physician or in collaboration with the designated site personnel. Physicians will be provided with written handouts/instructions and will be periodically contacted, at least monthly until completion and submission of all the forms. Completed forms will be thoroughly reviewed and coded after entry into the database.

At least 15% of the completed forms will be randomly selected for validations against the source document on key CRF data points such as informed consent date, diagnosis, safety events, and clinical outcomes etc. by clinical research associates (CRAs). In addition, data validation will include frequency counts, arrays, and distributions, running descriptive statistics on continuous variables, and 100% computer logic checks. Any outliers and/or missing data will be directly resolved with the participating physicians.

Treatment/cohort labels

1. Patients with CD who are newly initiating a biologic.
2. Patients with CD who are switching from another biologic.
3. Patients with CD who are transitioning from REMICADE to INFLECTRA.
4. Patients with UC who are newly initiating a biologic.
5. Patients with UC who are switching from another biologic.
6. Patients with UC who are transitioning from REMICADE to INFLECTRA.

2.2. Study Objectives

The purpose of this study is to collect and analyze data in adult patients with IBD (CD and UC) treated with INFLECTRA in a real-world setting. There will be no imposed experimental intervention, and treatment with INFLECTRA is determined solely by the patient's physician separately and irrespective of the decision to participate in this study.

The primary objective of this study is:

- *To describe drug utilization patterns and treatment in adult UC and CD cohorts treated with INFLECTRA in a real-world setting.*

Drug utilization patterns represent a collection of aspects around a patient's treatment. This study will analyze the following aspects:

a. Proportion of patients on treatment at each visit: number of patients still on INFLECTRA divided by total number enrolled at each visit.

b. Reason for treatment initiation: count data on the rationale for treatment intiatiaon.

c. Duration of treatment: difference between the treatment intiaition date and the visit date in days.

d. Current dose: mean dose in mg/kg at each visit.

e. Frequency of dose changes: count of number of dose changes since initiation.

f. Reason for dose changes: count data on the reason for dose changes.

g. Reason for discontinuation: count data on the rationale for discontinuation of INFLECTRA.

h. Use of imaging tests: count data on the type and frequency of imaging studies.

The secondary objectives of this study are:

- *To describe real-world clinical and economic outcomes in adult UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.*

Clinical outcomes represent a collection of aspects around patients' treatment. This study will analyze the following aspects:

a. Harvey Bradshaw Index: Score at each visit, change in score (Crohn's disease only).

b. Partial Mayo Schore: Score at each visit, change in score.

c. Use of C-Reactive Protein: Value at each visit, when available.

d. Fecal Calprotectin: Value at each visit, when available.

e. Therapeutic drug monitoring: value of drug level and anti-drug antibody value at each visit, when available.

- *To describe real-world patient reported quality of life in both the UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.*

Patient quality of life will be measured through various patient-reported outcome measures:

a. Short Inflammatory Bowel Disease Questionnaire (SIBDQ);

b. Visual Analog Scale (VAS) for General Well Being;

c. Work Productivity and Activity Impairment Index (WPAI);

d. Treatment Satisfaction Questionnaire-Medication (TSQM).

- *To describe the demographic and clinical characteristics of patients receiving INFLECTRA for the treatment of UC and CD.*

Basic demographic and clinical characteristics will be analyzed, including:

a. Age;

b. Sex;

c. Race/Ethnicity;

d. Body Mass Index (BMI);

e. Insurance Status;

f. Smoking Status;

g. Charlson Comorbidity Index (CCI);

h. Disease type (Crohn's Disease);

i. Duration of Disease;

j. Montreal Classificaiton;

k. Prior and current disease related medications.

- *To describe healthcare resource utilization and direct costs in adult patients receiving INFLECTRA for the treatment of UC or CD.*

Resource utilization and direct costs will be estimated based on the following healthcare encounters:

a. Gastroenterology outpatient visits;

b. General practioner outpatient visits;

c. Emergency department visits;

d. In-patient hospitalization visits.

CCI

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

3. INTERIM ANALYSES

Up to two interim descriptive analyses are planned. The first will be conducted after 100 patients have completed the baseline visit, and the second after 100 patients have completed the 6 month visit. All planned analyses will be conducted, however there will be a focus on baseline demographics and patient-reported quality of life CCI [redacted] CCI [redacted] in the first and a clinical outcomes focus for the second interim.

