NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS information

Title	Observational, real-world study of INFLECTRA in patients with inflammatory bowel disease (IBD) in the United States and Canada
Protocol number	C1231006
Version identifier of the final study report	1.0
Date	15 December 2020
EU Post Authorization Study (PAS) register number	EUPAS22444
Active substance	ATC: L04AB02
Medicinal product	INFLECTRA (infliximab-dyyb*) * infliximab-dyyb is the international nonproprietary name (INN) assigned by the US FDA and is used throughout this report to identify INFLECTRA in patients from the U.S and Canada.
Product reference	USA BLA 125544; Canada DIN 024194831
Procedure number	Not applicable
Marketing Authorization Holder (MAH)	Pfizer Inc. 235 E 42nd Street New York, NY 10017
Joint PASS	No
Research question and objectives	The primary objective of this study is: 1. To describe drug utilization patterns, treatment adherence and associated costs

	in adult UC and CD cohorts treated with infliximab-dyyb in a real-world setting. The secondary objectives of this study are: 2. To describe real-world clinical and economic outcomes in adult UC and CD cohorts who initiated therapy with infliximab-dyyb as their first biologic, switched to infliximab-dyyb from reference product infliximab (RP infliximab) or, switched to infliximab-dyyb from another biologic. 3. To describe real-world patient-reported quality of life in both the UC and CD cohorts who initiated therapy with infliximab-dyyb as their first biologic, switched to infliximab-dyyb from RP infliximab or, switched to infliximab-dyyb from another biologic 4. To describe the demographic and clinical characteristics of patients receiving infliximab-dyyb for the treatment of UC and CD 5. To describe healthcare resource utilization and indirect costs in adult patients receiving infliximab-dyyb for the treatment of UC or CD The tertiary objective of this study is: 6. To describe the psychosocial burden of patients receiving infliximab-dyyb for the treatment of UC and CD
Countries of study	USA and Canada
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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
ANOVA	Analysis of variance
CCI	Charlson comorbidity index
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRF	Case report form
CRP	C-reactive protein
CPI	Consumer price index
ED	Emergency department
EMEA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
FCP	Fecal calprotectin
FDA	Food and Drug Administration
IBD	Inflammatory bowel disease
NIS	Non-interventional study
PASS	Post-Authorization Safety Study
pMAYO	partial MAYO score
SAE	Serious Adverse event
SIBDQ	Short inflammatory bowel disease questionnaire
TNF-α	Tumor necrosis factor-alpha
TSQM	Treatment Satisfaction Questionnaire for Medication
UC	Ulcerative Colitis
VAS	Visual Analog Scale
WPAI	Work Productivity and Activity Impairment

3. INVESTIGATORS

Name, degree(s)	Title	Affiliation
Arif Soonasra, PharmD	Senior Medical Director, Biosimilars, NI Study Lead	Pfizer, Inc.

Lead Country Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Ahmed Shelbaya *Pfizer*	HEOR
Edie Owens *Pfizer*	Project Manager
Rosemarie Ciccarelli *Pfizer*	Study Manager
Richard Chambers *Pfizer*	Statistician
Jennifer Stephens *Pharmerit International*	Pharmerit HEOR Project Director
Hrishikesh Kale *Pharmerit International*	Pharmerit Senior Scientist
Chris Atzinger *Pharmerit International*	Pharmerit Study Lead
Dipen Patel *Pharmerit International*	Pharmerit HEOR Project Director
Elyse Skenderian *Pharmerit International*	Senior Clinical Research Associate
Patrick Edmundson *Pharmerit International*	Senior Clinical Research Associate

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol		28 November 2017	No planned date.
Start of data collection	01 February 2018	23 February 2018	
End of data collection	30 Jun 2019	07 February 2020	
Registration in the EU PAS register	29 January 2018	29 January 2018	
Final report of study results	7 January 2021	15 December 2020	

6. RATIONALE AND BACKGROUND

REMICADE® (infliximab) is a 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, the first infliximab 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 reference product, REMICADE® (RP 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 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 CT-P13 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 CT-P13 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 conducted a prospective, nationwide, multicenter observational cohort study of 210 consecutively enrolled patients with IBD (n=126 UC, n=84 UC) initiating treatment with CT-P13 (7). 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 RP infliximab [$p < 0.05$]. 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 conducted a prospective observational cohort study of 83 patients with IBD (57 CD, 24 UC, 2 IBD-Undefined) (11). 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 µ g/ml [range 0–18] to 4.2 µ g/ml [range 0–21] at week 16 [$p = 0.010$]. Two patients developed a new detectable anti-drug antibody response during follow-up and 5 patients discontinued CT-P13. 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 RP infliximab or switch to CT-P13. A total of 482 patients enrolled (241 to RP 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 RP 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 RP infliximab vs 21 [9%] for CT-P13. The NOR-SWITCH trial showed that switching from RP infliximab to CT-P13 was not inferior to continued treatment with RP infliximab.

In April 2016, INFLECTRA (infliximab-dyyb) 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, little is known about the real-world use of infliximab-dyyb and associated outcomes in the US population. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

Note: Although Infliximab-dyyb is the international nonproprietary name assigned by the U.S. FDA, for the purpose of this report it refers to INFLECTRA used by patients from the U.S and Canada.

7. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study was to collect and analyze data in adult patients with IBD (CD and UC) treated with infliximab-dyyb in a real-world setting. The priority of primary, secondary, and tertiary objectives changed through discussions with study investigators during data collection and analysis. Study investigators learned that data collected for objectives two, three, and six were of greater relevance to enrolling physicians. Thus, the results and discussion sections highlight results related to those objectives in greater priority than reflected in the original objectives list.

The primary objective of this study was:

1. To describe drug utilization patterns, treatment adherence and associated costs in adult UC and CD cohorts treated with infliximab-dyyb in a real-world setting.

The secondary objectives of this study were:

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

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

4. To describe the demographic and clinical characteristics of patients receiving infliximab-dyyb for the treatment of UC and CD

5. To describe healthcare resource utilization and indirect costs in adult patients receiving infliximab-dyyb for the treatment of UC or CD

The tertiary objective of this study was:

6. To describe the psychosocial burden of patients receiving infliximab-dyyb for the treatment of UC and CD

8. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	18-Oct-2017	Administrative	Study Information and Study Design	Psychosocial burden assessment objective changed to tertiary. Increased maximum patient enrollment from 225 to 300. Removed instability on current biologic as exclusionary criterion. Added Canada as a participating country.	External consultant and internal Pfizer study team clarified objective priorities
2	25-Jan-2018	Substantial	Study Information, Responsible Parties, Abstract, Milestones, Rationale and Background, and Research Methods	Voluntary PASS designation. Additional textual clarification.	Internal Pfizer process reviewers designated this study as PASS
3	26-Aug-2020	Administrative	Study size	Reason for change in recruitment strategy in 2019 was provided	Decision to stop study enrollment due to slow recruitment

9. RESEARCH METHODS

9.1. Study design

This was a prospective, observational study performed in 24 sites across the US and Canada. Adult (≥18 years) patients initiating treatment with infliximab-dyyb (an infliximab biosimilar) for IBD (CD or UC) were recruited between February 2018 and February 2019. Recruited subjects included IBD patients with no previous biologics use (biological naïve users), IBD patients switching from RP infliximab, and IBD patients switching from other biologics. Enrolled subjects were followed prospectively for 12 months after initiating infliximab-dyyb treatment.

A geographically dispersed group of physicians in the United States and Canada recruited subjects for this study (Figure 1). Due to this being an observational study the decision to treat a patient with infliximab-dyyb was made prior to enrollment in this study. Recruited physicians and/or their assigned staff were responsible for patient identification, qualification and selection, patient interview, exam recording, data abstraction, and completion of the patient case report form (CRF).

At baseline (the time of initiating infliximab-dyyb treatment), after obtaining informed consent, patient characteristics, clinical characteristics, prior procedures, and treatment characteristics were recorded (Table 1). During follow-up, data collection included the following: laboratory data; clinical outcomes (Harvey-Bradshaw Index [HBI] for CD and Partial Mayo Score [pMAYO] for UC); patient-reported outcomes (PROs); healthcare resource utilization (HCRU); healthcare costs; and adverse events.

Table 1 provides a detailed list of the outcomes of interest. There were no protocol required medical procedures for this study. Lab tests were not required, but if recent test results are available, they were provided in the CRF.

9.2. Setting

24 centers were recruited to conduct the C1231006 protocol in cities across the United States (US) and Canada. The distribution of these facilities is pictured in Figure 1. Among 24 centers that agreed to participate in C1231006, 15 provided patient data. 11 centers provided patient data in the US and 4 centers in Canada.

Figure 1 C1231006 Study Sites

9.2.1. Study Dates

IRB approval was received on the 28th of November 2017. Subject enrollment occurred between the 23rd of February 2018 and the 27th of February 2019. Data was collected until the last patient's last visit occurred on the 7th of February 2020.

9.2.2. Events marking the end of follow-up

Patients were followed until their last visit, which occurred between 11-13 months after their baseline visit, or lost to follow-up.

9.3. Subjects

9.3.1. Physician (Site Investigator) Selection

The following section provides an overview of the physician or site investigator (SI) inclusion and exclusion criteria. For a full description, please refer to the study protocol.

In each country, a geographically dispersed sample of gastroenterologists were screened based on pre-defined eligibility criteria and recruited from a list of gastroenterologists in each country. These physicians were asked to complete a self-administered survey questionnaire to describe the types of patients within their practice. These physicians (and/or their assigned staff) were responsible for abstracting clinical data from patient records.

Physician inclusion and exclusion criteria are described below:

Physician Inclusion Criteria:

- Certified to practice in their respective country
- Must agree to study rules including resolution of data queries including missing data
- Routinely uses standard lab testing to monitor patient health
- Access to certified laboratory for basic lab testing
- Available medical records and proper documentation for patients

Physician Exclusion Criteria:

- Unwilling or unable to follow study procedures
- Unwilling to prescribe biosimilars

9.3.2. Study Population

The following section provides an overview of patient inclusion and exclusion criteria. For a full description, please refer to the study protocol.

This was an observational study; therefore, the decision to treat a patient with infliximab-dyyb was made prior to a decision to enroll them in this study. Patients were eligible to participate if they had:

- initiated therapy with infliximab-dyyb as their first biologic;
- switched to infliximab-dyyb while in remission on a stable dose of RP infliximab; or,
- switched to infliximab-dyyb from another biologic, due to non-responsiveness, intolerance, or other reasons.

Patient inclusion criteria:

- 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 infliximab-dyyb for the treatment of their disease per approved drug label (patients with fistula, or stoma were eligible)

Patient exclusion criteria:

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

Variables

Table 1 provides a detailed list of the outcomes of interest and the timing of measurement and analysis

Table 1 Outcome Variables and Timing of Events

	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4
Variables	Day 0	Day 90 (±30 days)	Day 180 (±30 days)	Day 365 (±30 days)
Informed Consent	X			
Demographic/Clinical Characteristics	X			
- Demographics (age, sex, BMI, race/ethnicity)	X			
- Insurance Status	X			
- Smoking Status	X			
- Charlson Comorbidity Index	X			
- IBD Type (UC or CD)	X			
- Duration of disease	X			
Montreal Classification				
- pMAYO (UC cohort) or HBI (CD cohort) score	X	X	X	X
- Montreal Classification	X			
Prior Procedures				
- Proportion of patients who received disease-related surgery	X			
- Number of surgeries per patient	X			
- Reason for surgery	X			
Treatment Characteristics				
- Initiation (at baseline or follow-up visit) and reason	X			
- Dose and frequency (starting and at follow-up)	X	X	X	X
- Discontinuation of treatment and reason	X	X	X	X
Laboratory Outcomes				

- C-reactive protein (mg/L)	X	X	X	X
- Fecal calprotectin (µg/g)	X	X	X	X
- Drug level value (µg/mL)	X	X	X	X
- Anti-drug antibody value (µg/mL)	X	X	X	X
Clinical Outcomes				
- UC cohort: pMAYO score, response to treatment (reduction of pMAYO of ≥3 points from baseline) and remission (pMAYO < 3)	X	X	X	X
- CD cohort: HBI score, response to treatment (reduction of HBI of ≥3 points from baseline) and remission (HBI < 5)	X	X	X	X
Patient-reported Outcomes				
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)	X	X	X	X
- EuroQol-visual analogue scale (EQ-VAS)	X	X	X	X
- Work Productivity and Activity Impairment (WPAI)	X	X	X	X
- Treatment Satisfaction Questionnaire for Medication (TSQM)	X	X	X	X
- General Anxiety Disorder-7 (GAD-7)	X	X	X	X
- Patient Health Questionnaire Depression Scale (PHQ-8)	X	X	X	X
HCRU				
- Hospitalizations (any hospitalization, number of hospitalizations, total length of stay, average length of stay, presence of an IBD related admission, and presence of an IBD related admission within patients with an admission)	X	X	X	X
- Emergency Department (ED) visits (any ED visit, total number of ED visits, total number of IBD-related ED visits, and total number of other ED visits)	X	X	X	X
- Outpatient visits (any outpatient visit, mean number of outpatient visits, GP/internist visits, gastroenterologist visits, or other outpatient visits)	X	X	X	X
Healthcare Costs				
- Overall costs (IBD-related inpatient costs, IBD-related medical costs, IBD-related surgical costs, and general medical costs)	X	X	X	X
- Emergency room (ER) costs (IBD-related ER costs, general ER costs, total ER costs)	X	X	X	X
- Outpatient visit costs (general practitioner visit costs, gastroenterologist visit costs, other	X	X	X	X

outpatient visit costs, and total outpatient visit costs)				
Adverse Events (AE)				
- Patient level summary (proportion of patients with any AE, proportion of patients with any serious AE, and proportion of patients who died)				
- Event level summary (severity of AE, presence of a serious AE, relationship of AE to study treatment, action taken with study treatment among patients with an AE, and outcome of AE among patients with an AE)	X	X	X	X
- Frequency of AEs related to or unrelated to AE treatment. AE categories assessed were: cardiac, gastrointestinal, general, hepatotoxicity, hypersensitivity reaction, immunogenicity, infusion reaction, lack of response, lupus-like syndrome, malignancy, musculoskeletal system disorders, other, bleeding and clotting, respiratory, serious infection, and skin appendages disorders)	X	X	X	X

9.3.3. Baseline Demographic/Clinical Characteristics

Demographic/Clinical Characteristics

Patient demographics (age, gender, and race/ethnicity) were recorded at baseline. BMI was calculated according to the formula: (Weight in Kilograms/[Height in Meters x Height in Meters]) OR (Weight in Pounds/[Height in inches x Height in inches]) x 703. The frequency of enrollment in health plans (by type and network type) as of the baseline visit was also recorded. Clinical characteristics assessed during the baseline visit included smoking status (current smoker, never smoker, past smoker, or unknown), Charlson Comorbidity Index (mean score and frequency of scoring 0, 1, 2, or 3+), IBD type (CD or UC), and duration of disease (defined by subtracting the year of trial enrollment by the year of first IBD diagnosis).

Montreal Classification

The Montreal classification of inflammatory bowel diseases (Montreal Classification) was applied to both the UC and CD cohorts at baseline to define IBD severity and subtype at baseline. Montreal Classification reports pMAYO score in UC patients and HBI score in CD patients. Montreal Classification also defines UC subtypes according to the extent (ulcerative proctitis, left sided UC, or extensive UC) and severity (remission, mild, moderate, or severe). Montreal Classification defines CD subtypes according to age at diagnosis (below 16 years of age, between 17 and 40 years of age, or above 40 years of age), location (ileal, colonic, ileocolonic, or isolated upper disease), and behavior (non-stricturing, non-penetrating; structuring; or penetrating).

Prior Procedures

Patient history of IBD-related procedures were assessed at baseline. The number of prior surgeries (1 or 2 or more), as well as the reason for surgery (management of IBD, management of side effects/adverse experiences related to IBD, or unknown) were recorded.

Treatment Characteristics at Baseline

Patient initiation of infliximab-dyyb was recorded. The reason for starting or switching to infliximab-dyyb treatment was defined by the SI as one of the following reasons: different class or different mode/mechanism of action; improved efficacy; new drug availability; payer/formulary decision; reimbursement, insurance, or out-of-pocket costs; target therapy; or other. Infliximab-dyyb starting dose and frequency of treatment at baseline visit were recorded.

9.3.4. Clinical Outcomes

Treatment Characteristics During Follow-up

Average infliximab-dyyb dose and number of infusions per visit were recorded at each follow-up visit. For patients who discontinued treatment, the reason for discontinuation of treatment was defined by the SI as one of the following: loss of response, the occurrence of an adverse event or serious adverse event, patient decision, positive for antibodies, or other.

Laboratory Outcomes

Lab tests were not required, but if recent test results were available, they were provided in the CRF. At baseline and during the follow-up period, patient c-reactive protein (mg/L), fecal calprotectin (µg/g), drug level value (µg/mL), and anti-drug antibody value (µg/mL) were recorded.

Clinical Outcomes

Disease activity was measured by the pMAYO for UC patients and HBI for CD patients. Response to treatment was defined as a reduction in pMAYO or HBI of ⩾3 points for the UC and CD patient populations, respectively. Remission was defined in UC patients as any pMAYO under 3 and in CD patients as any HBI score under 5.

9.3.5. Patient-reported Outcomes

PROs were assessed by the SI at baseline and follow-up visits. The Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was used to measure IBD-specific physical, social, and emotional health-related quality of life and was scored from 10 (poor quality of life) to 70 (good quality of life). The EuroQol-visual analogue scale (EQ-VAS) was administered to describe the overall quality of life and was scored from 0 (poor quality of life) to 100 (good quality of life). The Work Productivity and Activity Impairment (WPAI) survey was used to measure impact of health problems on ability to work and perform regular activities and higher scores indicate greater impairment and less productivity. The Treatment Satisfaction Questionnaire for Medication (TSQM) was administered to determine patients' satisfaction

with treatment effectiveness, side effects, and convenience and was scored from 0 (poor satisfaction) to 100 (good satisfaction). The General Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire Depression Scale (PHQ-8) were also administered to evaluate patient mental health quality of life. The GAD-7 was scored from 0 (no anxiety) to 21 (severe anxiety) and the PHQ-8 was scored from 0 (no depression) to 24 (severe depression).

9.3.6. Healthcare Resource Use and Costs

Healthcare Resource Use (HCRU)

HCRU was monitored based on in-patient hospitalization visits, ED visits, and gastroenterology or general practitioner outpatient visits, which were assessed at baseline and each follow-up visit by SI review of patient medical chart. In-patient hospitalization HCRU metrics assessed were: any hospitalization, number of hospitalizations, total length of stay, average length of stay, presence of an IBD related admission. ED visit HCRU metrics assessed were: any ED visit, total number of ED visits, total number of IBD-related ED visits, and total number of other ED visits. Finally, gastroenterology or general practitioner outpatient visit metrics assessed were: any outpatient visit, mean number of outpatient visits, GP/internist visits, gastroenterologist visits, or other outpatient visits.

Costs

Direct healthcare costs were calculated by multiplying number of resources used by unit costs identified from the literature. Costs were assessed at baseline and at each follow-up visit. Unit costs derived from the literature are listed in Table 2. Overall direct costs assessed were: IBD-related inpatient costs, IBD-related medical costs, IBD-related surgical costs, and general medical costs. ER direct costs assessed were: IBD-related ER costs, general ER costs, total ER costs. Outpatient costs assessed were: general practitioner visit costs, gastroenterologist visit costs, other outpatient visit costs, and total outpatient visit costs. All costs were inflated to 2019 USD using medical component of consumer price index (CPI).

Table 2 Unit Cost Inputs Used for Calculation of Healthcare Costs.

Type	UC (US $)	Reference	CD (US $)	Reference
Hospitalization				
IBD-related medical	12,182	HCUPnet (15)	11,039	HCUPnet (15)
IBD-related surgical	8,093	Buchanan et al. (16)	10,731	Tang et al. (17)
general medical	11,715	HCUPnet (15)	11,715	HCUPnet (15)
general surgical	20,191	HCUP report (18)	20,191	HCUP report (19)
ER visit				
general	1,016	MEPS summary tables (20)	1,016	MEPS summary tables (20)
IBD-related	4,057	Ballau et al (21)	4,469	Ballau et al (21)
Outpatient visits				

General practitioner	110	CMS Physician Fee Schedule (22)	110	CMS Physician Fee Schedule (22)
Gastroenterologist	148	CMS Physician Fee Schedule (22)	148	CMS Physician Fee Schedule (22)
Other	110	CMS Physician Fee Schedule (22)	110	CMS Physician Fee Schedule (22)

9.3.7. Adverse Events

An AE was defined as any untoward medical occurrence in a patient administered a medicinal product. A SAE was defined as any untoward medical occurrence in a patient that: results in death; was life-threatening; required inpatient hospitalization or prolongation of hospitalization; resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); or, resulted in congenital anomaly/birth defect. Adverse Events (AE) and Serious Adverse Events (SAE) were monitored from each patient's first infusion of infliximab-dyyb until their last follow-up visit.

Site investigators recorded AE's and SAE's as defined above, and in alignment with common AE's described in the 2016 FDA Product Label and the 2018 Health Canada Label (23, 24). A complete description of the AE and SAE definitions and documentation procedures is available in the study protocol (Appendix 2).

Patient and event level summaries were created using endpoints that were collected for each AE or SAE. The end points collected for each AE and SAE are detailed in Table 3.

Table 3 Adverse Event Endpoints

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

Attribution	Patient medical chart	Definite; Possible; Probable; Unlikely; Unrelated

AE's were reported in a dichotomous manner as related to or unrelated to study treatment. AE's were considered to be related to treatment when site investigators defined the AE's attribution to be 'Definitely', Possible', or 'Probable' attributable to study intervention. AE's were considered to be unrelated to treatment when site investigators defined the AE's attribution to be 'Unlikely' or 'Unrelated' to study intervention.

9.4. Data Sources and Measurement

Detailed methods of collection and measurement on each variable are available in the study protocol (Appendix 2) and a statistical analysis plan (SAP; Appendix 4).

9.4.1. Data Sources

Patient interviews and chart review was performed by site physicians and/or their assigned staff. Recruited physicians and/or their assigned staff were responsible for patient identification, qualification and selection, patient interview, exam taking, chart review, and completion of the patient CRF.

Physicians and/or site staff were 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 was de-identified and reported in aggregate. Patient clinical data was abstracted from the patient's medical chart, or in the case of the patient-reported outcome measures, from the assessment tools themselves, which serve as the source document. No other source documents were used.

9.4.2. Data Management and Quality Assurance

This non-interventional retrospective study utilized the direct involvement of physicians acting as the SIs with the responsibility of patient selection, chart data abstraction and data validation/resolution. This responsibility and direct involvement enhances data quality through minimization of inaccurate, missing or incomplete data and data misinterpretation that may occur in such studies.

During the data collection period, data submitted on the study CRFs was submitted to quality control checking. Missing or contradictory data was flagged for follow-up directly with SIs. Quality control consisted of the following:

- Patient inclusion criteria were met.
- No conflicting data/information was reported. This includes the flow/sequence of dates, interconnected questions, the validity of treatment regimens, and dosing.
- Open-ended responses / unaided responses were in-line with question specifics.

Data review incorporated the assessment of each variable regarding outliers or inconsistencies. Marginals, frequency distributions, and logic checks were examined to determine number of responses for each question for identification of outliers.

Data verification of key data points (e.g., date of diagnosis, initial and most recent treatments received) was conducted on 30% of the total patient sample and validated against the source document (for example, patient medical charts).

9.5. Bias

Though efforts were made to ensure physician/patient inclusion/exclusion criteria were based on random selection, there were, nevertheless, risks of selection bias.

Treatment patterns and outcomes measured within this study represented only the practices of physicians who agreed to participate in this study, and may vary from non-responding physicians, i.e., those who refused study participation, or failed to complete the study requirements on time and were excluded from the study, or who were unresponsive to the screening invitation. Not all patient characteristics were included in the data collection (e.g., income and other variables which may influence physician-prescribing behavior or treatment decisions) and cannot be accounted for in the statistical analyses.

Information collected on the physician survey included best estimates of patients' treatment patterns. Although physicians sought to record all patient experiences through examination and review of the medical charts, there may have been some undercounting of events that are unknown to physicians, which may have occurred outside the office and were therefore under-represented. This may also refer to AEs. It has to be expected that not all non-serious AEs were documented in patient charts. Furthermore, information regarding hospitalizations, ER visits, or any associated HCRU may or may not have been documented within the chart. Given this, HCRU in particular may be underestimated. In addition, the study did not collect cost data, therefore unit costs from the literature were used to estimate healthcare costs. Therefore, our cost estimates are based on average costs at the population level and did not consider patient-level variability. Cost estimates are also subject to accuracy of the original source used to identify unit cost.

9.6. Study Size

A detailed methodology of sample size estimation is documented in the SAP (Appendix 4). C1231006 was initiated with a minimum sample size of 139, however, due to a protracted enrollment period, the recruitment of patients was stopped at 118 patients. 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 2 patients that ended up not receiving INFLECTRA and 1 patient due to not meeting inclusion criteria. 115 patients completed baseline (visit 1), 109 completed 3-month (visit 2), 99 completed 6-month (visit 3) and 84 completed 12-month visit.

9.7. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the SAP (Appendix 4).

9.8. Statistical methods

9.8.1. Main summary measures

Summary statistics were used to describe baseline patient demographic and clinical characteristics. Outcomes were summarized at each visit. All binary and categorical variables were summarized using both the number and percentage in each category (e.g. sex, race, insurance status). Demographic (e.g., age, weight, height) and clinical characteristics (e.g. lab values), and other continuous variables were summarized using the mean, standard deviation, median, inter-quartile range, range, number of subjects in the analysis set used.

9.8.2. Main statistical methods

Baseline demographic and clinical characteristics between biological naïve, patients switching from RP infliximab and switching from other biologics were compared using chi-square test or Fisher's exact test (in case of small sample size) for categorical variables (e.g. gender). ANOVA or Wilcoxon rank sum test was used to compare continuous variables (e.g. BMI).

Changes in outcomes over time from baseline were calculated using a mixed model for repeated measures (MMRM) for continuous outcomes (e.g. VAS score) and a generalized estimating equations (GEE) for categorical outcomes (e.g. employment – yes vs no) accounting for repeated nature of the data. Changes in resource use (e.g. hospital admissions) were calculated using GEE with negative binomial distribution and log link, whereas changes in costs were assessed using a gamma distribution and log link. Considering the overall sample size of the data, all analytical models were bivariate in nature, which included specific outcome of interest as a dependent variable and study visit as independent variable. All analyses were conducted at an α level of 0.05 using SAS v9.4. (SAS Institute Inc., Cary, NC, USA.)

9.8.3. Missing values

Due to study design considerations, our study was limited to data available in patient medical records. Note that missing data was rare due to the ability to query back to sites. Any missing or illegible data resulted in contacting the sites directly to validate the missing data against the patient's medical charts. All descriptive analysis was based on the observed values, no imputation was performed. No other imputation was performed for missing values.

9.8.4. Sensitivity analyses

None

9.8.5. Amendments to the statistical analysis plan

None

9.9. Quality control

Data validations include 30% of completed CRFs being randomly selected to have predetermined key data points validated directly with participating physicians against the source document, and 100% machine checks, reporting of the proportion of missing data at the item/individual variable level, examination of frequencies and distributions, as well as the generation of descriptive statistics.

Additionally, to ensure programming quality and accuracy, the following steps were taken:

- Methodology review: all methodology, from sample selection to variable calculation, was discussed and reviewed at the time of SAP drafting.
- Variable creation: all proposed variable definitions were reviewed by the principal SAS programmer and a senior statistician or scientist
- Statistical review: statistical methods were reviewed by a Pharmerit senior statistician as well as the Pharmerit SAS statistical programmer, project manager, and senior scientific leader.
- Output review: SAS output was initially reviewed by the SAS programmer for logic and reasonability. Output was then reviewed by the project manager and senior scientific leader. Additional reports were run by the SAS programmer, as needed, to ensure validation of SAS output. Patient counts will be verified for consistency with the expected counts when defining the cohort.

9.10. Protection of human subjects

Subject Information and Consent

Written informed consent (Appendix 6) was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by a local data protection agency for each site participating in the study.

Ethical Conduct of the Study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, management and reporting of adverse events/adverse reactions.

10. RESULTS

1.0. Results Summary

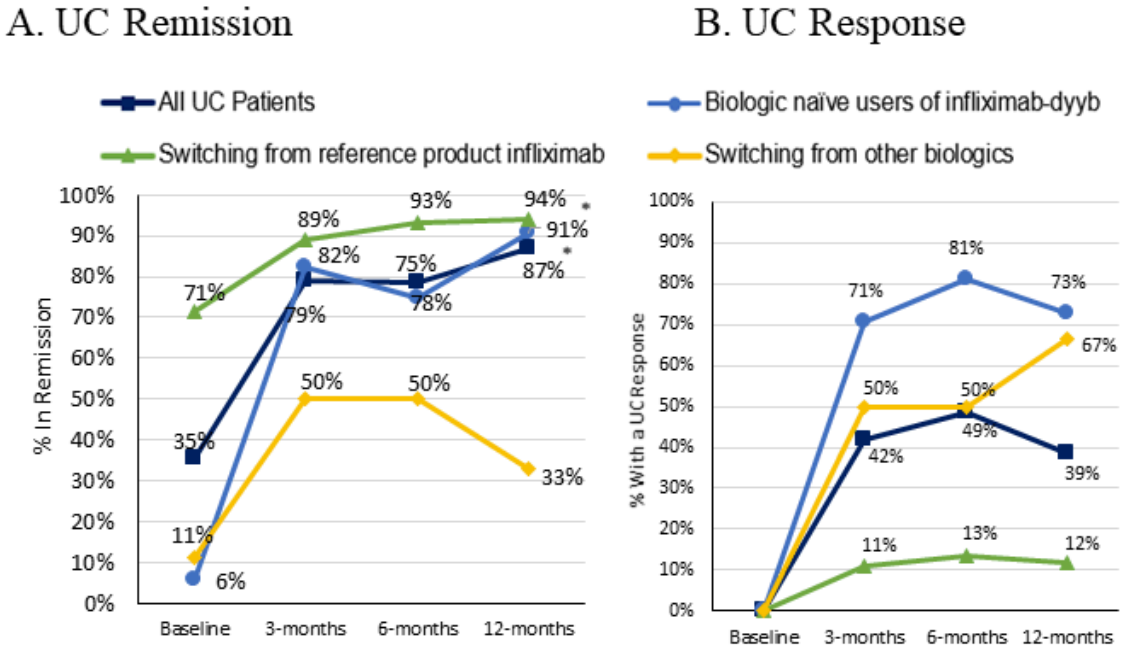
From February 2018 to February 2020, 115 IBD patients (67 CD and 48 UC) initiated infliximab-dyyb treatment and were followed for 12 months. 115 patients completed baseline (visit 1), 109 completed 3-month (visit 2), 99 completed 6-month (visit 3) and 84 completed 12-month visit. Of 115, 39 subjects were biological naïve, 57 subjects were switched from RP infliximab, and 19 subjects were switched from other biologics. Patient demographics are summarized in 10.3.1 and Table 9. In subjects switching from RP infliximab, the majority (80.4%) of subjects' reason for infliximab-dyyb treatment initiation was 'reimbursement, insurance, or out of pocket costs. In biological naïve subjects, the most frequent reasons for infliximab-dyyb treatment initiation was targeted therapy (64.1%), improved efficacy (15.4%), and new drug availability (12.8%). For detailed patient demographic and baseline clinical data and patient treatment characteristics, please refer to results section 10.3 and Table 9-Table 13.

10.1.1. Clinical Results Summary

UC patients were assessed for clinical remission at baseline and follow-up (defined as pMAYO score <3; Figure 2). At baseline, 35% of enrolled UC patients were classified as in remission. At 12-months follow-up, 87% of enrolled UC patients were classified as in remission ($p<0.0001$). In UC subjects that were biological naïve at baseline, 5.6% were classified as in remission. This proportion increased significantly at 12-months follow-up to 90.9% ($p=0.0015$). UC subjects switched from RP infliximab maintained rate of remission from 71.4% at baseline to 94.1% after 12-months follow-up ($p=0.1007$).

UC patients were also assessed for a clinical response to treatment (defined as pMAYO score improvement of 3 or more). Response to treatment occurred in 72.7% of biological naïve UC subjects and in 11.8% of UC subjects switched from RP infliximab at 12-months follow-up. Further detail on UC patients clinical results are available in results section 10.5.2 and Table 15.

Figure 2. Proportion of UC Patients in Clinical Remission and Proportion of UC Patients Exhibiting a Response to Treatment at Baseline and Follow-up

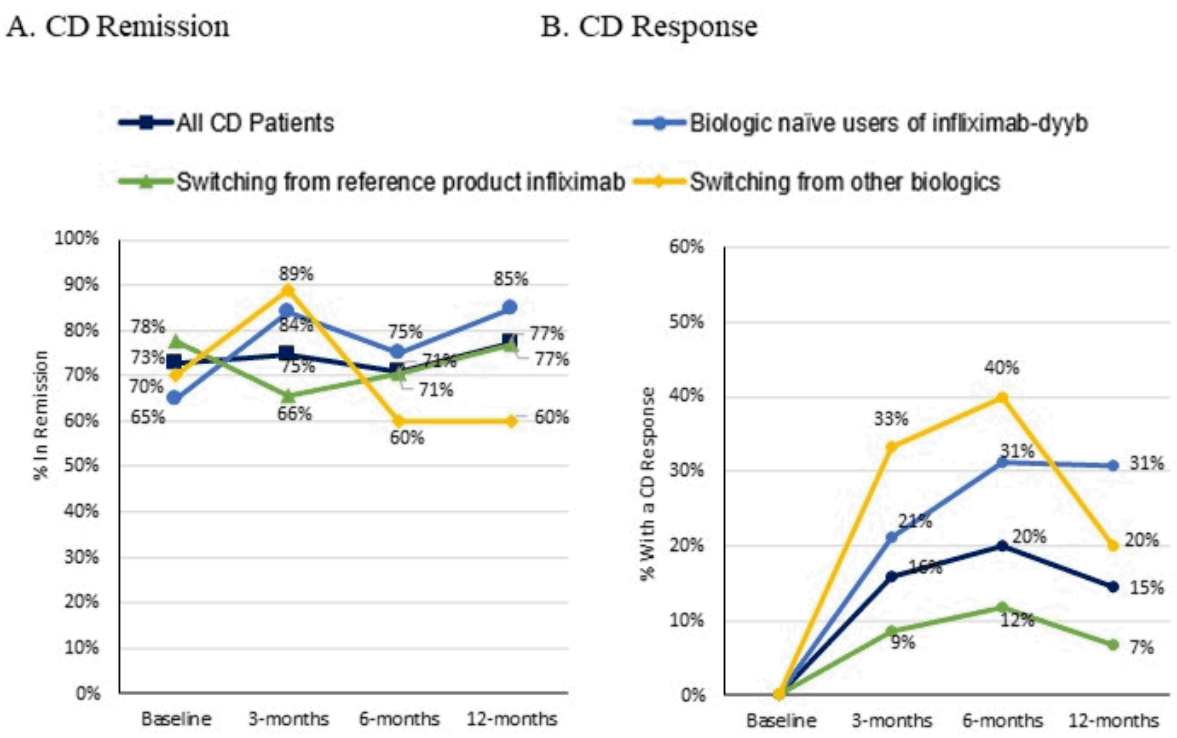


* suggest statistically significant p-value calculated from generalized estimating equations (GEE);
Abbreviations: UC=Ulcerative colitis

73.0% of enrolled CD patients were classified as in remission at baseline (defined as HBI score <5; Figure 3). After 12-months of infliximab-dyyb treatment, 77.7% of CD patients were classified as in remission (p=0.8011). In CD patients switched from RP infliximab, remission rate was maintained over the duration of the study from baseline rate of 77.8% to 12-month remission rate of 76.7% (p=0.1077).

30.8% of biological naïve users and 6.7% of switchers from RP infliximab demonstrated a clinical response to treatment (defined as HBI score improvement of 3 or more). Results section 10.5.3 and Table 16 contain more detail on CD patients' clinical results.

Figure 3 Proportion of CD Patients in Clinical Remission and Proportion of CD Patients Exhibiting a Response to Treatment at Baseline and Follow-up



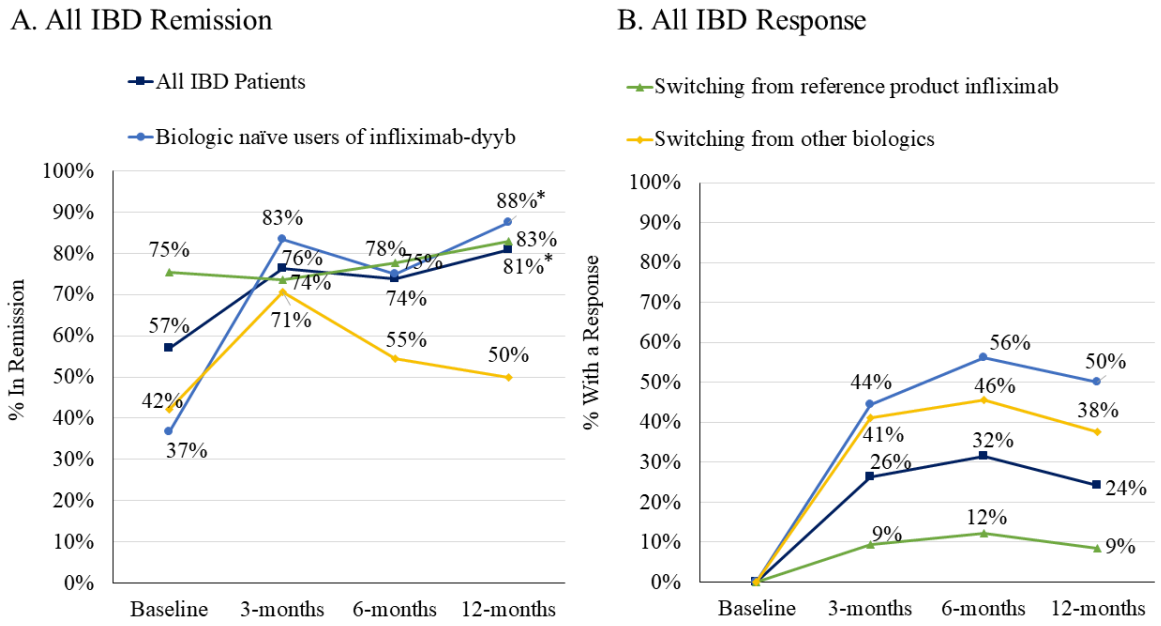
Abbreviations: CD=Crohn's disease

In the cohort of all enrolled patients, 57% of enrolled IBD patients were classified as in remission at baseline (either HBI score <5 or pMAYO score <3; Figure 4). After 12-months, 81% of all patients were classified as in remission (p<0.001). In all IBD patients switched from RP infliximab, remission rate was maintained over the duration of the study from baseline rate of 75% to 12-month remission rate of 83% (p=0.368). In all IBD patients that were biological naïve prior to enrollment, proportion in remission increased from 37% of patients at baseline to 88% at 12-month follow-up (p<0.001).

24% of all enrolled subjects demonstrated a clinical response to treatment after 12-months (p=0.801). 50% of biological naïve users of infliximab-dyyb demonstrated a clinical response (p=0.501).

It is important to note that a large proportion of CD patients were in remission at the baseline (HBI score <5). As a result, proportion of CD patients with response (reduction in score by ≥3 points) is low because patients have low scores at the beginning of the study. This was also the case for UC patients switching from RP infliximab as nearly 71% were in remission at the beginning of the study.

Figure 4 Proportion of All IBD Patients in Clinical Remission and Proportion of All Patients Exhibiting a Response to Treatment at Baseline and Follow-up



Abbreviations: IBD=Irritable Bowel Disease

10.1.2. Patient-reported Outcomes Results Summary

Patient-reported outcomes improved significantly from baseline to 12-month follow-up in nearly all questionnaires administered to enrolled patients (N=115). SIBDQ, EQ-VAS, all domains of WPAI, the effectiveness domain of TSQM, GAD-7, and PHQ-8 scores significantly improved from baseline to 12-months follow-up. All instruments' higher scores reflect better quality of life except in the WPAI, GAD-7, and PHQ-9 where lower scores reflect better quality of life. Patient-reported outcomes results for all patients are summarized in Table 4. Patient-reported outcomes results for each patient group and outcome measure are available in results section 10.5.4-10.5.8 and Table 17-Table 21.

Table 4 Patient-reported Outcomes Results at Baseline and Follow-up in IBD Patients Administered Infliximab-dyyb

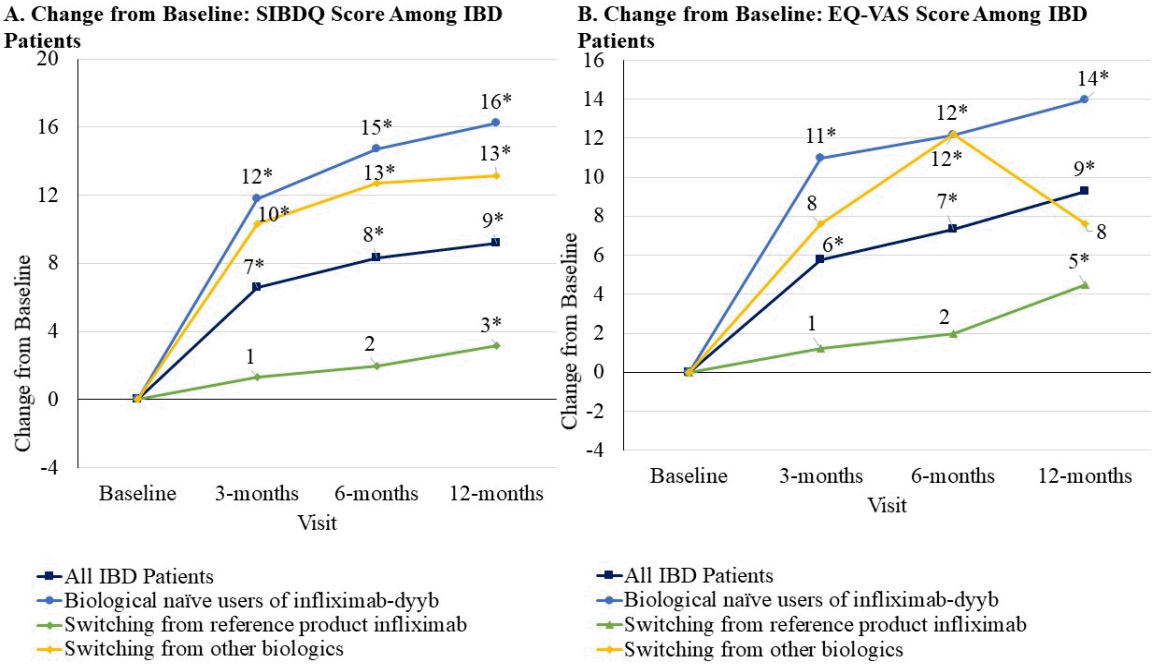
		Baseline (N = 115)	3 months (N = 109)	6 months (N = 99)	12 months (N = 84)	P value
Health-Related Quality of Life						
SIBDQ	Mean	43.77	50.41	52.75	54.47	<.0001
	(SD)	(14.13)	(11.82)	(10.91)	(11.06)	

EQ-VAS score	Mean (SD)	73.11 (19.38)	78.83 (16.90)	81.56 (14.82)	83.79 (14.55)	<.0001
Work Productivity						
Absenteeism score %	Mean (SD)	12.39 (25.53)	4.33 (14.93)	3.84 (13.68)	2.23 (9.30)	0.0059
Presenteeism score %	Mean (SD)	31.38 (30.97)	20.44 (26.68)	15.34 (23.74)	10.68 (19.55)	<.0001
Overall work impairment score %	Mean (SD)	35.34 (32.53)	22.08 (27.74)	18.82 (26.67)	11.78 (21.03)	<.0001
Daily activity impairment score %	Mean (SD)	37.70 (31.62)	26.98 (27.99)	20.16 (25.19)	15.63 (25.60)	<.0001
Treatment Satisfaction						
TSQM effectiveness	Mean (SD)	63.94 (26.00)	68.69 (26.65)	72.25 (25.35)	76.56 (25.44)	0.0035
TSQM side effects	Mean (SD)	74.88 (26.11)	78.75 (25.03)	81.51 (20.17)	84.54 (19.11)	0.0523
TSQM convenience	Mean (SD)	75.19 (18.88)	77.67 (16.84)	78.55 (16.54)	77.61 (15.20)	0.3524
Psychological Outcomes						
GAD-7 score	Mean (SD)	5.37 (5.32)	4.14 (4.60)	3.84 (4.53)	3.14 (3.69)	0.0005
PHQ-8 score	Mean (SD)	7.82 (6.29)	5.70 (5.14)	4.74 (4.43)	3.90 (4.08)	<.0001

P-Value was obtained from Mixed model for repeated measures (MMRM)
Abbreviations: IBD=Inflammatory bowel disease; SIBDQ=Short Inflammatory Bowel Disease; EQ-VAS=EuroQol-visual analogue scale Questionnaire; WPAI= Work Productivity and Activity; TSQM= Treatment Satisfaction Questionnaire for Medication; GAD-7=General Anxiety Disorder-7; PHQ-8=Patient Health Questionnaire Depression Scale

Results from MMRM model indicating change from baseline for SIBDQ and VAS at each visit is represented in Figure 5. Significant improvements were observed in SIBDQ scores from baseline to 12-month in each cohort (all $p<0.05$). EQ-VAS scores improved in the cohort of all enrolled patients (9 point improvement; $p<0.001$), in biological naïve users (14 point improvement; $p=0.002$), and in switchers from RP infliximab (5 point improvement; $p=0.010$).