4. HYPOTHESES AND DECISION RULES

The majority of outcomes are descriptive in nature and as such do not have specific hypotheses. Furthermore, this study is not statistically powered to detect a change in scores for any measure at any pre-specified time point.

4.1. Statistical Hypotheses

The final analysis will test the change from baseline for clinical outcomes such as the HBI and partial Mayo score, as well as patient-reported outcomes such as the SIBDQ, WPAI, VAS, among others at 3, 6 and 12 months.

4.1.1. Null Hypothesis 1

For patients who are newly initiating INFLECTRA and patients switching to INFLECTRA from another biologic (not REMICADE), there is no statistically significant difference between measures at baseline and 12 months (2-sided).

4.1.2. Alternative Hypothesis 1

For patients who are newly initiating INFLECTRA and patients switching to INFLECTRA from another biologic, there is a statistically significant difference between measures at baseline and 12 months (2-sided).

4.1.3. Null Hypothesis 2

For patients who are transitioning from REMICADE to INFLECTRA, there is no statistically significant difference between measures at baseline and 12 months (2-sided).

4.1.4. Alternative Hypothesis 2

For patients who are transitioning from REMICADE to INFLECTRA , there is a statistically significant difference between measures at baseline and 12 months (2-sided).

4.2. Statistical Decision Rules

All confidence intervals, statistical tests, and resulting p-values will be two-sided. All hypothesis testing will be performed at the 5% significance level. The third decimal place will be the least significant digit. If the p-value is less than 0.001, then it will be reported as "<0.001", and if the p-value is greater than 0.999, then it will be reported as ">0.999".

5. ANALYSIS SETS/POPULATIONS

5.1. Full Analysis Set

Defined analyses will include all patients who signed the informed consent and met the inclusion/exclusion criteria detailed in the study design, or the subgroups as specified below, ie, by those who newly initiated INFLECTRA, switched from a biologic, or transitioned from REMICADE. No additional analysis sets are defined for this study.

5.2. Safety Analysis Set

The safety analysis set will include all patients who signed an informed consent. Safety will be addressed according to Pfizer's CT-24 SOP for reporting of adverse events and serious adverse events in retrospective non-interventional studies.

5.3. Other Analysis Set

N/A.

5.4. Subgroups

The analyses will be stratified for the following subgroups:

- Patients with a diagnosis of UC,
    - This group will be further stratified by:
        - Those who newly initiated INFLECTRA with INFLECTRA as their first biologic,
        - Transitioned to INFLECTRA from REMICADE or,
        - Switched to INFLECTRA from another biologic.
- Patients with a diagnosis of CD,
    - This group will be further stratified by:
        - Those who newly initiated INFLECTRA with INFLECTRA as their first biologic,

- Transitioned to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy/Effectiveness Endpoint(s)

Table 3. Efficacy and Effectiveness Endpoints

Variable	Role	Data source	Operational definition
Reason for initiation	Primary objective	Patient medical chart	Reason for initiation of a biologic
Prescribed Drugs	Primary objective	Patient medical chart	Generic name of prescribed drug
Treatment Start Date	Primary objective	Patient medical chart	Date of first biologic dose
Infusion Start Time	Primary objective	Patient medical chart	Time infusion was started
Infusion Stop Time	Primary objective	Patient medical chart	Time infusion was stopped
Treatment End Date	Primary objective	Patient medical chart	Date of last dose, date of prescription + days' supply
Treatment Dose	Primary objective	Patient medical chart	Total mg/kg at each infusion
Treatment Dose Adjustment	Primary objective	Patient medical chart	Dosage, date, and rationale
Treatment Switch/discontinuation	Primary objective	Patient medical chart	Yes/No
Treatment Switch/discontinuation Reason	Primary objective	Patient medical chart	Defined list (Lack of response, Lack of tolerability, Chance in Insurance coverage, Patient Preference, Dosing schedule, Other-Specify)
Harvey-Bradshaw Index	Secondary objective	Patient medical chart	Calculated score based on patient completed Harvey-Bradshaw Index
Partial Mayo score	Secondary objective	Patient medical chart	Calculated score based on partial Mayo tool
Short Inflammatory Bowel Disease Questionnaire	Secondary objective	Patient reported questionnaire	Calculated score based on the patient completed short Inflammatory Bowel Disease Questionnaire
Visual Analog Scale	Secondary objective	Patient reported questionnaire	Score of the patient completed VAS instrument for overall well-being
WPAI	Secondary objective	Patient reported questionnaire	Calculated score of the patient completed WPAI instrument, and domain scores
TSQM	Secondary objective	Patient reported questionnaire	Calculated score of the TSQM instrument, and domain scores
Office visits	Secondary objective	Patient medical chart	Date of office visit
Infusion Visits	Secondary objective	Patient medical chart	Date of visit
ED Visits	Secondary objective	Patient medical chart	Date of ED visits during the observation period