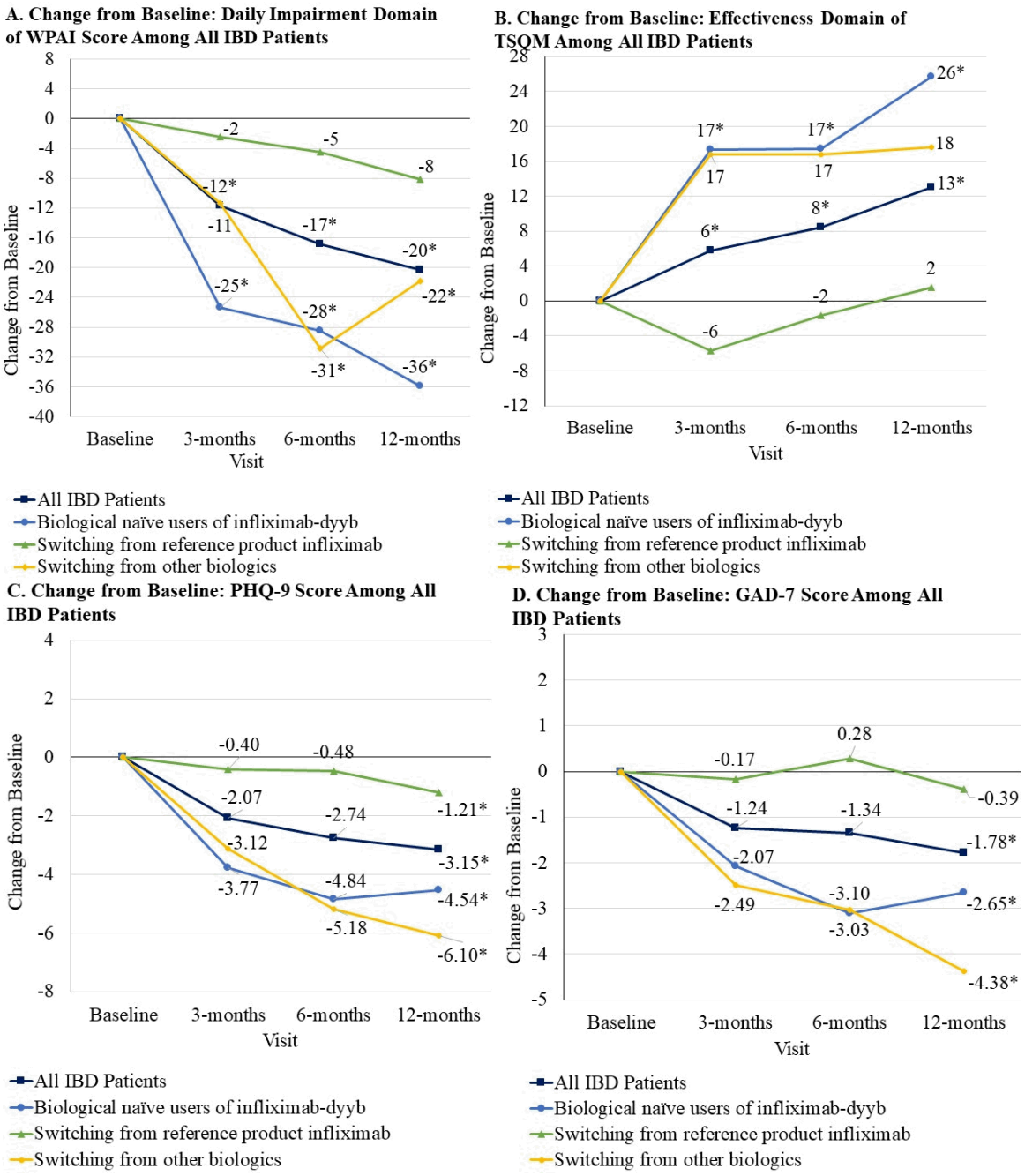
Figure 5 Change from Baseline: SIBDQ and EQ-VAS score



* suggest statistically significant ($p<0.05$) change from Mixed model for repeated measures (MMRM);
Abbreviations: IBD=Inflammatory bowel disease; SIBDQ=Short Inflammatory Bowel Disease Questionnaire; EQ-VAS=EuroQol-visual analogue scale

Results from MMRM model indicating change from baseline for the daily impairment domain of the WPAI, the effectiveness domain of the TSQM, PHQ-9, and GAD-7 at each visit is represented in Figure 6. From baseline to 12 months, IBD-related impairment in daily activities, measured by the WPAI, decreased significantly in the cohort of all patients, in biological naïve users, and in subjects switched from other biologics (all $p<0.05$). Patient-perceived treatment effectiveness, measured by the TSQM, also improved significantly in the cohort of all patients and in biological naïve users (both $p<0.001$). Patient-perceived treatment effectiveness was maintained from baseline to 12 months in patients switched from RP infliximab ($p=0.706$). PHQ-9 scores improved significantly from baseline to 12 months in each patient group (all $p<0.05$). GAD-7 also improved significantly from baseline to 12 months in the cohort of all subjects, in biological naïve users, and in subjects switched from other biologics (all $p<0.05$).

Figure 6 Change from Baseline: Daily Impairment (WPAI), Effectiveness (TSQM), PHQ-9, GAD-7



* suggest statistically significant ($p<0.05$) change from Mixed model for repeated measures (MMRM);
Abbreviations: IBD=Inflammatory bowel disease; SIBDQ=Short Inflammatory Bowel Disease Questionnaire; EQ-VAS=EuroQol-visual analogue scale

10.1.3. HCRU and Cost Results Summary

Results from HCRU for the entire study cohort is reported in Table 5. About 11.3% of patients recorded a hospitalization within the baseline observation period. 3.6% of patients recorded a hospitalization within the 12-month observation period. 10.4% of patients recorded an ED visit within the baseline period and 3.6% recorded an ED visit during the 12-month observation period. More detailed HCRU data within each treatment group is reported in results section 10.5.9-10.5.11 and in Table 22-Table 24.

Table 5 HCRU at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb

		Baseline (N = 115)	3 months (N = 109)	6 months (N = 99)	12 months (N = 84)	P-Value
Hospitalizations						
Mean number of hospitalizations	Mean (SD)	0.13 (0.39)	0.09 (0.37)	0.03 (0.17)	0.05 (0.26)	0.0366
Presence of an IBD related admission among patients with at least one hospitalization	N (%)	11 (84.6%)	6 (85.7%)	1 (33.3%)	1 (33.3%)	0.2551
ED Visits						
Patients with at least one ED visit	N (%)	12 (10.4%)	8 (7.3%)	3 (3.0%)	3 (3.6%)	0.0884
Total number of ED visits	Mean (SD)	0.11 (0.34)	0.14 (0.66)	0.03 (0.17)	0.08 (0.44)	0.0523
Outpatient Visits						
Patients with at least one outpatient visit	N (%)	54 (47.0%)	76 (69.7%)	57 (57.6%)	58 (69.0%)	0.0006
Mean number of outpatient visits	Mean (SD)	1.44 (3.45)	1.41 (1.36)	1.13 (1.51)	1.55 (1.66)	0.1674
Mean number of gastroenterologist visits	Mean (SD)	0.78 (1.67)	0.61 (0.71)	0.52 (0.75)	0.69 (0.78)	0.2836

P-Value: Generalized estimating equations (GEE); Abbreviations: HCRU=Healthcare Resource Utilization; IBD=Inflammatory bowel disease; GP=General Practitioner;

Table 6 shows the direct healthcare costs, calculated by multiplying number of resources used by unit costs identified from the literature, in all study patients. Further data, including direct costs in each patient switch group, is available in results section 10.5.12-10.5.14 and Table 25-Table 27.

Table 6 Healthcare Costs at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb

	Baseline US $, Mean (SD)	3 months US $, Mean (SD)	6 months US $, Mean (SD)	12 months US $, Mean (SD)	P-Value
	(N = 115)	(N = 109)	(N = 99)	(N = 84)	

Inpatient Costs					
IBD-related inpatient costs	1280.92 (4088.05)	899.63 (3997.72)	139.08 (1383.86)	152.59 (1398.52)	N/A
Total inpatient costs	1609.41 (4765.41)	1227.26 (5204.50)	499.80 (2958.75)	365.16 (1982.92)	N/A
Emergency Room (ER) Costs					
IBD related ER costs	339.56 (1248.83)	507.74 (3097.55)	0.00 (0.00)	152.29 (828.46)	N/A
Total ER costs	385.88 (1263.08)	546.84 (3128.55)	32.28 (183.55)	164.98 (887.48)	N/A
Outpatient Costs					
Gastroenterologist visit costs	115.64 (247.39)	89.47 (104.52)	76.12 (110.42)	51.01 (57.31)	0.0008 [A]
Total outpatient visit costs	201.88 (474.75)	187.79 (180.94)	155.05 (207.41)	104.08 (110.12)	0.0002 [A]

P-Value: A=Generalized estimating equations (GEE); N/A=not available because statistical model did not converge due to small sample size and since vast majority of patients had zero costs.
Abbreviations: IBD=Inflammatory bowel disease; ER=Emergency Room

10.1.4. Adverse Events Results Summary

31 patients in total (27%) did not reach a 12-month follow-up. 6 subjects discontinued due to an adverse event, 1 discontinued due to lack of efficacy, 17 were lost to follow-up, 3 subjects chose to withdraw, and 4 subjects discontinued for other reasons. The 6 AEs which caused study withdrawal were: 1 development of anti-drug antibodies, 1 case of community-acquired pneumonia, 1 hypersensitivity reaction, 1 liver abscess, 1 drug-induced lupus, and 1 psoriasiform dermatitis and joint pain.

59 AE's were reported in 40 (40/115; 34.8%) patients. The majority of AE's were mild to moderate in intensity. The most frequently reported AE's considered by the investigators to be related to the study treatment were: gastrointestinal disorders (n=8; 6.95%); infusion reaction (n=4; 3.5%); platelet, bleeding and clotting disorders (n=2; 1.72%); and hypersensitivity reactions (n=2; 1.72%; Table 7). Similar rates of AEs were reported between treatment groups, regardless of their switch groups. No deaths were reported during the study. Please see results section 10.7, Table 28 to Table 30, and Figure 8 and Figure 9 for more information on AEs.

Table 7 Adverse Events in IBD Patients Treated with Infliximab-dyyb: Frequency of Adverse Events Related to Treatment

	Infliximab-dyyb (n=115)
Average weeks of follow-up	52
Gastrointestinal Disorders	8 (36.364%)
General Disorders	1 (4.545%)
Hypersensitivity Reaction	2 (9.091%)

Immunogenicity	1 (4.545%)
Infusion reaction	4 (18.182%)
Lupus-like syndrome	1 (4.545%)
Musculoskeletal System Disorders	1 (4.545%)
Platelet, Bleeding and Clotting Disorders	2 (9.091%)
Respiratory	1 (4.545%)
Serious infection	1 (4.545%)

10.2. Participants

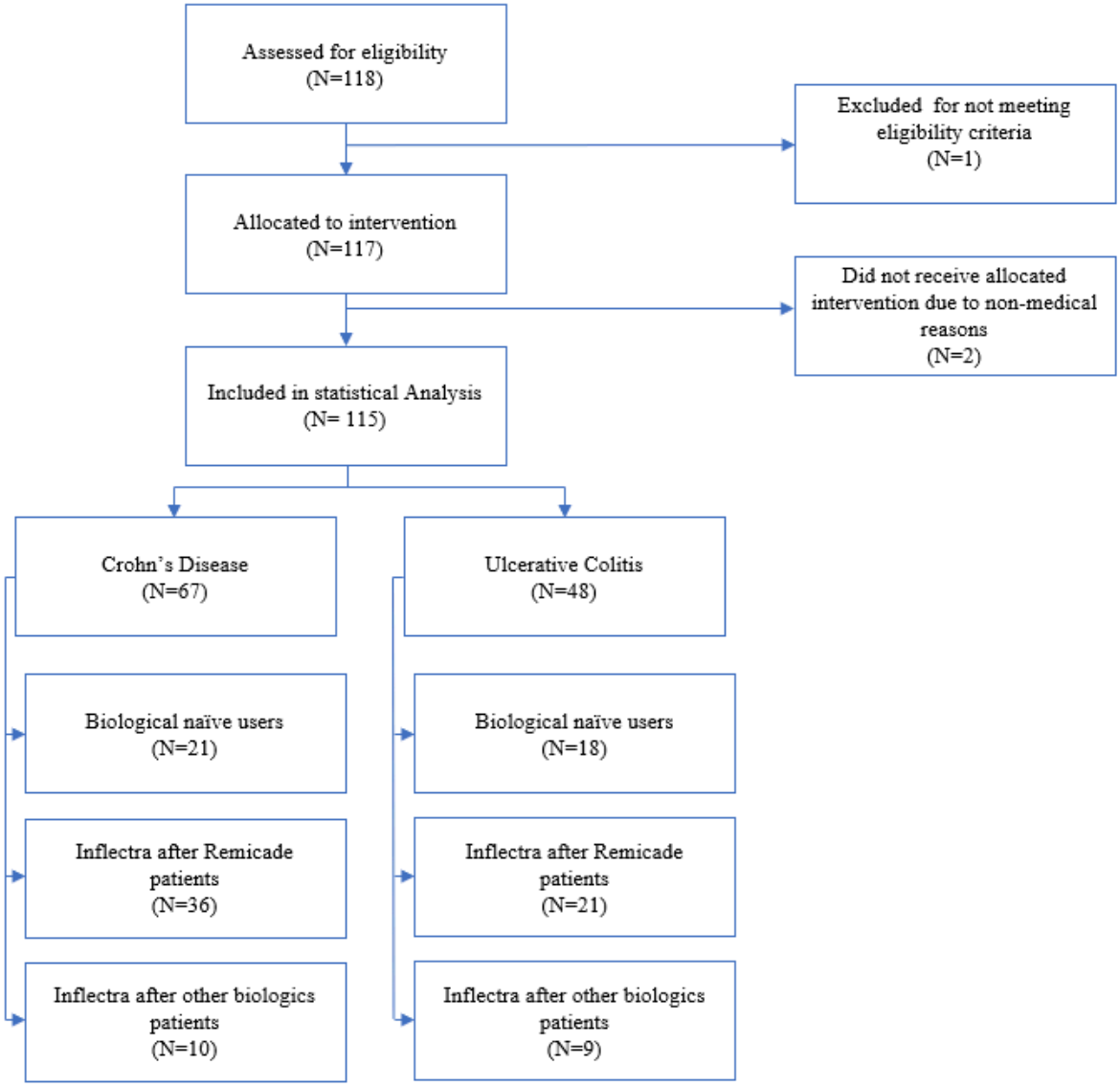


Figure 7 Selection of Sample and Patient Disposition Flowchart

10.2.1. Selection of Sample and Patient Disposition

A total of 118 subjects were screened for eligibility from the period of February 2018 – February 2019. Deviations from the study protocol occurred in three patients. For one patient, the enrolling nurse misread the patient's diagnosis of 'panniculitis' as 'pancolitis'. Also, two separate enrolled patients were prescribed infliximab-dyyb, but were administered RP infliximab due to being switched by the pharmacists at their respective infusion centers. All three patients were subsequently disenrolled from the study.

115 were allocated to treatment, met the full study inclusion criteria, and were enrolled in the study. A total of 67 patients received infliximab-dyyb for CD and 48 patients received infliximab-dyyb for UC. Figure 7 shows the sample selection and detailed disposition of patients enrolled into the study.

Of 115 subjects enrolled at baseline, 84 completed follow-up to 12 months. 6 subjects discontinued due to an adverse event, 1 discontinued due to lack of efficacy, 17 were lost to follow-up, 3 subjects chose to withdraw, and 4 subjects discontinued for other reasons.

10.3. Descriptive data

10.3.1. Demographic Characteristics of IBD Patients Treated with Infliximab-dyyb

Table 9 presents the baseline characteristics of the total sample enrolled into the study (N=115) as well as biological naïve users (N=39), patients switched from RP infliximab (N=57), and patients switched from other biologics (N=19).

The majority were female (51.3%; 59/115). The average age was 44.25 years. The average BMI was 27.86. The largest subgroup of Race/Ethnicity was White or Caucasian American (87.0%; 100/115) followed by Black or African America (7.0%; 8/115), Asian (2.6%; 3/115), and Hispanic or Latino (2.6%; 3/115). HMO plans were the most common insurance type (40.0%) followed by PPO (22.6%), Medicare/Medicaid (21.7%), and Canada Medicare (13.9%). In terms of smoker status, 51.3% of patients had no history of smoking, 30.4% of patients had previous smoking history, 11.3% of patients were active smokers, and smoking status was unknown in 7.0% of patients. The mean CCI was 0.30. About 87.8% of patients had a CCI of 0. 67 (58.3%) patients had CD and 48 (41.7%) patients had UC. Mean duration of disease was 8.24 years.

There were statistically significant differences in BMI and insurance status between patients switching to infliximab-dyyb. Mean (SD) BMI in biological naïve users was 25.99 which was significantly lower than other patients switching to infliximab-dyyb (p=0.034). The frequency of PPO insurance plans was 46.2% in biological naïve users, which was significantly higher than patients switching to infliximab-dyyb (p<0.001).

10.3.2. Montreal Classification of CD Patients Treated with Infliximab-dyyb

Table 10 summarizes the clinical characteristics of enrolled patients with CD according to the Montreal Classification of inflammatory bowel diseases.

The mean (SD) baseline HBI score was 3.56 (2.98). Age of onset was most frequently during ages 17-40 years (52.2%; 35/67) followed by over 40 years (25.4%; 17/67), 16 years or younger (11.9% 8/67), and unknown (10.4%; 7/67). L1 terminal ileum and L2 colon were tied for the most common location (both 32.8%;) followed by L3 ileocolon (26.9%), unknown (6.0%), and L4 upper GI (1.5%). Disease behavior was most frequently unknown (41.8%) followed by B1 non-stricturing, non-penetrating (29.9%); B2 stricturing (16.4%); B3 penetrating (7.5%); and P perianal (4.5%).

10.3.3. Montreal Classification of UC Patients Treated with Infliximab-dyyb

Table 11 summarizes the clinical characteristics of enrolled patients with UC according to the Montreal Classification of inflammatory bowel diseases.

The average baseline pMAYO score was 3.85. E3 extensive UC was the most common extent of UC (58.3%; 28/48) followed by E2 left-sided UC (27.1%; 13/48), E1 ulcerative proctitis (10.4%; 5/48), and Unknown (4.2%; 2/48). Frequency of baseline severity of UC patients were, in order of severity: S0 UC in clinical remission (8.3%), S1 mild UC (16.7%), S2 moderate UC (29.2%), S3 severe UC (29.2%), and unknown (16.7%).

Baseline pMAYO was greater in biological naïve and switched from other biologics users. Mean (SD) baseline pMAYO was 5.67 (2.25) in biological naïve users, 6.00 (2.65) in users switched from other biologics, and 1.38 (1.83) in users switched from RP infliximab ($p<0.001$).

10.3.4. Disease-Related Surgical History of IBD Patients Treated with Infliximab-dyyb

Table 12 summarizes the disease-related surgical history of enrolled patients. Overall, approximately one-fifth (20.9%; 24/115) of subjects reported having received an IBD-related surgery. Of subjects who had received an IBD-related surgery, 79.2% received one surgery and 20.8% received two surgeries. Management of side effects/adverse experiences related to IBD was the most common reason for surgery (54.2%) followed by management of IBD (37.5%) and unknown reason (8.3%). There were no significant differences in disease-related surgical history between patient groups.

10.3.5. Treatment Characteristics at Baseline of IBD Patients Treated with Infliximab-dyyb

Table 13 describes the baseline treatment characteristics of study patients. All patients except for 1 initiated infliximab-dyyb at baseline visit who initiated shortly afterward. The reason for treatment initiation varied between patient groups ($p<0.001$). The most frequent reasons for biological naïve patients to initiate infliximab-dyyb were: 64.1% for targeted therapy, 15.4% for improved efficacy, and 12.8% for new drug availability. In users switched from RP infliximab, however, the most frequent reasons for initiating infliximab-dyyb were: 80.4% reimbursement, insurance, or out-of-pocket costs and 10.7% for new drug availability. Mean (SD) starting infliximab-dyyb dose at baseline was 513.65 (233.65). Treatment frequency during the baseline period was most once every 8 weeks in 57.9% of patients.

10.4. Outcome data

115 subjects were included in the analysis. The following is a description of the numbers of subjects across categories of outcomes:

- Clinical Outcomes: 114 of 115 subjects were included in the primary analysis of clinical outcomes. One CD subject was not administered the HBI at baseline and could not be included in the primary analysis.

- Patient-reported Outcomes: 115 of 115 subjects were included in the analysis of patient-reported outcomes.
- HCRU and Cost Outcomes: 115 of 115 subjects were included in the analysis of HCRU and cost outcomes.
- Adverse Events: 115 of 115 subjects were included in the analysis of adverse events.

10.5. Main results

10.5.1. Laboratory Outcomes at Baseline and Follow-Up in IBD Patients Treated with Infliximab-dyyb

Laboratory outcomes were recorded at baseline and throughout a 12-month follow-up for a limited number of patients. Because this was a non-interventional study, results were only available in patients who received these tests as standard of care. These outcomes are available in Table 14.

10.5.2. Clinical Outcomes at Baseline and Follow-up in UC Patients Treated with Infliximab-dyyb

Table 15 summarizes clinical outcomes in UC patients from baseline to 12-month follow-up. Of 48 patients with UC, 31 (64.6%) completed 12-month follow-up clinical outcomes tests.

All UC Patients

In UC patients, pMAYO score improved significantly throughout the intervention from a mean (SD) of 3.85 (3.05) at baseline to 1.44 (1.94) at a 3-month follow-up and 0.90 (1.47) at 12-month follow-up ($p<0.0001$). 35.4% of UC patients were defined as in remission at baseline. This clinical measure improved to 79.1% of UC patients being defined as in remission at a 3-month follow-up and 87.1% at 12-month follow-up ($p<0.0001$). UC response to treatment, measured as a reduction of >3 points from baseline, was recorded in 41.9% of UC patients after 3 months of treatment, 48.6% of patients after 6 months of treatment, and 38.7% of patients after 12 months of treatment ($p=0.9792$).

Biological Naïve users

Among the subgroup of UC patients who were biological naïve, pMAYO score improved significantly over the course of the intervention from a mean (SD) of 5.67 (2.25) at baseline to 1.41 (1.42) at 3-month follow-up and 1.09 (1.22) at 12-month follow-up ($p<0.0001$). 5.6% of UC patients who were biological naïve were defined as in remission at baseline. This clinical measure improved to 82.4% of UC patients who were biological naïve being defined as in remission at a 3-month follow-up and 90.9% at 12-month follow-up ($p=0.0015$). UC response to treatment, measured as a reduction of >3 points from baseline, was recorded in 70.6% of UC patients who were biological naïve after 3 months of treatment, 81.3% of

patients after 6 months of treatment, and 72.7% of patients after 12 months of treatment (p=0.7079).

Patients Switched from RP Infliximab

Among the subgroup of UC patients switched from RP infliximab, pMAYO score did not change significantly over the course of the intervention from a mean (SD) of 1.38 (1.83) at baseline to 0.56 (1.20) at 3-month follow-up and to 0.29 (0.85) at 12-month follow-up (p=0.0103). 71.4% of UC patients switched from RP infliximab were defined as in remission at baseline. This clinical measure did not change significantly to 88.9% of UC patients switched from RP infliximab being defined as in remission at 3-month follow-up and 94.1% at 12-month follow-up (p=0.1007). UC response to treatment, measured as a reduction of >3 points from baseline, was recorded in 11.1% of UC patients who were switched from RP infliximab after 3 months of treatment, 13.3% of patients after 6 months of treatment, and 11.8% of patients after 12 months of treatment (p=0.4724).

Patients Switched from Other Biologics

Among the subgroup of UC patients switched from other biologics, pMAYO score did not change significantly over the course of the intervention from a mean (SD) of 6.00 (2.65) at baseline to 3.50 (2.78) at 3-month follow-up and to 3.67 (1.94) at 12-month follow-up (p=0.0697). 11.1% of UC patients switched from other biologics were defined as in remission at baseline. This clinical measure did not change significantly to 50.0% of UC patients switched from other biologics being defined as in remission at 3-month follow-up and 33.3% at 12-month follow-up (p=0.1723). UC response to treatment, measured as a reduction of >3 points from baseline, was recorded in 50.0% of UC patients who were switched from other biologics after 3 months of treatment, 50.0% of patients after 6 months of treatment, and 66.7% of patients after 12 months of treatment (p=0.4371).

10.5.3. Clinical Outcomes at Baseline and Follow-up in CD Patients Treated with Infliximab-dyyb

Table 16 summarizes clinical outcomes in CD patients from baseline to 12-month follow-up. Of 66 patients with UC, 48 (71.6%) completed 12-month follow-up clinical outcomes tests.

All UC Patients

During the follow-up period, HBI scores were maintained in the cohort of all CD patients. Mean (SD) HBI scores were 3.45 (3.04) at baseline, 3.11 (3.27) at 3-months follow-up, and 2.98 (2.61) at 12-month follow-up (p=0.3988). A high proportion of CD patients were in remission at baseline (72.7%) and this was maintained at 3-months (74.6%) and 12-month (77.1%) follow-up (p=0.8011). A clinical response to treatment, as measured by the HBI, was seen in 15.9% of CD patients after 3-months, 20.0% of CD patients after 6-months, and 14.6% of CD patients after 12-months (p=0.5068).

Biological Naïve users

Throughout the study, HBI scores did not change significantly in biological naïve users. Mean (SD) HBI scores were 4.30 (3.92) at baseline, 3.16 (4.46) at 3-months follow-up, and 2.23 (3.30) at 12-month follow-up (p=0.1650). A high proportion of biological naïve CD patients were in remission at baseline (65.0%) and this was maintained at 3-months (84.2%) and 12-month (84.6%) follow-up (p=0.1619). A clinical response to treatment, as measured by the HBI, was seen in 21.1% of biological naïve CD patients after 3-months, 31.3% after 6-months, and 30.8% after 12-month (p=0.4277).

Patients Switched from RP Infliximab

Throughout the study, HBI scores did not change significantly in patients switched from RP infliximab. Mean (SD) HBI scores were 3.00 (2.66) at baseline, 3.37 (2.73) at 3-months follow-up, and 3.07 (1.98) at 12-month follow-up (p=0.3822). A high proportion of CD patients switched from RP infliximab were in remission at baseline (77.8%) and this was maintained at 3-months (65.7%) and 12-month (76.7%) follow-up (p=0.1077). A clinical response to treatment, as measured by the HBI, was seen in 8.6% of CD patients switched from RP infliximab after 3-months, 11.8% after 6-months, and 6.7% after 12-months (p=0.4036).

Patients Switched from Other Biologics

Throughout the study, HBI scores did not change significantly in patients switched from other biologics. Mean (SD) HBI scores were 3.40 (2.12) at baseline, 2.00 (2.12) at 3-months follow-up, and 4.40 (3.78) at 12-month follow-up (p=N/A). A high proportion of CD patients switched from other biologics were in remission at baseline (70.0%) and this was maintained at 3-months (88.9%) and 12-month (60.0%) follow-up (p=0.2381). A clinical response to treatment, as measured by the HBI, was seen in 33.3% of CD patients switched from other biologics after 3-months follow-up, 40.0% after 6-months, and 20.0% after 12-months (p=0.6065).

10.5.4. Patient-Reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Table 17 summarizes patient changes in SIBDQ from baseline to 12 months follow-up.

In the entire study population, the SIBDQ score improved significantly from mean (SD) of 43.77 (14.13) at baseline to 50.41 (11.82) at 3-months follow-up, 52.75 (10.91) at 6-months follow-up, and 54.47 (11.06) at 12-months follow-up (p<0.0001). The biological naïve user subpopulation also showed significant improvement in SIBDQ. Biological naïve users' baseline SIBDQ scores of 39.85 (14.20) improved to 51.49 (13.09) at 3-months follow-up, 54.76 (10.30) at 6-months follow-up, and 57.80 (9.76) at 12-months follow-up (p<0.0001). In patients that switched from RP infliximab, SIBDQ was maintained from a baseline score of 49.16 (12.16) to 51.06 (10.13) at 3-months follow-up, 52.02 (11.31) at 6-months follow-up, and 54.36 (11.35) at 12-months follow-up (p=0.1348). Patients switched from other biologics SIBDQ score improved significantly from a baseline score of 35.63 (13.55) to 46.00 (13.58)

at 3-months follow-up, 50.33 (10.85) at 6-months follow-up, and 45.78 (8.79) at 12-months follow-up (p=0.0043).

10.5.5. Patient-Reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: EuroQol-visual analogue scale (EQ-VAS)

Table 18 reports EQ-VAS scores throughout the study.

In the 'all patients' study population, EQ-VAS scores improved over 10 points throughout the 12-month study from a mean (SD) baseline score of 73.11 (19.38) to 78.83 (16.90) at 3-months follow-up and 83.79 (14.55) at 12-months follow-up (p<0.001). EQ-VAS score improved to a greater degree in the biological naïve user subpopulation from 68.05 (20.71) at baseline to 78.54 (18.49) at 3-months follow-up and 85.36 (13.30) at 12-months follow-up (p=0.0135). EQ-VAS score was maintained in patients switched from RP infliximab from a mean baseline score of 78.49 (16.74) to 80.13 (17.02) at 3-months follow-up and 84.77 (12.79) at 12-months follow-up (p=0.0675). No significant change in EQ-VAS was observed in patients switched from other biologics with mean baseline scores of 67.37 (20.51), 3-month scores of 75.35 (12.81), and 12-months scores of 74.33 (23.05; p=0.1686).

10.5.6. Patient-Reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Treatment Satisfaction Questionnaire for Medication (TSQM)

Patient satisfaction with infliximab-dyyb, as measured by the TSQM, is reported in Table 19.

All UC Patients

The study cohort, consisting of patients initiating infliximab-dyyb for IBD, reported satisfaction with infliximab-dyyb's effectiveness. Patient satisfaction with infliximab-dyyb's effectiveness improved in the entire study population from a mean (SD) baseline score of 63.94 (26.00) to 76.56 (25.44) at 12-months follow-up (p=0.0035). Patient satisfaction with infliximab-dyyb's side effects did not change significantly from mean baseline scores of 74.88 (26.11) to 84.54 (19.11) at 12-months follow-up (p=0.0523). Similarly, patient satisfaction with infliximab-dyyb's convenience did not change significantly from a mean baseline score of 75.19 (18.88) to 77.61 (15.20) at 12-months follow-up (p=0.3524).

Biological naïve users

The subpopulation of biological naïve subjects reported significant improvements in satisfaction with infliximab-dyyb's effectiveness and side effects. Patient satisfaction with infliximab-dyyb's effectiveness improved in biological naïve users from mean (SD) baseline score of 56.31 (22.05) to 81.33 (22.86) at 12-months follow-up (p=0.0003). Patient satisfaction with infliximab-dyyb's side effects improved significantly in biological naïve users from mean baseline scores of 70.63 (23.86) to 92.19 (19.36) at 12-months follow-up (p=0.0020). Patient satisfaction with infliximab-dyyb's convenience did not change significantly in biological naïve users from a mean baseline score of 74.39 (17.28) to 77.00 (17.78) at 12-months follow-up (p=0.3924).

Patients Switched from RP Infliximab

Patient satisfaction with treatment effectiveness, side effects, and convenience was maintained in users switching from RP infliximab. Patient satisfaction with infliximab-dyyb's effectiveness did not change significantly in users switching from RP infliximab from mean (SD) baseline score of 73.46 (24.39) to 76.27 (24.84) at 12-months follow-up (p=0.2358). Patient satisfaction with infliximab-dyyb's side effects did not change significantly in users switching from RP infliximab from mean baseline scores of 81.09 (23.43) to 80.14 (19.07) at 12-months follow-up (p=0.9770). Patient satisfaction with infliximab-dyyb's convenience did not change significantly in users switching from RP infliximab from mean baseline score of 78.43 (19.50) to 79.67 (14.11) at 12-months follow-up (p=0.1742).

Patients Switched from Other Biologics

Similar to the cohort of patients switched from RP infliximab, patient satisfaction with treatment effectiveness, side effects, and convenience was maintained in users switching from other biologics. Patient satisfaction with infliximab-dyyb's effectiveness did not change significantly in users switching from other biologics from mean (SD) baseline score of 48.53 (27.04) to 64.81 (33.54) at 12-months follow-up (p=0.2335). Patient satisfaction with infliximab-dyyb's side effects did not change significantly in users switching from other biologics from mean baseline scores of 59.17 (33.90) to 86.11 (13.61) at 12-months follow-up (p=N/A). Patient satisfaction with infliximab-dyyb's convenience did not change significantly in users switching from other biologics from a mean baseline score of 66.18 (17.55) to 68.52 (10.02) at 12-months follow-up (p=0.0823).

10.5.7. Patient-Reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Work Productivity and Activity Impairment (WPAI)

Table 20 summarizes outcomes on work productivity and impairment from baseline through 12-month follow-up for all IBD patients initiating treatment with infliximab-dyyb.

All IBD Patients

In IBD patients initiating infliximab-dyyb, statistically significant improvements were observed across all work productivity and impairment metrics analyzed. Recent absenteeism score improved from a mean (SD) baseline score of 12.39 (25.53) to 4.33 (14.93) at 3-months follow-up and 2.23 (9.30) at 12-month follow-up (p=0.0059). Recent presenteeism score also improved significantly from a mean baseline score of 31.38 (30.97) to 20.44 (26.68) at 3-months follow-up and 10.68 (19.55) at 12-months follow-up (p<0.0001). The mean overall work impairment score improved from 35.34 (32.53) at baseline to 11.78 (21.03) at 12-months follow-up (p<0.0001). Similarly, the daily activity impairment score in the entire study population improved from a mean baseline score of 37.79 (31.62) to 15.63 (25.60) at 12-months follow-up (p<0.0001).

Biological Naïve users

In the subpopulation of biological naïve users, recent absenteeism score did not change significantly from a baseline mean (SD) score of 19.41 (32.33) to 2.30 (5.66) at 3-months follow-up and 4.50 (15.66) at 12-months follow-up (p=0.811). Recent presenteeism score improved significantly from a baseline mean score of 43.81 (36.53) to 16.19 (22.69) at 3-months follow-up and 7.37 (18.81) at 12-months follow-up (p=0.0008). Overall work impairment score also improved significantly in biological naïve users from a baseline mean score of 51.49 (37.20) to 15.89 (24.31) at 3-months follow-up and 8.89 (23.24) at 12-months follow-up (p=0.0038). Daily activity impairment score improved significantly from 46.58 (31.99) at baseline to 21.62 (25.00) at 3-months follow-up and 9.60 (19.89) at 12-months follow-up (p<0.0001).

Patients Switched from RP Infliximab

Baseline WPAI scores were lowest in the subpopulation of users switching from RP infliximab. Recent absenteeism score improved significantly from a baseline mean (SD) score 5.84 (11.66) to 1.78 (5.83) at 3-months follow-up and 0.57 (2.85) at 12-months follow-up (p=0.262). The recent presenteeism score did not change significantly from a baseline mean score of 22.70 (23.53) to 19.47 (24.49) at 3-months follow-up and 11.71 (20.51) at 12-months follow-up (p=0.1565). Overall work impairment score improved significantly in users switching from infliximab RP from a baseline mean score of 25.71 (25.91) to 20.73 (24.92) at 3-months follow-up and 12.21 (20.48) at 12-months follow-up (p=0.0342). Daily activity impairment score did not change significantly from 27.14 (27.28) at baseline to 25.93 (27.71) at 3-months follow-up and 16.09 (27.45) at 12-months follow-up (p=0.3327).

Patients Switched from Other Biologics

In the cohort of patients switching to infliximab-dyyb from other biologics, no significant change was observed in recent absenteeism score from a mean (SD) baseline score of 25.23 (42.53) to 19.63 (36.07) at 3-months follow-up and 4.80 (5.96) at 12-months follow-up. Similarly, recent presenteeism score did not change significantly from a baseline mean score of 40.00 (36.97) to 34.44 (40.35) at 3-months follow-up and 16.00 (16.73) at 12-months follow-up (p=N/A). Overall work impairment score did not significantly change in users switching from other biologics from a baseline mean score of 42.44 (36.01) to 41.48 (39.30) at 3-months follow-up and 19.15 (18.34) at 12-months follow-up (p=N/A). Daily activity impairment score improved significantly from 51.58 (33.54) at baseline to 44.00 (31.12) at 3-months follow-up and 30.00 (26.46) at 12-months follow-up (p=0.0249).

10.5.8. Patient-Reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: General Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire Depression Scale (PHQ-8)

Table 21 reports psychological outcomes at baseline and through follow-up in IBD patients initiating treatment with infliximab-dyyb.

All IBD Patients

During the follow-up period, mean GAD-7 and PHQ-8 scores improved significantly in the entire study population of patients initiating infliximab-dyyb for IBD. Mean (SD) GAD-7 scores improved significantly in the entire study population from 5.37 (5.32) at baseline to 3.14 (3.69) at 12-months follow-up (p=0.0005). Similarly, mean PHQ-8 improved significantly in the entire study population from 7.82 (6.29) at baseline to 3.90 (4.08) at 12-months follow-up (p<0.0001).

Biological Naïve users

Mean GAD-7 and PHQ-8 scores both improved significantly throughout the study period in the subpopulation of biological naive users initiating treatment with infliximab-dyyb. Mean (SD) GAD-7 scores improved significantly in the biological naïve users from 5.82 (5.68) at baseline to 2.48 (4.46) at 12-months follow-up (p=0.0001). Similarly, mean PHQ-8 improved significantly in the biological naïve users from 8.59 (7.00) at baseline to 3.00 (4.71) at 12-months follow-up (p=0.0009).

Patients Switched from RP Infliximab

GAD-7 and PHQ-8 scores were maintained throughout the study period in the subpopulation of patients switched from RP infliximab initiating treatment with infliximab-dyyb. Mean (SD) GAD-7 scores did not change significantly in the users switched from RP infliximab from 4.33 (4.24) at baseline to 3.49 (3.44) at 12-months follow-up (p=0.2876). Similarly, mean PHQ-8 did not change significantly in the users switched from RP infliximab from 5.86 (4.87) at baseline to 3.98 (3.36) at 12-months follow-up (p=0.0807).

Patients Switched from Other Biologics

Mean GAD-7 and PHQ-8 scores both improved significantly throughout the study period in the subpopulation of patients switched from other biologics initiating treatment with infliximab-dyyb. Mean (SD) GAD-7 scores improved significantly in the users switched from other biologics from 7.53 (6.82) at baseline to 3.11 (2.52) at 12-months follow-up (p=0.0076). Similarly, mean PHQ-8 improved significantly in the users switched from other biologics from 12.11 (6.38) at baseline to 6.00 (5.22) at 12-months follow-up (p=0.0062).

10.5.9. HCRU at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Hospitalizations

Table 22 summarizes HCRU due to hospitalizations from baseline to 12-month follow-up.

All IBD Patients

The frequency of patients recording any hospitalization decreased throughout the intervention from 11.3% during the baseline period to 3.6% at 12-months (p=0.0366). Mean (SD) number of hospitalizations also decreased from 0.13 (0.39) per patient at baseline to 0.05 (0.26) at 12-month follow-up (p=0.0366). Mean (SD) length of stay among patients with hospitalization during the baseline period was 7.23 (3.17) days. 8.4% of all patients had an

IBD-related admission during the baseline period. This HCRU measure decreased significantly to 1.2% of patients reporting an IBD-related hospitalization during the 12-month follow-up period (p=0.0176). Of patients with hospitalization during the baseline period, 84.6% reported a hospitalization related to IBD. Of patients with hospitalization during the 12-month follow-up period, 33.3% reported a hospitalization related to IBD.

Biological Naïve users

The frequency of biological naïve patients recording any hospitalization did not change throughout the intervention from 17.9% during the baseline period to 4.0% at 12-months (p=0.1712). Mean (SD) number of hospitalizations in biological naïve patients did not change significantly from 0.21 (0.47) per patient at baseline to 0.04 (0.20) at 12-month follow-up (p=0.0856). The length of stay among biological naïve patients with hospitalization during the baseline period was 6.43 (3.74) days. 15.4% of biological naïve patients had an IBD-related admission during the baseline period. 0 % of biological naïve patients had an IBD-related admission during the 12-month follow-up period (p=N/A). Of biological naïve patients with hospitalization during the baseline period, 85.7% reported a hospitalization related to IBD.

Patients Switched from RP Infliximab

No subjects switched from RP infliximab recorded a hospitalization during the baseline period and 1 (2.0%) of subjects switched from RP infliximab recorded a hospitalization during the 12-month follow-up period (although it was unrelated to IBD). 4 subjects switched from RP infliximab were hospitalized during the 3-month follow-up period, and 3 (75%) of those hospitalizations were related to IBD. However, throughout the baseline, 6-month, and 12-month follow-up periods there were no recorded hospitalizations due to IBD in subjects switched from RP infliximab.

Patients Switched from Other Biologics

5 subjects (31.6%) switched from other biologics were hospitalized during the baseline period and 5 of 6 (83.3%) of these hospitalizations were due to IBD. At 12-months follow-up, 1 subject (11.1%) was hospitalized due to IBD.

10.5.10. HCRU at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: ED Visits

Data on HCRU related to ED visits are available in Table 23.

All IBD Patients

Among all subjects, 10.4% had at least one ED visit during the baseline period and 3.6% had at least one ED visit during the 12-months follow-up period (p=0.0884). Mean (SD) number of IBD-related ED visits in all subjects was 0.07 (0.26) per patient during the baseline period and 0.06 (0.32) at 12-months follow-up (p=N/A).

Biological Naïve users

Among biological naive subjects, 17.9% had at least one ED visit during the baseline period and 0 (0%) had at least one ED visit during the 12-months follow-up period (p=N/A). Mean (SD) number of IBD-related ED visits in biological naive subjects was 0.18 (0.39) per patient during the baseline period and 0.00 (0.32) at 12-months follow-up (p=N/A).

Patients Switched from RP Infliximab

Among subjects switched from RP infliximab, 3.5% had at least one ED visit during the baseline period and 2.0% had at least one ED visit during the 12-months follow-up period (p=0.5708). Mean (SD) number of IBD-related ED visits in subjects switched from RP infliximab was 0.00 (0.00) per patient during the baseline period and 0.04 (0.28) at 12-months follow-up (p=N/A).

Patients Switched from Other Biologics

Among subjects switched from other biologics, 15.8% had at least one ED visit during the baseline period and 22.2% had at least one ED visit during the 12-months follow-up period (p=0.N/A). Mean (SD) number of IBD-related ED visits in subjects switched from other biologics was 0.05 (0.23) per patient during the baseline period and 0.33 (0.71) at 12-months follow-up (p=N/A).

10.5.11. HCRU at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Outpatient Visits

Table 24 describes HCRU related outpatient visits during the study period.

All IBD Patients

During the baseline period, 47% of all subjects had at least one outpatient visit. This frequency increased significantly to 69.0% of all subjects having at least one outpatient visit at 12-months (p=0.0006). The mean number of gastroenterologist visits did not change significantly in all patients throughout the study from baseline period mean (SD) of 0.78 (1.67) visits per patient to 0.69 (0.78) visits per patient at 12-months (p=0.2836).