Variable	Role	Data source	Operational definition
Hospitalizations	Secondary objective	Patient medical chart	Number and duration of hospital admissions during the observation period
C-reactive Protein	Secondary objective	Patient medical chart	Physician reported lab value of most recent CRP test
Fecal Calprotectin	Secondary objective	Patient medical chart	Physician reported lab value of most recent fecal calprotectin test
Therapeutic Drug Monitoring	Secondary objective	Patient medical chart	Physician reported lab value of most recent therapeutic drug monitoring test
Endoscopy Procedures	Secondary objective	Patient medical chart	Type and number of endoscopy procedures during the observation period
CCI	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]

The Harvey-Bradshaw Index (HBI) will be used for patients with Crohn's disease. The Partial Mayo score will be used for patients with ulcerative colitis. The following table details the cut-off values for defining response and remission.

Table 4. Definitions for Remission and Response by Disease

Indication	Definition
Crohn's disease (remission)	Harvey-Bradshaw Index score <5[16]
Ulcerative colitis (remission)	Partial Mayo score <3 points[7,17]
Crohn's disease (response)	Reduction of Harvey-Bradshaw Score of ≥3 points from[18] baseline
Ulcerative colitis (response)	Reduction of partial Mayo score of ≥3 points from baseline[7,17]

6.2. Safety Endpoints

Adverse events for this study are limited to the following adverse events of special interest (AESIs):

- Hepatitis B virus reactivation;
- Opportunistic infections;
- Tuberculosis;
- Acute hypersensitivity reactions (including anaphylactic shock)*;

- Serious infusion reactions during a re-induction regimen following disease flare;
- Serum sickness (delayed hypersensitivity reactions);
- Haematological reactions (i.e. abnormal blood cell counts);
- Systemic lupus erythematosus/lupus-like syndrome;
- Lymphoma (not HSTCL);
- Hepatosplenic T-cell lymphoma (HSTCL);
- Leukemia;
- Merkel cell carcinoma;
- Melanoma;
- Hepatobiliary events;
- Congestive heart failure;
- Demyelinating disorders;
- Sarcoidosis/sarcoid-like reactions;
- Intestinal or perianal abscess (in Crohn's disease);
- Serious infections including sepsis (excluding opportunistic infections and tuberculosis);
- Important potential risks;
- Malignancy (excluding lymphoma, HSTCL, pediatric malignancy, leukemia, melanoma, Merkel cell carcinoma, cervical cancer);
- Colon carcinoma/dysplasia (in ulcerative colitis);
- Skin cancer (excluding melanoma, Merkel cell carcinoma);
- Pregnancy exposure;
- Infusion reaction associated with shortened infusion duration;
- Important missing information;*

- Long-term safety in adult patients with ulcerative colitis;
- Use of infliximab during lactation.

Table 5 Safety Related Endpoints

Variable	Role	Data source(s)	Operational definition
Event Description	Secondary objective	Patient medical chart	Description of the adverse event
Date Onset	Secondary objective	Patient medical chart	Date the event started
Date Stop	Secondary objective	Patient medical chart	Date the event resolved
Resolution	Secondary objective	Patient medical chart	Fatal; Not recovered/not resolved; recovered with sequelae possible; recovered without sequelae, recovered/resolved
Severity/Grade	Secondary objective	Patient medical chart	Mild; moderate; severe; life-threatening; fatal
Serious	Secondary objective	Patient medical chart	Yes/No
AE treatment	Secondary objective	Patient medical chart	None, medications, non-medication treatment
Action Taken	Secondary objective	Patient medical chart	None; Interrupted, Discontinued, Dose reduced, Dose increased, Not applicable
Attribution	Secondary objective	Patient medical chart	Definite; Probable; Unlikely; Unrelated

CCI [redacted]

CCI [redacted]

6.4. Covariates

The list of covariates below represent demographic and clinical data collected at baseline.