Biological Naïve users

During the baseline period, 43.6% of biological naive subjects had at least one outpatient visit. This frequency did not change significantly to 64.0% of biological naive subjects having at least one outpatient visit at 12-months (p=0.0796). The mean number of gastroenterologist visits did not change significantly in biological naive patients throughout the study from baseline period mean (SD) of 0.92 (1.58) visits per patient to 0.60 (0.71) visits per patient at 12-months (p=0.5714).

Patients Switched from RP Infliximab

During the baseline period, 43.9% of subjects switched from RP infliximab had at least one outpatient visit. This frequency increased significantly to 68.0% of subjects switched from

RP infliximab having at least one outpatient visit at 12-months (p=0.0119). The mean number of gastroenterologist visits did not change significantly in subjects switched from RP infliximab throughout the study from baseline period mean (SD) of 0.35 (0.69) visits per patient to 0.68 (0.82) visits per patient at 12-months (p=0.1011).

Patients Switched from Other Biologics

During the baseline period, 63.2% of subjects switched from other biologics had at least one outpatient visit. This frequency did not change significantly to 88.9% of subjects switched from other biologics having at least one outpatient visit at 12-months (p=0.1836). The mean number of gastroenterologist visits did not change significantly in subjects switched from other biologics throughout the study from baseline period mean (SD) of 1.79 (3.05) visits per patient to 1.00 (0.71) visits per patient at 12-months (p=0.5136).

10.5.12. Healthcare Costs at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Overall Costs

Overall healthcare costs are described in Table 25.

All IBD Patients

In all enrolled subjects, mean (SD) IBD-related inpatient costs were $1,280.92 (4088.05) during the baseline period and $152.59 (1398.52) during the 12-month follow-up period. IBD-related medical costs were $1,280.92 (4088.05) during the baseline period and $70.63 (647.35) during the 12-month follow-up period. No IBD-related surgical costs were incurred in the baseline period and $81.96 (751.17) were incurred during the 12-month follow-up period. General medical costs in all enrolled subjects were $328.50 (2616.47) during the baseline period and $74.95 (686.97) during the 12-month follow-up period. Total inpatient costs in all enrolled subjects were $1609.41 (4765.41) during the baseline period and $365.16 (1982.92) during the 12-month follow-up period.

Biological Naïve users

In biological naive subjects, mean (SD) IBD-related inpatient costs were $2224.28 (5539.92) during the baseline period and $0 (0.0) during the 12-month follow-up period. IBD-related medical costs were $2224.28 (5539.92) during the baseline period and $0 (0.00) during the 12-month follow-up period. No IBD-related surgical costs were incurred. General medical costs in biological naive subjects were $322.88 (2016.40) during the baseline period and $0 (0.00) during the 12-month follow-up period. Total inpatient costs in biological naive subjects were $2547.16 (5769.09) during the baseline period and $462.38 (2311.89) during the 12-month follow-up period.

Patients Switched from RP Infliximab

Subjects switched from RP infliximab incurred no overall costs within the baseline period. During the 12-month follow-up period, subjects switched from RP infliximab incurred mean (SD) $125.92 (890.42) in general medical and total inpatient costs.

Patients Switched from Other Biologics

In subjects switched from other biologics, mean (SD) IBD-related inpatient costs were $3187.28 (5485.61) during the baseline period and $1424.18 (4272.55) during the 12-month follow-up period. IBD-related medical costs were $3187.28 (5485.61) during the baseline period and $659.22 (1977.67) during the 12-month follow-up period. No IBD-related surgical costs were incurred in the baseline period and $764.96 (2294.87) were incurred during the 12-month follow-up period. General medical costs in subjects switched from other biologics were $1325.52 (5777.79) during the baseline period and $0 (0.00) during the 12-month follow-up period. Total inpatient costs in subjects switched from other biologics were $4512.80 (7386.19) during the baseline period and $1424.18 (4272.55) during the 12-month follow-up period.

10.5.13. Healthcare Costs at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Emergency Room Costs

Emergency room costs for the entire study cohort and each switch group are detailed in Table 26.

All IBD Patients

In the entire study cohort, mean (SD) IBD related ER costs were $339.56 (1248.83) during the baseline period and $152.29 (828.46) during the 12-month follow-up period. General ER costs were $46.32 (259.86) during the baseline period and $12.68 (81.70) during the 12-month follow-up period. Total ER costs were $385.88 (1263.08) during the baseline period and $164.98 (887.48) during the 12-month follow-up period.

Biological Naïve users

In biological naïve subjects, mean (SD) IBD related and total ER costs were $870.06 (1887.25) during the baseline period. There were no reported ER costs for biological naïve users in the 12-month follow-up period.

Patients Switched from RP Infliximab

In subjects switched from RP infliximab, there were no IBD related ER costs during the baseline and mean (SD) $102.34 (723.66) during the 12-month follow-up period. General ER costs were $56.07 (313.27) during the baseline period and $10.65 (75.33) during the 12-month follow-up period. Total ER costs were $56.07 (313.27) during the baseline period and $112.99 (798.99) during the 12-month follow-up period.

Patients Switched from Other Biologics

In subjects switched from other biologics, mean (SD) IBD related ER costs were $269.32 (1173.93) during the baseline period and $852.84 (1809.15) during the 12-month follow-up period. General ER costs were $112.14 (335.91) during the baseline period and $59.19 (177.56) during the 12-month follow-up period. Total ER costs were $381.46 (1194.65) during the baseline period and $912.03 (1879.28) during the 12-month follow-up period.

10.5.14. Healthcare Costs at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Outpatient Visits Costs

Outpatient visit costs are available in Table 27 for all study subjects in addition to each patient switch group.

All IBD Patients

In the entire study cohort, mean (SD) total outpatient costs during the baseline period were $201.88 (474.75). Outpatient costs during the baseline period were comprised of a mean $33.56 (128.32) for general practitioner visits, $115.64 (247.39) for gastroenterologist visits, and $52.68 (218.98) for other outpatient visits. In the entire study cohort, mean (SD) total outpatient costs during the 12-month follow-up period were $104.08 (110.12). Outpatient costs during the 12-month follow-up period were comprised of a mean $30.20 (51.64) for general practitioner visits, $51.01 (57.31) for gastroenterologist visits, and $22.87 (52.53) for other outpatient visits.

Biological Naïve users

In biological naïve subjects, mean (SD) total outpatient costs during the baseline period were $216.81 (541.00). Outpatient costs during the baseline period were comprised of a mean $19.79 (66.32) for general practitioner visits, $136.39 (233.35) for gastroenterologist visits, and $60.62 (308.30) for other outpatient visits. In biological naïve subjects, mean (SD) total outpatient costs during the 12-month follow-up period were $80.41 (76.57). Outpatient costs during the 12-month follow-up period were comprised of a mean $24.26 (39.25) for general practitioner visits, $44.33 (52.24) for gastroenterologist visits, and $11.82 (27.64) for other outpatient visits.

Patients Switched from RP Infliximab

In subjects switched from RP infliximab, mean (SD) total outpatient costs during the baseline period were $122.34 (232.13). Outpatient costs during the baseline period were comprised of a mean $29.02 (70.76) for general practitioner visits, $51.85 (102.57) for gastroenterologist visits, and $41.48 (138.93) for other outpatient visits. In subjects switched from RP infliximab, mean (SD) total outpatient costs during the 12-month follow-up period were $96.66 (97.60). Outpatient costs during the 12-month follow-up period were comprised of a mean $24.26 (43.37) for general practitioner visits, $50.24 (60.52) for gastroenterologist visits, and $22.16 (54.33) for other outpatient visits.

Patients Switched from Other Biologics

In subjects switched from other biologics, mean (SD) total outpatient costs during the baseline period were $409.86 (758.80). Outpatient costs during the baseline period were comprised of a mean $75.45 (277.66) for general practitioner visits, $264.41 (450.28) for gastroenterologist visits, and $69.99 (205.27) for other outpatient visits. In subjects switched from other biologics, mean (SD) total outpatient costs during the 12-month follow-up period were $210.99 (186.85). Outpatient costs during the 12-month follow-up period were

comprised of a mean $79.65 (91.90) for general practitioner visits, $73.88 (52.24) for gastroenterologist visits, and $57.46 (80.74) for other outpatient visits.

10.6. Other analyses

Not applicable.

10.7. Adverse events / adverse reactions

10.7.1. Adverse Events in IBD Patients Treated with Infliximab-dyyb: Patient-Level Summary

A patient-level summary of AE occurrences is available in Table 28.

59 AE's were reported in 40 (40/115; 34.8%) patients. 11 biological naïve users experienced any AE (11/39; 28.2%), 19 subjects switched from RP infliximab experienced any AE (19/57; 33.3%), and 10 subjects switched from other biologics experienced any AE (10/19; 52.6%). 19 patients in the total cohort had any serious AE (19/115; 16.5%). Serious AE's occurred in 5 biological naïve users (5/39; 12.8%), 11 subjects switched from RP infliximab (11/57; 19.3%), and 3 subjects switched from other biologics (3/19; 15.8%). No deaths were reported during the study.

10.7.2. Adverse Events in IBD Patients Treated with Infliximab-dyyb: Event-level Summary

Each AE occurrence is summarized in terms of severity, relationship to study treatment, and outcome in the AE event-level summary in Table 29.

All IBD Patients

Of 59 AE's occurring over the study duration, 29 (49.2%) were mild severity, 23 (39.0%) were moderate severity, and 7 (11.9%) were severe. Among all subjects who had an AE, 24 (40.7%) had a serious AE. 22 AE's were related to study treatment (22/59; 37.3%) and the remainder were not. The actions taken among all subjects who experienced an AE were: medication administered (4/59; 6.8%), no action taken (26/59; 44.1%), procedure change (1/59; 1.7%), study drug changed (4/59; 6.8%), study drug stopped (18/59; 30.5%), and other action (6/59; 10.2%). The outcome of AEs among all subjects who experienced an AE were: not recovered/not resolved (8/59; 13.6%), recovered/resolved (37/59; 62.7%), recovering/resolving (9/59; 15.3%), and unknown outcome (5/59; 8.5%).

Biological Naïve users

Of 18 AE's that occurred in biological naïve users, 8 (44.4%) were mild severity, 9 (50.0%) were moderate severity, and 1 (5.6%) were severe. Among biological naïve subjects who had an AE, 6 (33.3%) had a serious AE. 10 AE's were related to study treatment in biological naïve subjects (10/18; 55.6%) and the remainder were not. The actions taken among biological naïve subjects who experienced an AE were: medication administered (2/18; 11.1%), no action taken (11/18; 61.1%), and study drug stopped (5/18; 27.8%). The outcome of AEs among biological naïve subjects who experienced an AE were: not recovered/not

resolved (3/18; 16.7%), recovered/resolved (12/18; 66.7%), recovering/resolving (1/18; 5.6%), and unknown outcome (2/18; 11.1%).

Patients Switched from RP Infliximab

Of 24 AE's that occurred in subjects switched from RP infliximab, 11 (45.8%) were mild severity, 9 (37.5%) were moderate severity, and 4 (16.7%) were severe. Among subjects switched from RP infliximab who had an AE, 12 (50.0%) had a serious AE. 10 AE's were related to study treatment in subjects switched from RP infliximab (10/24; 41.7%) and the remainder were not. The actions taken among subjects switched from RP infliximab who experienced an AE were: medication administered (1/24; 4.2%), no action taken (12/24; 50.0%), study drug changed (3/24 12.5%), and study drug stopped (8/24; 33.3%). The outcome of AEs among subjects switched from RP infliximab who experienced an AE were: not recovered/not resolved (2/24; 8.3%), recovered/resolved (15/24; 62.5%), recovering/resolving (5/24; 20.8%), and unknown outcome (2/24; 8.3%).

Patients Switched from Other Biologics

Of 17 AE's that occurred in subjects switched from other biologics, 10 (58.8%) were mild severity, 5 (29.4%) were moderate severity, and 2 (11.8%) were severe. Among subjects switched from other biologics who had an AE, 6 (35.3%) had a serious AE. 7 AE's were related to study treatment in subjects switched from other biologics (7/17; 41.2%) and the remainder were not. The actions taken among subjects switched from other biologics who experienced an AE were: medication administered (1/17; 5.9%), no action taken (3/17; 17.6%), procedure change (1/17; 5.9%), study drug changed (1/17 5.9%), study drug stopped (5/17; 29.4%), and other action (6/17; 35.3%). The outcome of AEs among subjects switched from other biologics who experienced an AE were: not recovered/not resolved (3/17; 17.6%), recovered/resolved (10/17; 58.8%), recovering/resolving (3/17; 17.6%), and unknown outcome (1/17; 5.9%).

10.7.3. Adverse Events in IBD Patients Treated with Infliximab-dyyb: Frequency of Adverse Events Related to or Unrelated to Treatment

Table 30 and Figure 8 describe the category and event term of all AE's (n=59) which occurred, related to infliximab-dyyb treatment or unrelated, during the study trial.

10.7.4. Adverse Events in IBD Patients Treated with Infliximab-dyyb: Frequency of Adverse Events Related to Treatment

Table 7 and Figure 9 describe the category and event term of AE's (n=59) which occurred, related to infliximab-dyyb treatment or unrelated, during the study trial.

11. DISCUSSION

11.1. Key results

Because the use of biosimilars in the treatment of IBD is a focus of attention, the additional real-world data reported here plays an important role in understanding the safe and appropriate use of infliximab-dyyb and its benefits and risks in a real-world setting.

The demographics and baseline clinical characteristics of enrolled subjects were consistent with the indicated populations for infliximab-dyyb. Adverse events occurred at a rate consistent with the known AE profile for RP infliximab. 22 AEs were observed which were related to study treatment (Table 7).

Although the current analysis is limited in terms of statistical power, improvements in outcomes were observed across clinical, patient-reported, and economic outcomes (Table 8). Clinical improvements in pMAYO score were observed in UC patients in biological naïve subjects and subjects switching from RP infliximab. Clinical improvements in remission classification were also observed in UC patients in biological naïve subjects. In CD patients, 72.7% were in remission at baseline, and this rate was maintained at 12-months follow-up. Patient-reported outcomes improved significantly from baseline to 12-month follow-up in nearly all outcomes measures in the cohort of all enrolled subjects. SIBDQ, EQ-VAS, all domains of WPAI, the effectiveness domain of TSQM, GAD-7, and PHQ-8 scores significantly improved from baseline to 12-months follow-up. HCRU and cost analysis showed some positive impacts but were generally not significant.

Table 8 Overview of Improvement or Worsening of Outcomes Measures

Outcome Measures		All patients	Biological Naive	Switched from RP infliximab	Switched from other biologic
UC clinical outcomes	pMAYO score	+	+	+	ns
	UC Remission	+	+	ns	ns
	UC Response	ns	ns	ns	ns
CD clinical outcomes	HBI Score	ns	ns	ns	ns
	CD Remission	ns	ns	ns	ns
	CD Response	ns	ns	ns	ns
Health-Related Quality of Life	SIBDQ	+	+	ns	+
Health-Related Quality of Life	EQ-VAS score	+	+	ns	ns
Work Productivity	Currently Employed	+	+	ns	ns
	Absenteeism	+	ns	+	ns
	Presenteeism	+	+	ns	ns
	Overall work impairment score %	+	+	+	ns

	Daily activity impairment score %	+	+	ns	+
Treatment Satisfaction	TSQM effectiveness	+	+	ns	ns
	TSQM side effects	ns	+	ns	ns
	TSQM convenience	ns	ns	ns	ns
Psychological Outcomes	GAD-7 score	+	+	ns	+
	PHQ-8 score	+	+	ns	+
HCRU	Mean number of hospitalizations	+	ns	ns	ns
Cost	Total inpatient costs	ns	ns	ns	ns
	Outpatient costs	+	+	+	ns

+ signifies improvement ($p<0.05$), 'ns' signifies no change ($p>0.05$)
Acronyms: pMAYO=partial MAYO score; UC=ulcerative colitis; CD=Crohn's disease; HBI=Harvey Bradshaw Index; SIBDQ= Short Inflammatory Bowel Disease Questionnaire; EQ-VAS=EuroQol-visual analogue scale; TSQM=Treatment Satisfaction Questionnaire for Medication; GAD-7=General Anxiety Disorder-7; PHQ-8=Patient Health Questionnaire Depression Scale; ED=emergency department

11.2. Strengths and Limitations

11.2.1. Strengths

- The prospective, observational, multicenter study design was an efficient, reliable, and verifiable method of data collection. Prospective chart review and outcomes data collection facilitated accurate documentation of real-world treatment patterns and clinical outcomes.

- The number and geographic distribution of participating physicians and the robust samples of patient data including an extensive range of patient-reported outcomes provided a rich, detailed dataset for analyses and hypothesis generation.

- This study fills an important gap in existing knowledge of the real-world clinical outcomes of North American IBD patients treated with an infliximab biosimilar (infliximab-dyyb).

11.2.2. Limitations

- Due to a lack of formulary availability/insurance coverage of infliximab-dyyb during patient enrollment, study sample size (N=115) is below the minimum sample size (N=139) determined to be necessary. Ultimately due to the lack of uptake of biosimilars/infliximab-dyyb in the US, fewer study sites than planned were able to identify and recruit patients because infliximab-dyyb was not on formulary or patient insurance would not cover infliximab-dyyb. Enrollment occurred from February 2018 to February 2019. Since then, access to biosimilars and biosimilars formulary replacement has modestly improved.

- Patients in this trial were selected to initiate treatment independently by enrolling physicians. Due to selection bias they may represent a more stable population that is less at risk of relapse.

- Endoscopic findings were not included in the efficacy endpoints.

- Standard of care, clinical outcomes and resource use data only represent the practices of participating study physicians/sites and may vary from non-participating physicians, e.g., those who refused study participation, failed to complete the study requirements on time and were excluded from the study, or were unresponsive to the screening invitation. Also, patients of non-participating physicians may have profiles, treatments, and outcomes that differ from those of study patients; thus, the generalizability of study results may be limited.

- Although physicians seek to record all patient experiences in the medical charts, there may be some undercounting of events that are unknown to physicians or that may have occurred outside the physician or site's practice setting.

- Because this is a post-marketing study and is open-label and nonrandomized, it may lead to an overestimate of efficacy and patient-reported outcomes.

11.3. Interpretation

Clinical Outcomes Interpretation

While the analysis was based on a low sample size, this study showed positive response and remission outcomes in biological naïve IBD patients. We observed a clinical response to treatment in 72.7% of UC and 30.8% of CD biological naïve users initiating infliximab-dyyb treatment. At the end of 12-months follow-up 90.9% of UC and 84.6% of CD biological naïve users were in remission. These rates compare favorably with other studies of infliximab-dyyb as a patient's first biologic therapy for IBD. A 2017 meta-analysis by Komaki et al reviewed 11 observational studies of patients with active CD or UC treated with CT-P13 (switched from RP infliximab or biological naïve) (25). Consistent with our findings, pooled clinical response rates at 24-30 weeks were 77% in UC and 77% in CD and pooled clinical remission rates were 42% in UC and 60% in CD. Several other groups have suggested that infliximab-dyyb is effective and safe in biological naïve patients (26-30). A large comparative study of infliximab-naïve patients with IBD initiating either RP infliximab or CT-P13 concluded that infliximab-dyyb was equally efficacious with no clinically meaningful differences (31).

Numerous observational studies have reported on infliximab-dyyb's sustained effectiveness after switching from RP infliximab (8, 11, 13, 28, 32-44). In the present study, at 12 months follow-up, clinical remission was maintained in 94.1% of UC and 76.7% of CD patients switched from RP infliximab to infliximab-dyyb. Jung et al. studied a total of 59 IBD patients switching from RP infliximab to CT-P13 and observed that 92.6% of CD patients and 66.7% of UC patients maintained similar efficacy compared with infliximab (8). Smits et

al studied 83 RP infliximab-treated IBD patients who switched to CT-P13 (11). Smits et al similarly found that over 80% of patients maintained clinical remission and that IBD activity remained stable after switching (11). Only one published study, Chaparro et al 2019, has found unfavorable results in users switched from RP infliximab to CT-P13 (45). However, Chaparro et al explain that the higher risk of clinical relapse they observed in patients switched to CT-P13 was not supported by objective markers of inflammation and may have been due to the placebo effect.

Patient-Reported Outcomes Interpretation

Significant improvements were observed at 12-month follow-up for nearly all patient-reported outcomes domains in the total sample of patients initiating infliximab-dyyb (N=115). SIBDQ, EQ-VAS, all domains of WPAI, the effectiveness domain of TSQM, GAD-7, and PHQ-8 scores significantly improved from baseline to 12-months follow-up.

In biological naïve users, the current study observed a 15.95-point improvement in SIBDQ score from baseline to 12-months follow-up. In a randomized phase 3 non-inferiority study, Ye et al in 2019 observed a 18.6 and 16.7 point improvement in 30-week SIBDQ score in biological naïve patients initiating RP infliximab or CT-P13, respectively, for CD (44). In the present study, biological naïve patients initiating infliximab-dyyb also demonstrated significant improvements in EQ-VAS; the presenteeism, overall work impairment, and daily activity impairment domains of WPAI; the effectiveness and side effects domains of TSQM; GAD-7; and PHQ-8 scores.

Patient-reported outcomes were maintained in users switched from RP infliximab to infliximab-dyyb. SIBDQ, EQ-VAS, TSQM, GAD-7, and PHQ-8 patient-reported outcomes measures were maintained from baseline to 12-month follow-up in the cohort of patients switching from RP infliximab to infliximab-dyyb. WPAI scores improved significantly in this cohort in the domains of absenteeism and overall work impairment. Other reports of patient-reported outcomes in patients switched from RP infliximab to infliximab-dyyb have found similar results. The randomized, non-inferiority, double-blind NOR-SWITCH study, which assigned patients on stable RP infliximab treatment in a 1:1 ratio to either continue treatment with RP infliximab or be switched to CT-P13, observed that improvements in SF-36, EQ-5D, and WPAI scores were not statistically different between RP infliximab and infliximab-dyyb users (13).

To our knowledge this is the first study to prospectively evaluate treatment satisfaction in patients switched from RP infliximab to infliximab-dyyb for IBD. Baseline to 12-month outcomes in the Treatment Satisfaction Questionnaire for Medication suggest that patients switched from RP infliximab maintained satisfaction with infliximab-dyyb in terms of its effectiveness, side effects, and convenience.

HCRU and Cost Outcomes Interpretation

Mean number of hospitalizations per patient, a key driver of HCRU, decreased in the cohort of all patients. Previous evaluations of HCRU in biosimilars have indicated that patients that

are non-medically switched from biologic to biosimilar exhibit elevated HCRU after switching medications (46). Approximately half of our population was non-medically switched either from RP infliximab or other biologics. The observed decrease in number of hospitalizations from the baseline observation period to the 12-month follow-up observation period may reflect an elevated baseline observation period.

The current study also reports non-significant decreases in medical costs from baseline to 12-month follow-up in IBD-related inpatient costs, IBD-related medical costs, IBD related ER costs, general ER costs, and total ER costs. However, we were unable to determine statistical significance due to small sample sizes. In previous investigations, infliximab biosimilars have shown potential to generate cost savings. In a 2016 budget impact analysis of six European countries, Brodszky et al showed that replacing RP infliximab with infliximab biosimilars would provide budget savings that would allow 700-1500 additional patients to be treated (47). In a stochastic economic model designed to simulate the introduction of biosimilars for IBD in the Netherlands, Severs et al showed that potential cost savings would be around 30% (48). Also, in 2015, annual direct drug cost savings in five European countries through the introduction of biosimilar infliximab were projected to range from 10-30% (49). The findings in the current analysis, though limited in their applicability, do not contradict the cost savings potential of infliximab-dyyb.

Adverse Events Interpretation

No new safety signals were observed during the conduct of this study. Although the number of patients in this study is small and direct comparisons cannot be made, the adverse event rates observed in this study were in line with what has previously been reported with RP infliximab (50-53).

Immunogenicity is a risk associated with use of biologic agents in the management of inflammatory bowel disease. Immunogenicity rates have been shown to vary in different biologic and biosimilar agents, including infliximab. For example, Balint et al's 2017 report on the use of biosimilar infliximab in 384 patients with IBD found a 7.3% (28 of 384 patients) incidence of infusion reactions (54). Incidence of infusion reactions in the PROSIT trial was 8.8% (71 of 810 IBD patients) (30). The incidence of infusion reactions in the current study was relatively lower at 3.45% (4 of 115 patients). This may reflect the high number of biological naïve users in the cohort.

11.4. Generalizability

The findings from this study may be generalized to the IBD patients from the practice settings in the U.S and Canada. However, the generalizability is limited due to the small sample size in the study.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In this prospective, observational study, we evaluated real-world clinical, patient-reported, and economic outcomes of infliximab-dyyb for IBD among biological naïve patients and patients switching from RP infliximab or other biologics. Among biological naïve patients, clinical outcomes improved significantly for UC and were maintained for CD patients. Consistent with findings across other immunological diseases, patients who switched from RP infliximab to infliximab-dyyb maintained clinical outcomes and remission status. The patient-reported quality of life and work productivity outcomes improved among biological naïve subjects and were maintained for subjects switched from RP infliximab. Although the number of patients in this study is small and direct comparisons cannot be made, adverse events occurred at a rate consistent with the known adverse event profile for RP infliximab. To our knowledge, this is the first prospective study of real-world outcomes in IBD patients treated with infliximab-dyyb in North America. The results of this study provide valuable data concerning the use of infliximab-dyyb in clinical practice for patients with IBD.

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15. LIST OF SOURCE TABLES AND FIGURES

15.1. Baseline Demographic/Clinical Characteristics

Table 9 Patient Characteristics of IBD Patients Treated with Infliximab-dyyb

		All	Biological Naïve Users	Switched From RP Infliximab	Switched From Other Biologics	P-Value
		(N = 115)	(N = 39)	(N = 57)	(N = 19)	
Sex						0.231[C]
Female	N (%)	59 (51.3%)	16 (41.0%)	31 (54.4%)	12 (63.2%)	
Male	N (%)	56 (48.7%)	23 (59.0%)	26 (45.6%)	7 (36.8%)	
Age (years)	Mean (SD)	44.25 (16.29)	45.97 (17.65)	42.79 (15.43)	45.00 (16.34)	0.641[W]
BMI	Mean (SD)	27.86 (6.00)	25.99 (4.26)	28.57 (6.99)	29.45 (4.84)	0.034[W]
Race/Ethnicity						0.719[C]
Asian	N (%)	3 (2.6%)	1 (2.6%)	1 (1.8%)	1 (5.3%)	
Black or African American	N (%)	8 (7.0%)	2 (5.1%)	4 (7.0%)	2 (10.5%)	
Hispanic or Latino	N (%)	3 (2.6%)	2 (5.1%)	0 (0.0%)	1 (5.3%)	
White or Caucasian American	N (%)	100 (87.0%)	34 (87.2%)	51 (89.5%)	15 (78.9%)	
Other	N (%)	1 (0.9%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	
Insurance Status						<0.001[C]
Canada Medicare	N (%)	16 (13.9%)	8 (20.5%)	0 (0.0%)	8 (42.1%)	
HMO	N (%)	46 (40.0%)	4 (10.3%)	40 (70.2%)	2 (10.5%)	
Medicare/Medicaid	N (%)	25 (21.7%)	9 (23.1%)	12 (21.1%)	4 (21.1%)	
POS	N (%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	
PPO	N (%)	26 (22.6%)	18 (46.2%)	4 (7.0%)	4 (21.1%)	
Unknown	N (%)	1 (0.9%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	
Smoking status						0.611[C]
Current smoker	N (%)	13 (11.3%)	4 (10.3%)	7 (12.3%)	2 (10.5%)	
Never smoker	N (%)	59 (51.3%)	18 (46.2%)	31 (54.4%)	10 (52.6%)	
Past smoker	N (%)	35 (30.4%)	14 (35.9%)	17 (29.8%)	4 (21.1%)	

Unknown	N (%)	8 (7.0%)	3 (7.7%)	2 (3.5%)	3 (15.8%)	
Charlson Comorbidity Index						0.342[W]
Charlson Comorbidity Index	Mean (SD)	0.30 (0.98)	0.56 (1.43)	0.19 (0.69)	0.11 (0.32)	
0	N (%)	101 (87.8%)	32 (82.1%)	52 (91.2%)	17 (89.5%)	
1	N (%)	4 (3.5%)	1 (2.6%)	1 (1.8%)	2 (10.5%)	
2	N (%)	6 (5.2%)	3 (7.7%)	3 (5.3%)	0 (0.0%)	
3+	N (%)	4 (3.5%)	3 (7.7%)	1 (1.8%)	0 (0.0%)	
IBD Type						0.571[C]
CD	N (%)	67 (58.3%)	21 (53.8%)	36 (63.2%)	10 (52.6%)	
UC	N (%)	48 (41.7%)	18 (46.2%)	21 (36.8%)	9 (47.4%)	
Duration of disease (years)	Mean (SD)	8.24 (8.34)	5.92 (6.20)	9.88 (9.48)	8.63 (8.22)	

P-Value: C= CHISQ; W= Wilcoxon Rank Sum
Abbreviations: IBD=Inflammatory bowel disease; BMI=Body Mass Index; HMO=Health Maintenance Organization; POS=point of service plan; PPO=Preferred Provider Organization; CD=Crohn's disease; UC=Ulcerative colitis
Source MS Excel Tables: 4.1 – 4.2

Table 10 Montreal Classification of CD Patients Treated with Infliximab-dyyb

		All (N = 67)	Biological Naïve Users (N = 21)	Switched From RP Infliximab (N = 36)	Switched From Other Biologics (N = 10)	P-Value
Baseline HBI Score	Mean (SD)	3.56 (2.98)	3.95 (3.15)	3.11 (3.05)	3.57 (2.51)	0.628[W]
Age at onset						0.185[C]
16 years or younger	N (%)	8 (11.9%)	2 (9.5%)	4 (11.1%)	2 (20.0%)	
17-40 years	N (%)	35 (52.2%)	11 (52.4%)	18 (50.0%)	6 (60.0%)	
Over 40 years	N (%)	17 (25.4%)	8 (38.1%)	7 (19.4%)	2 (20.0%)	
Unknown	N (%)	7 (10.4%)	0 (0.0%)	7 (19.4%)	0 (0.0%)	
Location						0.606[C]
L1 Terminal ileum	N (%)	22 (32.8%)	7 (33.3%)	12 (33.3%)	3 (30.0%)	
L2 Colon	N (%)	22 (32.8%)	6 (28.6%)	12 (33.3%)	4 (40.0%)	
L3 Ileocolon	N (%)	18 (26.9%)	8 (38.1%)	7 (19.4%)	3 (30.0%)	
L4 Upper GI	N (%)	1 (1.5%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	
Unknown	N (%)	4 (6.0%)	0 (0.0%)	4 (11.1%)	0 (0.0%)	
Behavior						<0.001[C]
B1 Non-stricturing, Non-penetrating	N (%)	20 (29.9%)	11 (52.4%)	3 (8.3%)	6 (60.0%)	
B2 Stricturing	N (%)	11 (16.4%)	4 (19.0%)	6 (16.7%)	1 (10.0%)	
B3 Penetrating	N (%)	5 (7.5%)	4 (19.0%)	0 (0.0%)	1 (10.0%)	
P Perianal disease	N (%)	3 (4.5%)	0 (0.0%)	2 (5.6%)	1 (10.0%)	
Unknown	N (%)	28 (41.8%)	2 (9.5%)	25 (69.4%)	1 (10.0%)	

P-Value: C= CHISQ; W= Wilcoxon Rank Sum
Abbreviations: CD=Crohn's disease; HBI=Harvey Bradshaw Index
Source MS Excel Table: 4.3

Table 11 Montreal Classification of UC Patients Initiating Infliximab-dyyb

		All (N = 48)	Biological Naïve Users (N = 18)	Switched From RP Infliximab (N = 21)	Switched From Other Biologics (N = 9)	P-Value
Baseline MAYO Score	Mean (SD)	3.85 (3.05)	5.67 (2.25)	1.38 (1.83)	6.00 (2.65)	<0.001[W]
	Extent					0.383[C]
E1 Ulcerative proctitis	N (%)	5 (10.4%)	3 (16.7%)	1 (4.8%)	1 (11.1%)	
E2 Left-sided UC	N (%)	13 (27.1%)	6 (33.3%)	3 (14.3%)	4 (44.4%)	
E3 Extensive UC	N (%)	28 (58.3%)	8 (44.4%)	16 (76.2%)	4 (44.4%)	
Unknown	N (%)	2 (4.2%)	1 (5.6%)	1 (4.8%)	0 (0.0%)	
	Severity					0.187[C]
S0 UC in clinical remission	N (%)	4 (8.3%)	0 (0.0%)	3 (14.3%)	1 (11.1%)	
S1 Mild UC	N (%)	8 (16.7%)	2 (11.1%)	5 (23.8%)	1 (11.1%)	
S2 Moderate UC	N (%)	14 (29.2%)	8 (44.4%)	5 (23.8%)	1 (11.1%)	
S3 Severe UC	N (%)	14 (29.2%)	6 (33.3%)	3 (14.3%)	5 (55.6%)	
Unknown	N (%)	8 (16.7%)	2 (11.1%)	5 (23.8%)	1 (11.1%)	

P-Value: C= CHISQ; W= Wilcoxon Rank Sum
Abbreviations: UC=Ulcerative colitis; pMAYO=partial MAYO score
Source MS Excel Table: 4.4

Table 12 Disease-Related Surgical History of IBD Patients Treated with Infliximab-dyyb

		All (N = 115)	Biological Naïve Users (N = 39)	Switched From RP Infliximab (N = 57)	Switched From Other Biologics (N = 19)	P-Value
Proportion of patients who received disease-related surgery	N (%)	24 (20.9%)	4 (10.3%)	17 (29.8%)	3 (15.8%)	0.061[E]
Number of surgeries per patient						
1	N (%)	19 (79.2%)	4 (100.0%)	13 (76.5%)	2 (66.7%)	0.584[E]
2 or more	N (%)	5 (20.8%)	0 (0.0%)	4 (23.5%)	1 (33.3%)	
Reason for surgery						
Management of IBD	N (%)	9 (37.5%)	4 (100.0%)	4 (23.5%)	1 (33.3%)	0.075[C]
Management of side effects/adverse experiences related to IBD	N (%)	13 (54.2%)	0 (0.0%)	11 (64.7%)	2 (66.7%)	
Unknown	N (%)	2 (8.3%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	

P-Value: C= CHISQ; E= Exact Fisher;
Abbreviations: IBD=Inflammatory bowel disease;
Source MS Excel Table: 4.5

Table 13 Treatment Characteristics at Baseline of IBD Patients Treated with Infliximab-dyyb

		All (N = 115)	Biological Naïve Users (N = 39)	Switched From RP Infliximab (N = 57)	Switched From Other Biologics (N = 19)	P-Value
Initiation of Infliximab-dyyb at any visit	Yes, N (%)	115 (100.0%)	39 (100.0%)	57 (100.0%)	19 (100.0%)	
Initiation of Infliximab-dyyb at baseline visit	Yes, N (%)	114 (99.1%)	39 (100.0%)	56 (98.2%)	19 (100.0%)	>0.999[E]
	No, N (%)	1 (0.9%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	
Reason for treatment initiation at baseline visit	Different class or different mode/mechanism of action, N (%)	5 (4.4%)	1 (2.6%)	0 (0.0%)	4 (22.2%)	<0.001[C]
	Improved efficacy, N (%)	14 (12.4%)	6 (15.4%)	0 (0.0%)	8 (44.4%)	
	New drug availability, N (%)	12 (10.6%)	5 (12.8%)	6 (10.7%)	1 (5.6%)	
	Payer/formulary decision, N (%)	2 (1.8%)	0 (0.0%)	2 (3.6%)	0 (0.0%)	
	Reimbursement; insurance; or out of pocket costs, N (%)	47 (41.6%)	1 (2.6%)	45 (80.4%)	1 (5.6%)	
	Targeted therapy, N (%)	29 (25.7%)	25 (64.1%)	2 (3.6%)	2 (11.1%)	
	Other, N (%)	4 (3.5%)	1 (2.6%)	1 (1.8%)	2 (11.1%)	
Starting dose at baseline visit (mg)	Mean (SD)	513.65 (233.65)	448.45 (146.48)	546.68 (285.05)	548.56 (180.23)	0.106[A]
Frequency of treatment at baseline visit	Once every 2 weeks, N (%)	13 (11.4%)	9 (23.1%)	1 (1.8%)	3 (15.8%)	<0.001[C]
	Once every 6 weeks, N (%)	11 (9.6%)	1 (2.6%)	10 (17.9%)	0 (0.0%)	
	Once every 7 weeks, N (%)	3 (2.6%)	0 (0.0%)	3 (5.4%)	0 (0.0%)	
	Once every 8 weeks, N (%)	66 (57.9%)	15 (38.5%)	41 (73.2%)	10 (52.6%)	
	Other, N (%)	21 (18.4%)	14 (35.9%)	1 (1.8%)	6 (31.6%)	

P-Value: A= ANOVA; C= CHISQ; E= Exact Fisher;
Abbreviations: IBD=Inflammatory bowel disease;
Source MS Excel Table: 1.1

Table 14 Laboratory Outcomes at Baseline and Follow-Up in IBD Patients Treated with Infliximab-dyyb

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
Recent C-reactive protein (mg/L)	N	73	40	26	17	0.1699[B]
	Mean (SD)	10.49 (22.69)	53.27 (239.09)	234.67 (1115.28)	8.19 (24.26)	
Recent fecal calprotectin (µg/g)	N	21	6	4	9	0.0312[B]
	Mean (SD)	932.84 (802.00)	142.45 (121.27)	78.58 (69.99)	271.47 (290.05)	
Recent drug level value (µg/mL)	N	5	13	12	9	0.6561[B]
	Mean (SD)	8.65 (14.35)	722.09 (2568.34)	8.27 (10.44)	15.51 (16.90)	
Recent anti-drug antibody value (µg/mL)	N	5	0	0	0	N/A
	Mean (SD)	5.82 (5.23)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
Recent C-reactive protein (mg/L)	N	32	23	12	5	0.1894[B]
	Mean (SD)	15.64 (30.70)	75.44 (311.50)	499.12 (1638.53)	21.56 (44.98)	
Recent fecal calprotectin (µg/g)	N	6	2	3	1	0.3743[B]
	Mean (SD)	1000.75 (625.54)	103.30 (13.15)	99.57 (68.58)	14.10 (.)	
Recent drug level value (µg/mL)	N	0	7	8	5	0.0399[B]
	Mean (SD)	0.00 (0.00)	1330.80 (3500.87)	6.74 (6.00)	15.10 (14.78)	
Recent anti-drug antibody value (µg/mL)	N	0	0	0	0	N/A
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
Recent C-reactive protein (mg/L)	N	24	12	8	11	0.0997[B]
	Mean (SD)	2.65 (3.62)	31.65 (76.96)	2.60 (2.96)	2.80 (2.27)	
Recent fecal calprotectin (µg/g)	N	8	3	1	6	0.4129[B]
	Mean (SD)	534.28 (509.45)	140.77 (177.95)	15.60 (.)	229.68 (273.94)	
Recent drug level value (µg/mL)	N	4	4	2	3	N/A

	Mean (SD)	10.73 (15.68)	6.77 (6.98)	18.50 (26.16)	20.80 (23.84)	
Recent anti-drug antibody value (µg/mL)	N	4	0	0	0	N/A
	Mean (SD)	6.35 (5.88)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
Recent C-reactive protein (mg/L)	N	17	5	6	1	0.7407[B]
	Mean (SD)	11.85 (17.98)	3.14 (3.95)	15.18 (30.30)	0.70 (.)	
Recent fecal calprotectin (µg/g)	N	7	1	0	2	0.4425[B]
	Mean (SD)	1330.14 (1055.73)	225.80 (.)	0.00 (0.00)	525.50 (303.35)	
Recent drug level value (µg/mL)	N	1	2	2	1	N/A
	Mean (SD)	0.36 (.)	22.22 (7.10)	4.15 (0.64)	1.70 (.)	
Recent anti-drug antibody value (µg/mL)	N	1	0	0	0	N/A
	Mean (SD)	3.70 (.)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	

P-Value: B: Mixed model for repeated measures (MMRM); N/A: not available due to small sample size; Abbreviations: IBD=Inflammatory bowel disease;
Source MS Excel Tables: 2.1.1- 2.1.4

15.2. Clinical Outcomes

Table 15 Clinical Outcomes at Baseline and Follow-up in UC Patients Treated with Infliximab-dyyb

		Baseline	3 months	6 months	12 months	P-value
All UC Patients		**(N = 48)**	**(N = 43)**	**(N = 37)**	**(N = 31)**	
pMAYO	Mean (SD)	3.85 (3.05)	1.44 (1.94)	1.11 (1.93)	0.90 (1.47)	<.0001[B]
UC remission	Yes, N (%)	17 (35.4%)	34 (79.1%)	29 (78.4%)	27 (87.1%)	<.0001[A]
	No, N (%)	31 (64.6%)	9 (20.9%)	8 (21.6%)	4 (12.9%)	
UC response	Yes, N (%)	-	18 (41.9%)	18 (48.6%)	12 (38.7%)	0.9792[A]
	No, N (%)	-	25 (58.1%)	19 (51.4%)	19 (61.3%)	
Biological Naïve Users		**(N = 18)**	**(N = 17)**	**(N = 16)**	**(N=11)**	
pMAYO	Mean (SD)	5.67 (2.25)	1.41 (1.42)	1.25 (2.18)	1.09 (1.22)	<.0001[B]
UC remission	Yes, N (%)	1 (5.6%)	14 (82.4%)	12 (75.0%)	10 (90.9%)	0.0015[A]
	No, N (%)	17 (94.4%)	3 (17.6%)	4 (25.0%)	1 (9.1%)	
UC response	Yes, N (%)	--	12 (70.6%)	13 (81.3%)	8 (72.7%)	0.7079[A]
	No, N (%)	--	5 (29.4%)	3 (18.8%)	3 (27.3%)	
Switched From RP Infliximab		**(N = 21)**	**(N = 18)**	**(N = 15)**	**(N = 17)**	
pMAYO	Mean (SD)	1.38 (1.83)	0.56 (1.20)	0.27 (1.03)	0.29 (0.85)	0.0103[B]
UC remission	Yes, N (%)	15 (71.4%)	16 (88.9%)	14 (93.3%)	16 (94.1%)	0.1007[A]
	No, N (%)	6 (28.6%)	2 (11.1%)	1 (6.7%)	1 (5.9%)	
UC response	Yes, N (%)	--	2 (11.1%)	2 (13.3%)	2 (11.8%)	0.4724[A]
	No, N (%)	--	16 (88.9%)	13 (86.7%)	15 (88.2%)	
Switched From Other Biologics		**(N = 9)**	**(N = 8)**	**(N = 6)**	**(N = 3)**	
pMAYO	Mean (SD)	6.00 (2.65)	3.50 (2.78)	2.83 (1.94)	3.67 (2.08)	0.0697[B]
UC remission	Yes, N (%)	1 (11.1%)	4 (50.0%)	3 (50.0%)	1 (33.3%)	0.1723[A]
	No, N (%)	8 (88.9%)	4 (50.0%)	3 (50.0%)	2 (66.7%)	
UC response	Yes, N (%)	--	4 (50.0%)	3 (50.0%)	2 (66.7%)	0.4371[A]
	No, N (%)	--	4 (50.0%)	3 (50.0%)	1 (33.3%)	

P-Value: A: Generalized estimating equations (GEE); B: Mixed model for repeated measures (MMRM)
Abbreviations: UC=Ulcerative colitis; pMAYO=partial MAYO score
Source MS Excel Tables: 2.2.1- 2.2.4

Table 16 Clinical Outcomes at Baseline and Follow-up in CD Patients Treated with Infliximab-dyyb