Table 6 Baseline Covariates

Variable	Role	Data source(s)	Operational definition
Age	Patient baseline characteristic	Patient medical chart	Patient age at baseline
Sex	Patient baseline characteristic	Patient medical chart	Female/Male
Race/ethnicity	Patient baseline characteristic	Patient medical chart	Hispanic or Latino/Not Hispanic or Latino; American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other
Height	Patient baseline characteristic	Patient medical chart	Height in meters/Height in inches

Variable	Role	Data source(s)	Operational definition
Weight	Patient baseline characteristic	Patient medical chart	Weight in Kilograms/Weight in Pounds
Body Mass Index	Patient baseline characteristic	Patient medical chart	(Weight in Kilograms/[Height in Meters x Height in Meters]) OR (Weight in Pounds/[Height in inches x Height in inches]) x 703
Comorbidities	Patient baseline characteristic	Patient medical chart	Comorbidities listed in the CCI, plus additional diseases of interest
Healthcare insurance coverage	Patient baseline characteristic	Patient medical chart	Plan coverage type (PPO, POS, HMO, Medicare/Medicaid, etc.)
Smoking Status	Patient baseline characteristic	Patient medical chart	Smoking history, as well as current tobacco use
Concomitant medications	Patient baseline characteristic	Patient medical chart	All current medications (prescription only)
Diagnosis	Clinical/disease characteristic	Patient medical chart	Ulcerative Colitis, Crohn's Disease
Diagnosis Year	Clinical/disease characteristic	Patient medical chart	Year of Diagnosis
Age at Onset	Clinical/disease characteristic	Patient medical chart	Diagnosis Year-Birth year
Disease Activity	Clinical/disease characteristic	Patient medical chart	Harvey-Bradshaw Index (CD only), partial Mayo score (UC only)
Montreal Classification	Clinical/disease characteristic	Patient medical chart	Montreal Classification of disease at baseline
Previous Surgery	Clinical/disease characteristic	Patient medical chart	Disease related surgical procedures
Previous Surgery Date	Clinical/disease characteristic	Patient medical chart	Date of disease related surgical procedures
Previous Medications	Clinical/disease characteristic	Patient medical chart	Disease related medications

7. HANDLING OF MISSING VALUES

Due to study design considerations, our study will be limited to data available in patient medical records. For descriptive reporting of categorical and outcomes, missing will be treated as a category when present and reported. In cases where outcomes for a subject are present, but data on a few predictors other than therapy are missing (multivariate analysis such as multivariate logistic regression), an assessment of the handling of this missing data will be conducted. This will include discussion of the advantages and disadvantages of data imputation versus using a strictly complete case analysis. Method to handle missing data will depend on the extent and nature of missing data. Note that missing data is anticipated to be rare due to the ability to query back to sites. Any missing or illegible data will result in contacting the sites directly to validate the missing data against the patient's medical charts.

All descriptive analysis will be based on the observed values, no imputation will be performed. No other imputation will be performed for missing values. For all dichotomous outcome measures, such as health insurance status, number of subjects with non-missing observation will be reported.

For incomplete dates, the following methodology will be employed. If month is missing in presence of year, the date will be assigned to July 1 of the corresponding year. Similarly, if the date is missing in presence of month, the date will be assigned to the 15th of the corresponding month. (eg, 2016 will be reassigned as July 1, 2016; May 2016 will be reassigned as May 15, 2016).

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Analysis for Binary and Categorical Endpoints

All binary and categorical endpoints will be summarised using both the number and percentage in each category (eg. sex, race, insurance status). The number of subjects included in the calculation of a percentage is determined by the analysis set used (see Section 5) and the rules for handling missing values (see the previous section). Due to longitudinal nature of data, McNemar test will be used to compare outcomes for patient groups across assessment time points (eg. proportion of patients that had remissions, responses, dose change, individual reasons for discontinuation).