		Baseline	3 months	6 months	12 months	P-value
All CD Patients		**(N = 66)**	**(N = 63)**	**(N = 55)**	**(N = 48)**	
HBI score	Mean (SD)	3.45 (3.04)	3.11 (3.27)	3.45 (3.45)	2.98 (2.61)	0.3988[B]
CD remission	Yes, N (%)	48 (72.7%)	47 (74.6%)	39 (70.9%)	37 (77.1%)	0.8011[A]
	No, N (%)	18 (27.3%)	16 (25.4%)	16 (29.1%)	11 (22.9%)	
CD response	Yes, N (%)	-	10 (15.9%)	11 (20.0%)	7 (14.6%)	0.5068[A]
	No, N (%)	-	53 (84.1%)	44 (80.0%)	41 (85.4%)	
Biological Naïve Users		**(N = 20)**	**(N = 19)**	**(N = 16)**	**N=13**	
HBI score	Mean (SD)	4.30 (3.92)	3.16 (4.46)	2.75 (3.71)	2.23 (3.30)	0.1650[B]
CD remission	Yes, N (%)	13 (65.0%)	16 (84.2%)	12 (75.0%)	11 (84.6%)	0.1619[A]
	No, N (%)	7 (35.0%)	3 (15.8%)	4 (25.0%)	2 (15.4%)	
CD response	Yes, N (%)	--	4 (21.1%)	5 (31.3%)	4 (30.8%)	0.4277[A]
	No, N (%)	--	15 (78.9%)	11 (68.8%)	9 (69.2%)	
Switched From RP Infliximab		**(N = 36)**	**(N = 35)**	**(N = 34)**	**(N = 30)**	
HBI score	Mean (SD)	3.00 (2.66)	3.37 (2.73)	3.59 (3.06)	3.07 (1.98)	0.3822[B]
CD remission	Yes, N (%)	28 (77.8%)	23 (65.7%)	24 (70.6%)	23 (76.7%)	0.1077[A]
	No, N (%)	8 (22.2%)	12 (34.3%)	10 (29.4%)	7 (23.3%)	
CD response	Yes, N (%)	--	3 (8.6%)	4 (11.8%)	2 (6.7%)	0.4036[A]
	No, N (%)	--	32 (91.4%)	30 (88.2%)	28 (93.3%)	
Switched From Other Biologics		**(N = 10)**	**(N = 9)**	**(N = 5)**	**(N = 5)**	
HBI score	Mean (SD)	3.40 (2.12)	2.00 (2.12)	4.80 (5.22)	4.40 (3.78)	N/A
CD remission	Yes, N (%)	7 (70.0%)	8 (88.9%)	3 (60.0%)	3 (60.0%)	0.2381[A]
	No, N (%)	3 (30.0%)	1 (11.1%)	2 (40.0%)	2 (40.0%)	
CD response	Yes, N (%)	--	3 (33.3%)	2 (40.0%)	1 (20.0%)	0.6065[A]
	No, N (%)	--	6 (66.7%)	3 (60.0%)	4 (80.0%)	

P-Value: A: Generalized estimating equations (GEE); B: Mixed model for repeated measures (MMRM); N/A: not available because statistical model did not converge due to small sample size.
Abbreviations: CD=Crohn's disease; HBI=Harvey Bradshaw Index
Source MS Excel Tables: 2.3.1- 2.3.4

15.3. Patient-reported Outcomes

Table 17 Patient-reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

	Baseline	3 months	6 months		12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
SIBDQ score	Mean (SD)	43.77 (14.13)	50.41 (11.82)	52.75 (10.91)	54.47 (11.06)	<.0001[B]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
SIBDQ score	Mean (SD)	39.85 (14.20)	51.49 (13.09)	54.76 (10.30)	57.80 (9.76)	<.0001[B]
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
SIBDQ score	Mean (SD)	49.16 (12.16)	51.06 (10.13)	52.02 (11.31)	54.36 (11.35)	0.1348[B]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
SIBDQ score	Mean (SD)	35.63 (13.55)	46.00 (13.58)	50.33 (10.85)	45.78 (8.79)	0.0043[B]

P-Value: B: Mixed model for repeated measures (MMRM)
Abbreviations: IBD=Inflammatory bowel disease; SIBDQ=Short Inflammatory Bowel Disease Questionnaire
Source MS Excel Tables: 3.1.1- 3.1.4

Table 18 Patient-reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: EuroQol-visual analogue scale (EQ-VAS)

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
EQ-VAS Score	Mean (SD)	73.11 (19.38)	78.83 (16.90)	81.56 (14.82)	83.79 (14.55)	<.0001[B]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
EQ-VAS Score	Mean (SD)	68.05 (20.71)	78.54 (18.49)	82.52 (15.27)	85.36 (13.30)	0.0135[B]
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
EQ-VAS Score	Mean (SD)	78.49 (16.74)	80.13 (17.02)	81.39 (14.48)	84.77 (12.79)	0.0675[B]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
EQ-VAS Score	Mean (SD)	67.37 (20.51)	75.35 (12.81)	79.67 (16.06)	74.33 (23.05)	0.1686[B]

P-Value: B: Mixed model for repeated measures (MMRM)
Abbreviations: IBD=Inflammatory bowel disease; EQ-VAS=EuroQol-visual analogue scale
Source MS Excel Tables: 3.1.1- 3.1.4

Table 19 Patient-reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Treatment Satisfaction Questionnaire for Medication (TSQM)

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
TSQM effectiveness	Mean (SD)	63.94 (26.00)	68.69 (26.65)	72.25 (25.35)	76.56 (25.44)	0.0035[B]
TSQM side effects	Mean (SD)	74.88 (26.11)	78.75 (25.03)	81.51 (20.17)	84.54 (19.11)	0.0523[B]
TSQM convenience	Mean (SD)	75.19 (18.88)	77.67 (16.84)	78.55 (16.54)	77.61 (15.20)	0.3524[B]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
TSQM effectiveness	Mean (SD)	56.31 (22.05)	73.20 (24.54)	74.24 (27.11)	81.33 (22.86)	0.0003[B]
TSQM side effects	Mean (SD)	70.63 (23.86)	85.14 (20.05)	89.69 (17.70)	92.19 (19.36)	0.0020[B]
TSQM convenience	Mean (SD)	74.39 (17.28)	78.15 (15.69)	75.76 (18.95)	77.00 (17.78)	0.3924[B]
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
TSQM effectiveness	Mean (SD)	73.46 (24.39)	66.98 (27.78)	72.62 (25.97)	76.27 (24.84)	0.2358[B]
TSQM side effects	Mean (SD)	81.09 (23.43)	79.73 (23.53)	76.75 (21.29)	80.14 (19.07)	0.977[B]
TSQM convenience	Mean (SD)	78.43 (19.50)	78.45 (17.65)	82.87 (13.15)	79.67 (14.11)	0.1742[B]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
TSQM effectiveness	Mean (SD)	48.53 (27.04)	64.22 (27.60)	65.28 (16.98)	64.81 (33.54)	0.2335[B]
TSQM side effects	Mean (SD)	59.17 (33.90)	60.42 (33.52)	80.36 (16.09)	86.11 (13.61)	N/A
TSQM convenience	Mean (SD)	66.18 (17.55)	74.18 (17.20)	68.98 (17.32)	68.52 (10.02)	0.0823[B]

P-Value: B: Mixed model for repeated measures (MMRM); N/A: not available because statistical model did not converge due to small sample size;
Abbreviations: IBD=Inflammatory bowel disease; TSQM= Treatment Satisfaction Questionnaire for Medication;
Source MS Excel Tables: 3.3.1- 3.3.4

Table 20 Patient-reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Work Productivity and Activity Impairment (WPAI)

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
Recent Absenteeism Score	Mean (SD)	12.39 (25.53)	4.33 (14.93)	3.84 (13.68)	2.23 (9.30)	0.0059[B]
Recent Presenteeism Score	Mean (SD)	31.38 (30.97)	20.44 (26.68)	15.45 (23.74)	10.68 (19.55)	<.0001[B]
Overall work impairment score	Mean (SD)	35.34 (32.53)	22.08 (27.74)	18.82 (26.67)	11.78 (21.03)	<.0001[B]
Daily activity impairment score	Mean (SD)	37.79 (31.62)	26.98 (27.99)	20.16 (25.19)	15.63 (25.60)	<0.001[B]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
Recent Absenteeism Score	Mean (SD)	19.41 (32.33)	2.30 (5.66)	6.59 (22.15)	4.50 (15.66)	0.811[B]
Recent Presenteeism Score	Mean (SD)	43.81 (36.53)	16.19 (22.69)	12.38 (21.66)	7.37 (18.81)	0.0008[B]
Overall work impairment score	Mean (SD)	51.49 (37.20)	15.89 (24.31)	19.00 (28.57)	8.89 (23.24)	0.0038[B]
Daily activity impairment score	Mean (SD)	46.58 (31.99)	21.62 (25.00)	17.50 (23.56)	9.60 (19.89)	<.0001[B]
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
Recent Absenteeism Score	Mean (SD)	5.84 (11.66)	1.78 (5.83)	2.86 (6.52)	0.57 (2.85)	0.0262[B]
Recent Presenteeism Score	Mean (SD)	22.70 (23.53)	19.47 (24.49)	17.63 (24.87)	11.71 (20.51)	0.1565[B]
Overall work impairment score	Mean (SD)	25.71 (25.91)	20.73 (24.92)	19.33 (26.17)	12.21 (20.48)	0.0342[B]
Daily activity impairment score	Mean (SD)	27.14 (27.28)	25.93 (27.71)	22.35 (26.48)	16.09 (27.45)	0.3327[B]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
Recent Absenteeism Score	Mean (SD)	25.23 (42.53)	19.63 (36.07)	0.00 (0.00)	4.80 (5.96)	N/A
Recent Presenteeism Score	Mean (SD)	40.00 (36.97)	34.44 (40.35)	12.86 (25.63)	16.00 (16.73)	N/A
Overall work impairment score	Mean (SD)	42.44 (36.01)	41.48 (39.30)	15.00 (27.39)	19.15 (18.34)	N/A
Daily activity impairment score	Mean (SD)	51.58 (33.54)	44.00 (31.12)	18.18 (25.23)	30.00 (26.46)	0.0249[B]

P-Value: B: Mixed model for repeated measures (MMRM); N/A: not available because statistical model did not converge due to small sample size.
Abbreviations: IBD=Inflammatory bowel disease; WPAI= Work Productivity and Activity Impairment
Source MS Excel Tables: 3.2.1- 3.2.4

Table 21 Patient-reported Outcomes at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: General Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire Depression Scale (PHQ-8)

	Baseline	3 months	6 months		12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
GAD-7 score	Mean (SD)	5.37 (5.32)	4.14 (4.60)	3.84 (4.53)	3.14 (3.69)	0.0005[B]
PHQ-8 score	Mean (SD)	7.82 (6.29)	5.70 (5.14)	4.74 (4.43)	3.90 (4.08)	<.0001[B]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
GAD-7 score	Mean (SD)	5.82 (5.68)	3.84 (4.75)	2.64 (4.69)	2.48 (4.46)	0.0001[B]
PHQ-8 score	Mean (SD)	8.59 (7.00)	4.89 (5.07)	3.64 (4.59)	3.00 (4.71)	0.0009[B]
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
GAD-7 score	Mean (SD)	4.33 (4.24)	4.17 (4.41)	4.69 (4.51)	3.49 (3.44)	0.2876[B]
PHQ-8 score	Mean (SD)	5.86 (4.87)	5.31 (4.39)	5.24 (4.25)	3.98 (3.36)	0.0807[B]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
GAD-7 score	Mean (SD)	7.53 (6.82)	4.71 (5.10)	3.58 (3.60)	3.11 (2.52)	0.0076[B]
PHQ-8 score	Mean (SD)	12.11 (6.38)	8.71 (6.59)	5.67 (4.50)	6.00 (5.22)	0.0062[B]

P-Value: B: Mixed model for repeated measures (MMRM)
Abbreviations: IBD=Inflammatory bowel disease; GAD-7=General Anxiety Disorder-7; PHQ-8=Patient Health Questionnaire Depression Scale
Source MS Excel Tables: 6.1.1- 6.1.4

15.4. HCRU and Costs

Table 22 HCRU at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Hospitalizations

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
Patients with at least one hospitalization	N (%)	13 (11.3%)	7 (6.4%)	3 (3.0%)	3 (3.6%)	0.0628[A]
Mean number of hospitalizations	Mean (SD)	0.13 (0.39)	0.09 (0.37)	0.03 (0.17)	0.05 (0.26)	0.0366[A]
Mean length of stay (days) among patients with at least one hospitalization	Mean (SD)	7.23 (3.17)	8.00 (11.63)	7.67 (11.55)	3.67 (2.89)	N/A
Length of stay (days) per hospitalization among patients with at least one hospitalization	Mean (SD)	6.54 (3.12)	4.57 (5.51)	7.67 (11.55)	2.50 (0.87)	N/A
Presence of an IBD related admission among all patients	N (%)	11 (9.6%)	6 (5.5%)	1 (1.0%)	1 (1.2%)	0.0176[A]
Presence of an IBD related admission among patients with at least one hospitalization	N (%)	11 (84.6%)	6 (85.7%)	1 (33.3%)	1 (33.3%)	0.2551[A]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
Patients with at least one hospitalization	N (%)	7 (17.9%)	2 (5.4%)	1 (3.0%)	1 (4.0%)	0.1712[A]
Mean number of hospitalizations	Mean (SD)	0.21 (0.47)	0.05 (0.23)	0.03 (0.17)	0.04 (0.20)	0.0856[A]
Mean length of stay (days) among patients with at least one hospitalization	Mean (SD)	6.43 (3.74)	2.50 (0.71)	21.00 (.)	2.00 (.)	N/A
Length of stay (days) per hospitalization among patients with at least one hospitalization	Mean (SD)	5.93 (3.88)	2.50 (0.71)	21.00 (.)	2.00 (.)	N/A
Presence of an IBD related admission among all patients	N (%)	6 (15.4%)	2 (5.4%)	1 (3.0%)	0 (0.0%)	N/A
Presence of an IBD related admission among patients with at least one hospitalization	N (%)	6 (85.7%)	2 (100.0%)	1 (100.0%)	0 (0.0%)	N/A
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
Patients with at least one hospitalization	N (%)	0 (0.0%)	4 (7.3%)	1 (1.9%)	1 (2.0%)	N/A
Mean number of hospitalizations	Mean (SD)	0.00 (0.00)	0.11 (0.42)	0.02 (0.14)	0.02 (0.14)	N/A

Mean length of stay (days) among patients with at least one hospitalization	Mean (SD)	0.00 (0.00)	12.00 (14.85)	1.00 (.)	2.00 (.)	0.7395[B]
Length of stay (days) per hospitalization among patients with at least one hospitalization	Mean (SD)	0.00 (0.00)	6.38 (7.09)	1.00 (.)	2.00 (.)	0.7480[B]
Presence of an IBD related admission among all patients	N (%)	0 (0.0%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	N/A
Presence of an IBD related admission among patients with at least one hospitalization	N (%)	0 (0.0%)	3 (75.0%)	0 (0.0%)	0 (0.0%)	N/A
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
Patients with at least one hospitalization	N (%)	6 (31.6%)	1 (5.9%)	1 (8.3%)	1 (11.1%)	0.1667[A]
Mean number of hospitalizations	Mean (SD)	0.37 (0.60)	0.12 (0.49)	0.08 (0.29)	0.22 (0.67)	0.1406[A]
Mean length of stay (days) among patients with at least one hospitalization	Mean (SD)	8.17 (2.32)	3.00 (.)	1.00 (.)	7.00 (.)	N/A
Length of stay (days) per hospitalization among patients with at least one hospitalization	Mean (SD)	7.25 (2.04)	1.50 (.)	1.00 (.)	3.50 (.)	N/A
Presence of an IBD related admission among all patients	N (%)	5 (26.3%)	1 (5.9%)	0 (0.0%)	1 (11.1%)	N/A
Presence of an IBD related admission among patients with at least one hospitalization	N (%)	5 (83.3%)	1 (100.0%)	0 (0.0%)	1 (100.0%)	N/A

P-Value: A: Generalized estimating equations (GEE); B: Mixed model for repeated measures (MMRM); N/A: not available because statistical model did not converge due to small sample size.
Abbreviations: HCRU=Healthcare Resource Utilization; IBD=Inflammatory bowel disease;
Source MS Excel Tables: 5.1.1.1 – 5.1.4.2

Table 23 HCRU at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: ED Visits

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
Patients with at least one ED visit	N (%)	12 (10.4%)	8 (7.3%)	3 (3.0%)	3 (3.6%)	0.0884[A]
Mean number of ED visits	Mean (SD)	0.11 (0.34)	0.14 (0.66)	0.03 (0.17)	0.08 (0.44)	0.0523[A]
Mean number of IBD related ED visits	Mean (SD)	0.07 (0.26)	0.10 (0.61)	0.00 (0.00)	0.06 (0.32)	N/A
Total number of other ED visits	Mean (SD)	0.04 (0.24)	0.04 (0.19)	0.03 (0.17)	0.02 (0.15)	0.8998[A]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
Patients with at least one ED visit	N (%)	7 (17.9%)	3 (8.1%)	2 (6.1%)	0 (0.0%)	N/A
Mean number of ED visits	Mean (SD)	0.18 (0.39)	0.22 (1.00)	0.06 (0.24)	0.00 (0.00)	N/A
Mean number of IBD related ED visits	Mean (SD)	0.18 (0.39)	0.19 (1.00)	0.00 (0.00)	0.00 (0.00)	N/A
Total number of other ED visits	Mean (SD)	0.00 (0.00)	0.03 (0.16)	0.06 (0.24)	0.00 (0.00)	N/A
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
Patients with at least one ED visit	N (%)	2 (3.5%)	4 (7.3%)	1 (1.9%)	1 (2.0%)	0.5708[A]
Mean number of ED visits	Mean (SD)	0.05 (0.29)	0.09 (0.35)	0.02 (0.14)	0.06 (0.42)	0.4758[A]
Mean number of IBD related ED visits	Mean (SD)	0.00 (0.00)	0.05 (0.23)	0.00 (0.00)	0.04 (0.28)	N/A
Total number of other ED visits	Mean (SD)	0.05 (0.29)	0.04 (0.19)	0.02 (0.14)	0.02 (0.14)	0.8300[A]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
Patients with at least one ED visit	N (%)	3 (15.8%)	1 (5.9%)	0 (0.0%)	2 (22.2%)	N/A
Mean number of ED visits	Mean (SD)	0.16 (0.37)	0.12 (0.49)	0.00 (0.00)	0.44 (0.88)	N/A
Mean number of IBD related ED visits	Mean (SD)	0.05 (0.23)	0.06 (0.24)	0.00 (0.00)	0.33 (0.71)	N/A
Total number of other ED visits	Mean (SD)	0.11 (0.32)	0.06 (0.24)	0.00 (0.00)	0.11 (0.33)	N/A

P-Value: A: Generalized estimating equations (GEE); N/A: not available because statistical model did not converge due to small sample size.
Abbreviations: HCRU=Healthcare Resource Utilization; IBD=Inflammatory bowel disease; ED=Emergency Department; N/A: Not available because statistical model did not converge due to small sample size and since vast majority of patients had zero costs.
Source MS Excel Tables: 5.1.1.1 – 5.1.4.2

Table 24 HCRU at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Outpatient Visits

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
Patients with at least one outpatient visit	N (%)	54 (47.0%)	76 (69.7%)	57 (57.6%)	58 (69.0%)	0.0006[A]
Mean number of outpatient visits	Mean (SD)	1.44 (3.45)	1.41 (1.36)	1.13 (1.51)	1.55 (1.66)	0.1674[A]
Mean number of GP/internist visits	Mean (SD)	0.30 (1.16)	0.56 (0.81)	0.32 (0.59)	0.55 (0.94)	0.0262[A]
Mean number of gastroenterologist visits	Mean (SD)	0.78 (1.67)	0.61 (0.71)	0.52 (0.75)	0.69 (0.78)	0.2836[A]
Mean number of other outpatient visits	Mean (SD)	0.36 (1.48)	0.25 (0.58)	0.29 (0.72)	0.31 (0.71)	0.7469[A]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
Patients with at least one outpatient visit	N (%)	17 (43.6%)	27 (73.0%)	25 (75.8%)	16 (64.0%)	0.0796[A]
Mean number of outpatient visits	Mean (SD)	1.51 (3.78)	1.51 (1.43)	1.36 (1.25)	1.20 (1.15)	0.7265[A]
Mean number of GP/internist visits	Mean (SD)	0.18 (0.60)	0.54 (0.77)	0.27 (0.45)	0.44 (0.71)	0.1299[A]
Mean number of gastroenterologist visits	Mean (SD)	0.92 (1.58)	0.73 (0.73)	0.79 (0.82)	0.60 (0.71)	0.5714[A]
Mean number of other outpatient visits	Mean (SD)	0.41 (2.09)	0.24 (0.64)	0.30 (0.77)	0.16 (0.37)	0.7594[A]
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
Patients with at least one outpatient visit	N (%)	25 (43.9%)	36 (65.5%)	25 (46.3%)	34 (68.0%)	0.0119[A]
Mean number of outpatient visits	Mean (SD)	0.89 (1.70)	1.35 (1.39)	0.85 (1.38)	1.42 (1.43)	0.0889[A]
Mean number of GP/internist visits	Mean (SD)	0.26 (0.64)	0.64 (0.89)	0.28 (0.53)	0.44 (0.79)	0.0616[A]
Mean number of gastroenterologist visits	Mean (SD)	0.35 (0.69)	0.45 (0.63)	0.31 (0.61)	0.68 (0.82)	0.1011[A]
Mean number of other outpatient visits	Mean (SD)	0.28 (0.94)	0.25 (0.55)	0.26 (0.68)	0.30 (0.74)	0.9697[A]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
Patients with at least one outpatient visit	N (%)	12 (63.2%)	13 (76.5%)	7 (58.3%)	8 (88.9%)	0.1836[A]
Mean number of outpatient visits	Mean (SD)	2.95 (5.72)	1.41 (1.18)	1.75 (2.38)	3.22 (2.91)	0.2581[A]
Mean number of GP/internist visits	Mean (SD)	0.68 (2.52)	0.35 (0.61)	0.67 (0.98)	1.44 (1.67)	0.3341[A]
Mean number of gastroenterologist visits	Mean (SD)	1.79 (3.05)	0.82 (0.81)	0.67 (0.89)	1.00 (0.71)	0.5136[A]
Mean number of other outpatient visits	Mean (SD)	0.47 (1.39)	0.24 (0.56)	0.42 (0.79)	0.78 (1.09)	0.3525[A]

P-Value: A: Generalized estimating equations (GEE)
Abbreviations: HCRU=Healthcare Resource Utilization; IBD=Inflammatory bowel disease; GP=General Practitioner;

Source MS Excel Tables: 5.1.1.1 – 5.1.4.2

Table 25 Healthcare Costs at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Inpatient Costs

		Baseline	3 months	6 months	12 months	P-value
All IBD Patients						
		(N = 115)	**(N = 109)**	**(N = 99)**	**(N = 84)**	
IBD-related inpatient costs	$, Mean (SD)	1280.92 (4088.05)	899.63 (3997.72)	139.08 (1383.86)	152.59 (1398.52)	N/A
IBD-related medical costs	$, Mean (SD)	1280.92 (4088.05)	773.31 (3378.45)	0.00 (0.00)	70.63 (647.35)	N/A
IBD-related surgical costs	$, Mean (SD)	0.00 (0.00)	126.32 (1318.85)	139.08 (1383.86)	81.96 (751.17)	N/A
General medical costs	$, Mean (SD)	328.50 (2616.47)	115.53 (1206.13)	127.20 (1265.58)	74.95 (686.97)	N/A
Total inpatient costs	$, Mean (SD)	1609.41 (4765.41)	1227.26 (5204.50)	499.80 (2958.75)	365.16 (1982.92)	N/A
Biological Naïve Users						
		(N = 39)	**(N = 37)**	**(N = 33)**	**(N = 25)**	
IBD-related inpatient costs	$, Mean (SD)	2224.28 (5539.92)	674.60 (2864.65)	417.25 (2396.92)	0.00 (0.00)	N/A
IBD-related medical costs	$, Mean (SD)	2224.28 (5539.92)	674.60 (2864.65)	0.00 (0.00)	0.00 (0.00)	N/A
IBD-related surgical costs	$, Mean (SD)	0.00 (0.00)	0.00 (0.00)	417.25 (2396.92)	0.00 (0.00)	N/A
General medical costs	$, Mean (SD)	322.88 (2016.40)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N/A
Total inpatient costs	$, Mean (SD)	2547.16 (5769.09)	674.60 (2864.65)	417.25 (2396.92)	462.38 (2311.89)	N/A
Switched From RP Infliximab						
		(N = 57)	**(N = 55)**	**(N = 54)**	**(N = 50)**	
IBD-related inpatient costs	$, Mean (SD)	0.00 (0.00)	897.59 (4069.90)	0.00 (0.00)	0.00 (0.00)	N/A
IBD-related medical costs	$, Mean (SD)	0.00 (0.00)	647.24 (2719.51)	0.00 (0.00)	0.00 (0.00)	N/A
IBD-related surgical costs	$, Mean (SD)	0.00 (0.00)	250.35 (1856.64)	0.00 (0.00)	0.00 (0.00)	N/A
General medical costs	$, Mean (SD)	0.00 (0.00)	228.95 (1697.96)	0.00 (0.00)	125.92 (890.42)	N/A
Total inpatient costs	$, Mean (SD)	0.00 (0.00)	1546.88 (6210.00)	428.13 (3146.08)	125.92 (890.42)	N/A
Switched From Other Biologics						
		(N = 19)	**(N = 17)**	**(N = 12)**	**(N = 9)**	
IBD-related inpatient costs	$, Mean (SD)	3187.28 (5485.61)	1396.00 (5755.87)	0.00 (0.00)	1424.18 (4272.55)	N/A
IBD-related medical costs	$, Mean (SD)	3187.28 (5485.61)	1396.00 (5755.87)	0.00 (0.00)	659.22 (1977.67)	N/A

IBD-related surgical costs	$, Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	764.96 (2294.87)	N/A
General medical costs	$, Mean (SD)	1325.52 (5777.79)	0.00 (0.00)	1049.37 (3635.11)	0.00 (0.00)	N/A
Total inpatient costs	$, Mean (SD)	4512.80 (7386.19)	1396.00 (5755.87)	1049.37 (3635.11)	1424.18 (4272.55)	N/A

P-Value: N/A: Not available because statistical model did not converge due to small sample size and since vast majority of patients had zero costs.
Abbreviations: IBD=Inflammatory bowel disease
Source MS Excel Tables: 5.2.1 – 5.2.4

Table 26 Healthcare Costs at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Emergency Room (ER) Costs

		Baseline	3 months	6 months	12 months	P value
All IBD Patients						
		(N = 115)	**(N = 109)**	**(N = 99)**	**(N = 84)**	
IBD related ER costs	$, Mean (SD)	339.56 (1248.83)	507.74 (3097.55)	0.00 (0.00)	152.29 (828.46)	N/A
General ER costs	$, Mean (SD)	46.32 (259.86)	39.10 (201.23)	32.28 (183.55)	12.68 (81.70)	0.3430[A]
Total ER costs	$, Mean (SD)	385.88 (1263.08)	546.84 (3128.55)	32.28 (183.55)	164.98 (887.48)	N/A
Biological Naïve Users						
		(N = 39)	**(N = 37)**	**(N = 33)**	**(N = 25)**	
IBD related ER costs	$, Mean (SD)	870.06 (1887.25)	955.34 (5083.85)	0.00 (0.00)	0.00 (0.00)	N/A
General ER costs	$, Mean (SD)	0.00 (0.00)	28.79 (175.14)	64.57 (258.14)	0.00 (0.00)	0.3559[A]
Total ER costs	$, Mean (SD)	870.06 (1887.25)	984.13 (5081.30)	64.57 (258.14)	0.00 (0.00)	N/A
Switched From RP Infliximab						
		(N = 57)	**(N = 55)**	**(N = 54)**	**(N = 50)**	
IBD related ER costs	$, Mean (SD)	0.00 (0.00)	279.11 (1172.74)	0.00 (0.00)	102.34 (723.66)	N/A
General ER costs	$, Mean (SD)	56.07 (313.27)	38.74 (201.27)	19.73 (144.98)	10.65 (75.33)	0.5776[A]
Total ER costs	$, Mean (SD)	56.07 (313.27)	317.85 (1263.22)	19.73 (144.98)	112.99 (798.99)	N/A
Switched From Other Biologics						
		(N = 19)	**(N = 17)**	**(N = 12)**	**(N = 9)**	
IBD related ER costs	$, Mean (SD)	269.32 (1173.93)	273.25 (1126.65)	0.00 (0.00)	852.84 (1809.15)	N/A
General ER costs	$, Mean (SD)	112.14 (335.91)	62.67 (258.39)	0.00 (0.00)	59.19 (177.56)	0.2727[A]
Total ER costs	$, Mean (SD)	381.46 (1194.65)	335.92 (1385.04)	0.00 (0.00)	912.03 (1879.28)	N/A

P-Value: A: Generalized estimating equations (GEE); N/A: Not available because statistical model did not converge due to small sample size and since vast majority of patients had zero costs.
Abbreviations: IBD=Inflammatory bowel disease; ER= Emergency Room
Source MS Excel Tables: 5.2.1 – 5.2.4

Table 27 Healthcare Costs at Baseline and Follow-up in IBD Patients Treated with Infliximab-dyyb: Outpatient Costs

		Baseline	3 months	6 months	12 months	P value
All IBD Patients		**(N = 115)**	**(N = 109)**	**(N = 99)**	**(N = 84)**	
General practitioner visit costs	$, Mean (SD)	33.56 (128.32)	61.72 (89.33)	35.65 (64.63)	30.20 (51.64)	0.0136[A]
Gastroenterologist visit costs	$, Mean (SD)	115.64 (247.39)	89.47 (104.52)	76.12 (110.42)	51.01 (57.31)	0.0008[A]
Other outpatient visit costs	$, Mean (SD)	52.68 (218.98)	36.60 (85.68)	43.28 (106.07)	22.87 (52.53)	0.2854[A]
Total outpatient visit costs	$, Mean (SD)	201.88 (474.75)	187.79 (180.94)	155.05 (207.41)	104.08 (110.12)	0.0002[A]
Biological Naïve Users		**(N = 39)**	**(N = 37)**	**(N = 33)**	**(N = 25)**	
General practitioner visit costs	$, Mean (SD)	19.79 (66.32)	59.61 (84.61)	30.08 (49.88)	24.26 (39.25)	0.0739[A]
Gastroenterologist visit costs	$, Mean (SD)	136.39 (233.35)	107.82 (108.18)	116.42 (121.16)	44.33 (52.24)	0.0038[A]
Other outpatient visit costs	$, Mean (SD)	60.62 (308.30)	35.94 (94.78)	44.78 (113.77)	11.82 (27.64)	0.3262[A]
Total outpatient visit costs	$, Mean (SD)	216.81 (541.00)	203.38 (192.41)	191.27 (176.44)	80.41 (76.57)	0.0034[A]
Switched From RP Infliximab		**(N = 57)**	**(N = 55)**	**(N = 54)**	**(N = 50)**	
General practitioner visit costs	$, Mean (SD)	29.02 (70.76)	70.18 (98.10)	30.63 (58.34)	24.26 (43.37)	0.0186[A]
Gastroenterologist visit costs	$, Mean (SD)	51.85 (102.57)	67.16 (93.53)	46.52 (89.97)	50.24 (60.52)	0.5526[A]
Other outpatient visit costs	$, Mean (SD)	41.48 (138.93)	37.61 (81.52)	38.31 (100.20)	22.16 (54.33)	0.6766[A]
Total outpatient visit costs	$, Mean (SD)	122.34 (232.13)	174.95 (180.23)	115.46 (189.80)	96.66 (97.60)	0.0371[A]
Switched From Other Biologics		**(N = 19)**	**(N = 17)**	**(N = 12)**	**(N = 9)**	
General practitioner visit costs	$, Mean (SD)	75.45 (277.66)	38.92 (66.87)	73.52 (108.60)	79.65 (91.90)	0.5972[A]
Gastroenterologist visit costs	$, Mean (SD)	264.41 (450.28)	121.68 (119.53)	98.51 (131.16)	73.88 (52.24)	0.2280[A]
Other outpatient visit costs	$, Mean (SD)	69.99 (205.27)	34.77 (83.08)	61.57 (117.17)	57.46 (80.74)	0.5845[A]
Total outpatient visit costs	$, Mean (SD)	409.86 (758.80)	195.37 (163.92)	233.59 (317.41)	210.99 (186.85)	0.6559[A]

P-Value: A: Generalized estimating equations (GEE); Abbreviations: IBD=Inflammatory bowel disease
Source MS Excel Tables: 5.2.1 – 5.2.4

15.5. Adverse Events

Table 28 Adverse Events in IBD Patients Treated with Infliximab-dyyb: Patient Level Summary

		All	Biological Naïve Users	Switched From RP Infliximab	Switched From Other Biologics	P value
		(N = 115)	**(N = 39)**	**(N = 57)**	**(N = 19)**	
Proportion of patients with any AE	Yes, N (%)	40 (34.8%)	11 (28.2%)	19 (33.3%)	10 (52.6%)	0.177[C]
	No, N (%)	75 (65.2%)	28 (71.8%)	38 (66.7%)	9 (47.4%)	
Proportion of patients with any serious AE	Yes, N (%)	19 (16.5%)	5 (12.8%)	11 (19.3%)	3 (15.8%)	0.795[E]
	No, N (%)	96 (83.5%)	34 (87.2%)	46 (80.7%)	16 (84.2%)	
Proportion of patients who died	Yes, N (%)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	N/A
	No, N (%)	115 (100.0%)	39 (100.0%)	57 (100.0%)	19 (100.0%)	

P-Value: C= CHISQ; E= Exact Fisher;
Abbreviations: IBD=Inflammatory bowel disease; AE=adverse event; N/A: not applicable because no patient had death during the study period.
Source MS Excel Table: 6.2.1

Table 29 Adverse Events in IBD Patients Treated with Infliximab-dyyb: Event Level Summary

		All	Biological Naïve Users	Switched From RP Infliximab	Switched From Other Biologics	P value
		(N = 59)	(N = 18)	(N = 24)	(N = 17)	
Severity of AE among patients with an AE	Mild, N (%)	29 (49.2%)	8 (44.4%)	11 (45.8%)	10 (58.8%)	0.644[C]
	Moderate, N (%)	23 (39.0%)	9 (50.0%)	9 (37.5%)	5 (29.4%)	
	Severe, N (%)	7 (11.9%)	1 (5.6%)	4 (16.7%)	2 (11.8%)	
Presence of a serious AE among patients with an AE	Yes, N (%)	24 (40.7%)	6 (33.3%)	12 (50.0%)	6 (35.3%)	0.479[C]
	No, N (%)	35 (59.3%)	12 (66.7%)	12 (50.0%)	11 (64.7%)	
Relationship of AE to study treatment among patients with an AE	Definite, N (%)	9 (15.3%)	1 (5.6%)	6 (25.0%)	2 (11.8%)	0.151[C]
	Possible, N (%)	6 (10.2%)	2 (11.1%)	3 (12.5%)	1 (5.9%)	
	Probable, N (%)	7 (11.9%)	2 (11.1%)	1 (4.2%)	4 (23.5%)	
	Unlikely, N (%)	14 (23.7%)	2 (11.1%)	8 (33.3%)	4 (23.5%)	
	Unrelated, N (%)	23 (39.0%)	11 (61.1%)	6 (25.0%)	6 (35.3%)	
Action taken with study treatment among patients with an AE	Medication, N (%)	4 (6.8%)	2 (11.1%)	1 (4.2%)	1 (5.9%)	0.006[C]
	None, N (%)	26 (44.1%)	11 (61.1%)	12 (50.0%)	3 (17.6%)	
	Procedure, N (%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	
	Study drug changed, N (%)	4 (6.8%)	0 (0.0%)	3 (12.5%)	1 (5.9%)	
	Study drug stopped, N (%)	18 (30.5%)	5 (27.8%)	8 (33.3%)	5 (29.4%)	
	Other, N (%)	6 (10.2%)	0 (0.0%)	0 (0.0%)	6 (35.3%)	
Outcome of AE among patients with an AE	Not Recovered / Not Resolved, N (%)	8 (13.6%)	3 (16.7%)	2 (8.3%)	3 (17.6%)	0.827[C]

	Recovered / Resolved, N (%)	37 (62.7%)	12 (66.7%)	15 (62.5%)	10 (58.8%)
	Recovering / Resolving, N (%)	9 (15.3%)	1 (5.6%)	5 (20.8%)	3 (17.6%)
	Unknown, N (%)	5 (8.5%)	2 (11.1%)	2 (8.3%)	1 (5.9%)

P-Value: C= CHISQ
Abbreviations: IBD=Inflammatory bowel disease; AE=adverse event;
Source MS Excel Table: 6.2.2

Table 30 Adverse Events in IBD Patients Treated with Infliximab-dyyb: Frequency of Adverse Events Related to or Unrelated to Treatment

	Infliximab-dyyb (n=115)
Average weeks of follow-up	52
Cardiac	1 (4.5%)
Gastrointestinal Disorders	17 (77.3%)
General Disorders	2 (9.1%)
Hepatotoxicity	1 (4.5%)
Hypersensitivity Reaction	2 (9.1%)
Immunogenicity	1 (4.5%)
Infusion reaction	4 (18.2%)
Lupus-like syndrome	1 (4.5%)
Malignancy	4 (18.2%)
Musculoskeletal System Disorders	5 (22.7%)
Other	2 (9.1%)
Platelet, Bleeding and Clotting Disorders	2 (9.1%)
Respiratory	9 (40.9%)
Serious infection	5 (22.7%)
Skin and Appendages Disorders	3 (13.6%)

Source MS Excel Table: N/A

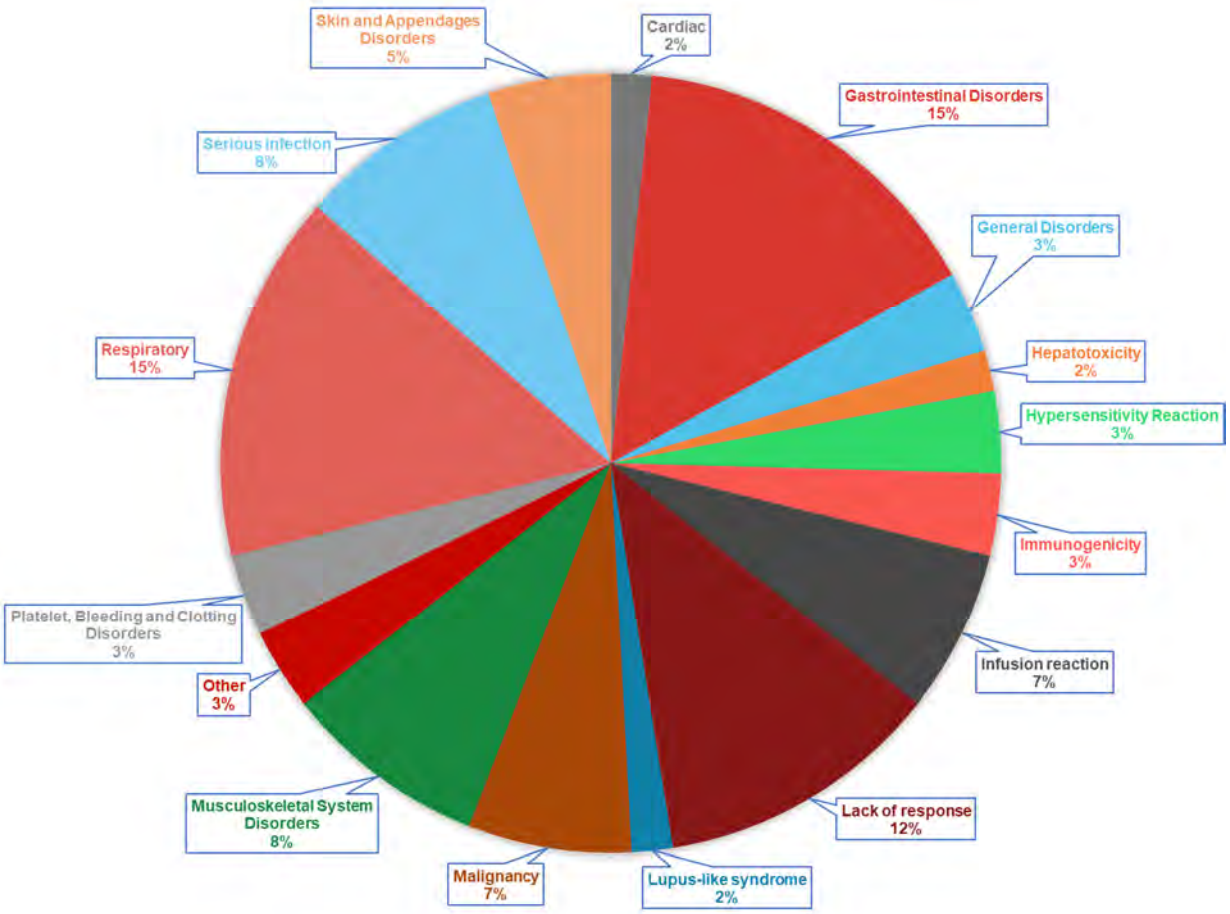

Figure 8 Adverse Events in IBD Patients Treated with Infliximab-dyyb: Frequency of Adverse Events Related to or Unrelated to Treatment

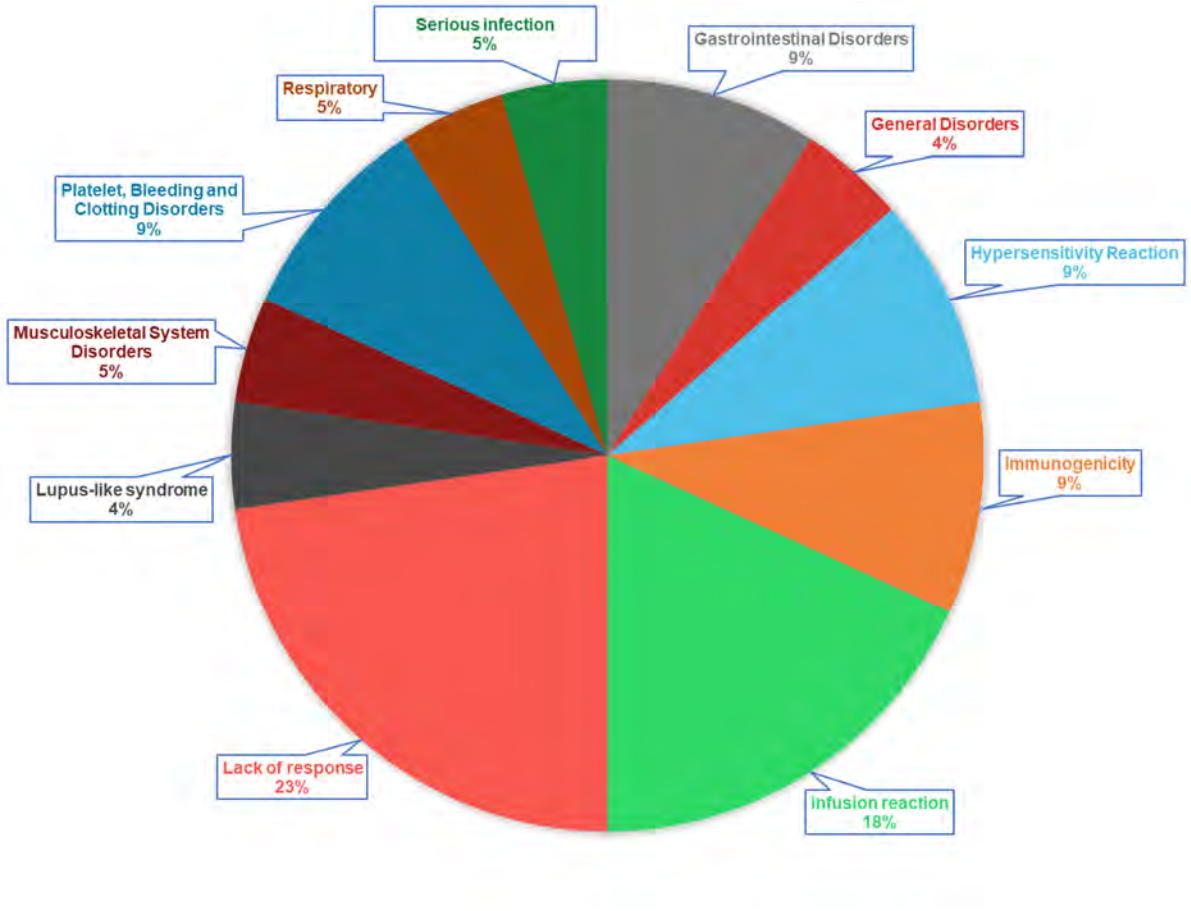

Figure 9 Adverse Events in IBD Patients Treated with Infliximab-dyyb: Frequency of Adverse Events Related to Treatment

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