Based on the results of descriptive analysis, a decision will be made regarding whether to conduct multivariable regression analysis to compare outcomes from baseline to each assessment time point. In that case, to account for repeated nature of the data, analysis will be conducted using multivariable regression model with generalized estimating equations (GEE).

8.1.2. Analyses for Continuous Endpoints

Demographic (eg, age, weight, height) and clinical characteristics (eg. lab values), and other continuous variables will be summarised using the summary statistics of mean, standard deviation, median, inter-quartile range, range, number of subjects in the analysis set used and number of subjects having a non-missing value of that endpoint. Due to repeated nature of data, continuous endpoints will be compared across visits using paired ttest, Wilcoxon sign rank test or using repeated measures ANOVA depending on the nature of variable and its distribution.

Based on the results of descriptive analysis, a decision will be regarding whether to conduct multivariable regression analysis, which would compare outcomes from baseline to each assessment time point. To account for repeated nature of data, linear mixed models or in case of non-linear data, generalized linear mixed models will be used to analyze continuous outcomes (eg, PRO measures, lab values, duration of therapy). Healthcare resource use related variables will be assessed using negative binomial distribution whereas, costs will be assessed using gamma distribution with log or identity link.

8.2. Statistical Analyses

8.2.1. Safety Analyses

Safety findings will be addressed according to Pfizer's CT-24 SOP for reporting of adverse events and serious adverse events in retrospective non-interventional studies.

8.2.2. Summary of Analyses

Table 7 Summary of Analyses

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
	Primary Objective						
1.1	Treatment regimens	FAS	1	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
1.2	Reason for treatment initiation	FAS	1	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type	Excluded
1.3	Time to initiation of treatment regimen	FAS	1	Disease Cohorts, Disease Subcohorts	Kaplan-Meier analysis	Stratified by disease subcohort, insurance type	Excluded
1.4	Duration of each therapy (defined as the number of days on treatment between the first and last dose), time between lines of therapy	FAS	1	Disease Cohorts, Disease Subcohorts	Kaplan-Meier analyses	Stratified by disease subcohort, insurance type, disease severity	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
1.5	Average current dose	FAS	1	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded
1.6	Frequency of treatment	FAS	1	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded
1.7	Dose change since last infusion	FAS	1	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded
1.8	Reason for dose change	FAS	1	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded
1.9	Reasons for discontinuation	FAS	1	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
	Secondary Objectives						
2.1	Recent C-reactive protein at each visit	FAS	2	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded
2.1	Recent calprotectin at each visit	FAS	2	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded
2.1	Recent drug level at each visit	FAS	2	Disease Cohorts, Disease Subcohorts	.Descriptive statistics	Stratified by disease subcohort, insurance type, disease severity	Excluded
2.1	Recent anti-drug antibody value at each visit	FAS	2	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Age, Sex, BMI, Race/Ethinicity, Insurance, Smoking status, comorbidity, Montreal classification, Prior biologics	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
2.1	Recent partial MAYO score at each visit	FAS	2	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded
2.1	Frequency of UC remission at day 90, 180 and 365	FAS	2	Disease Cohorts, Disease Subcohorts	Descriptive statistics, GEE model	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded
2.1	Recent HBI score	FAS	2	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable
2.1	Frequency of CD remission at day 90, 180 and 365	FAS	2	Disease Cohorts, Disease Subcohorts	Descriptive statistic, GEE model	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable
3.1	SIBDQ Scoring: Recent score at each visit and change in score from baseline at day 90, 180 and 365	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
3.2	VAS Scoring: Recent score at each visit and change in score from baseline at day 90, 180 and 365	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable
3.3	WPAI Scoring: Recent score and change in score from baseline at day 90, 180 and 365	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable
3.3.1	Absenteeism score	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity,	Excluded/ Imputation as applicable
3.3.2	Presenteeism score	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity	Excluded/ Imputation as applicable
3.3.4	Overall work impairment score	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity	Excluded/ Imputation as applicable

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
3.3.5	Daily activity impairment score	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity	Excluded/ Imputation as applicable
3.4	TSQM global: Recent score and change in score from baseline	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable
	TSQM effectiveness domain: Recent score and change in score from baseline	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable
	TSQM side effects domain: Recent score and change in score from baseline	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable
	TSQM convenience domain: Recent score and change in score from baseline	FAS	3	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Linear Mixed Models	Stratified by disease subcohort, disease severity, age, sex, BMI, insurance, rationale for switch	Excluded/ Imputation as applicable

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
4.01	Gender	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.02	Age baseline	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.03	Race/ethnicity	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.04	Height	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.05	Weight	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
4.06	Body Mass Index	FAS	4	Disease Cohorts, Disease Subcohorts	Weight/Height2, Descriptive statistics	Stratified by disease subcohort	Excluded
4.07	Insurance	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.08	Smoking status and use	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.09	Charlson Comorbidity Index	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.1	Diagnosis	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
4.11	Type of CD	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.12	Duration of disease	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.13	Prior disease-related non-biologic medications	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.14	Prior disease related biologics	FAS		Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.15	Current disease-related medications	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
4.16	Frequency of patients receiving disease-related surgery	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.17	Number of surgeries	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.18	Reason for surgery	FAS	4	Disease Cohorts, Disease Subcohorts	Discriptive statistics	Stratified by disease subcohort	Excluded
4.19	Age at onset	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.2	Location	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
4.21	Behavior	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.22	Baseline HBI Scores	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.23	Extent	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.24	Severity	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded
4.25	Baseline MAYO scores	FAS	4	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort	Excluded

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
5.1	Healthcare resource utilization (ie, hospitalizations, ER visits, and outpatient visits including general practitioner and gastroenterologist)	FAS	5	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Generalized Linear Mixed Models	Stratified by disease subcohort, comorbidity, disease severity	Excluded/ Imputation as applicable
5.2	HCRU-related costs	FAS	5	Disease Cohorts, Disease Subcohorts	Descriptive statistics, Generalized Linear Mixed Models	Stratified by disease subcohort, comorbidity, disease severity	Excluded/ Imputation as applicable
C [redacted] CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C [redacted] CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ID: Table Shell	Outcome(s)	Analysis Set	Supports Protocol Objective Number	Sub-Groups	Statistical Methods	Covariates/Strata	Missing Data
7	Adverse Events Reporting	SAS	NA	Disease Cohorts, Disease Subcohorts	Descriptive statistics	Stratified by disease subcohort, severity	Excluded

9. LIST OF TABLES AND TABLE SHELLS

List of Tables for Reporting

Objective 1: To describe drug utilization patterns and treatment adherence in adult UC and CD cohorts treated with INFLECTRA in a real-world setting.

Table 1.1 INFLECTRA Treatment Characteristics Among All Patients at Each Visit
Table 1.2 INFLECTRA Treatment Characteristics Among All UC and All CD Patients at Each Visit
Table 1.3 INFLECTRA Treatment Characteristics Among New Inflectra Patients at Each Visit
Table 1.4 INFLECTRA Treatment Characteristics Among Inflectra after Remicade Patients at Each Visit
Table 1.5 INFLECTRA Treatment Characteristics Among Inflectra after Other Biologics Patients at Each Visit

Objective 2: To describe real world clinical and economic outcomes in adult UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.

Table 2.1.1 Clinical Lab Outcomes Among All Patients at Each Visit
Table 2.1.2 Clinical Lab Outcomes Among All UC and All CD Patients at Each Visit
Table 2.1.3 Clinical Lab Outcomes Among New Inflectra Patients at Each Visit
Table 2.1.4 Clinical Lab Outcomes Among Inflectra after Remicade Patients at Each Visit
Table 2.1.5 Clinical Lab Outcomes Among Inflectra after Other Biologics Patients at Each Visit
Table 2.2.1 Clinical Lab Outcomes Among All UC Patients at Each Visit
Table 2.2.2 Clinical Lab Outcomes Among New Inflectra Patients at Each Visit
Table 2.2.3 Clinical Lab Outcomes Among Inflectra after Remicade Patients at Each Visit

Table 2.2.4 Clinical Lab Outcomes Among Inflectra after Other Biologics Patients at Each Visit
Table 2.3.1 Clinical Lab Outcomes Among All UC Patients at Each Visit
Table 2.3.2 Clinical Lab Outcomes Among New Inflectra Patients at Each Visit
Table 2.3.3 Clinical Lab Outcomes Among Inflectra after Remicade Patients at Each Visit
Table 2.3.4 Clinical Lab Outcomes Among Inflectra after Other Biologics Patients at Each Visit

Objective 3: To describe real world patient reported quality of life in both the UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic

Table 3.1.1 Patient-Reported QOL Outcomes Among All Patients at Each Visit
Table 3.1.2 Patient-Reported QOL Outcomes Among All UC and All CD Patients at Each Visit
Table 3.1.3 Patient-Reported QOL Outcomes Among New Inflectra Patients at Each Visit
Table 3.1.4 Patient-Reported QOL Outcomes Among Inflectra after Remicade Patients at Each Visit
Table 3.1.5 Patient-Reported QOL Outcomes Among Inflectra after Other Biologics Patients at Each Visit
Table 3.2.1 Patient-Reported Productivity Among All Patients at Each Visit
Table 3.2.2 Patient-Reported Productivity Among All UC and All CD Patients at Each Visit
Table 3.2.3 Patient-Reported Productivity Among New Inflectra Patients at Each Visit
Table 3.2.4 Patient-Reported Productivity Among Inflectra after Remicade Patients at Each Visit
Table 3.2.5 Patient-Reported Productivity Among Inflectra after Other Biologics Patients at Each Visit
Table 3.3.1 Patient-Reported Treatment Satisfaction Among All Patients at Each Visit
Table 3.3.2 Patient-Reported Treatment Satisfaction Among All UC and All CD Patients at Each Visit
Table 3.3.3 Patient-Reported Treatment Satisfaction Among New Inflectra Patients at Each Visit
Table 3.3.4 Patient-Reported Treatment Satisfaction Among Inflectra after Remicade Patients at Each Visit
Table 3.3.5 Patient-Reported Treatment Satisfaction Among Inflectra after Other Biologics Patients at Each Visit

Objective 4: To describe the demographic and clinical characteristics of patients receiving INFLECTRA for the treatment of UC and CD.

Table 4.1 Patient Demographic Characteristics, by Subgroups
Table 4.2 Patient UC/CD Diagnosis, by Subgroups
Table 4.3 Disease Characteristic (Montreal Classification) of CD Patients, by CD subgroups

Table 4.4 Disease Characteristic (Montreal Classification) of UC Patients, by UC subgroups
Table 4.5 Disease Related Medication Characteristics, by subgroups
Table 4.6 Disease-Related Surgeries, by Subgroups

Objective 5: To describe healthcare resource utilization and direct costs in adult patients receiving INFLECTRA for the treatment of UC or CD.

Table 5.1.1 Resource Utilization Among All Patients at Each Visit
Table 5.1.2 Resource Utilization Among All UC and All CD Patients at Each Visit
Table 5.1.3 Resource Utilization Among New Inflectra Patients at Each Visit
Table 5.1.4 Resource Utilization Among Inflectra after Remicade Patients at Each Visit
Table 5.1.5 Resource Utilization Among Inflectra after Other Biologics Patients at Each Visit
Table 5.2.1 Resource Utilization Among All Patients at Each Visit
Table 5.2.2 Resource Utilization Among All UC and All CD Patients at Each Visit
Table 5.2.3 Resource Utilization Among New Inflectra Patients at Each Visit
Table 5.2.4 Resource Utilization Among Inflectra after Remicade Patients at Each Visit
Table 5.2.5 Resource Utilization Among Inflectra after Other Biologics Patients at Each Visit

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11. APPENDICES

11.1. APPENDIX 1: DATA DERIVATION DETAILS

N/A.

11.1.1. A1.1 Definition and Use of Visit Windows in Reporting

Table 8 Definition of Visit Dates and Timing

Visit Label	Endpoint	Definition [Day window]
Visit 1	All	= Day 0 (±14days) from first dose of INFLECTRA
Visit 2	All	= Day 90 (±30days) from first dose of INFLECTRA
Visit 3	All	= Day 180 (±30days) from first dose of INFLECTRA
Visit 4	All	= Day 365 (±30days) from first dose of INFLECTRA

11.1.2. A1.2 Further Definition of Endpoints

11.2. APPENDIX 2: Additional Statistical Methodology Details

Please see table shells in the Excel workbook that correspond with the described analyses.

11.2.1. A2.1 Further Details of the Statistical Methods

N/A.