

## **Vedolizumab and Anti-TNF $\alpha$ Real-World Outcomes in Biologic-Naïve Inflammatory Bowel Disease Patients: Results from the EVOLVE Study**

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## Author's Contributions

ICMJE criteria for authorship were read and met by all authors. All authors agree with the manuscript's results and conclusions. BB, AY, GJM, MSS, DD, MB, and DS designed the study. All authors contributed to data collection. MB, DS, DD, analysed the data with data interpretation led by BB, AY and GJM and contributions by all authors. MB, DS and DD wrote the first draft of the manuscript and all authors critically reviewed the manuscript. All authors approved the final version of the manuscript.

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## Abbreviations

Abbreviation	Definition
AE	Adverse event
Anti-TNF $\alpha$	Anti-tumour necrosis factor–alpha
ASA	Aminosalicylate
BMI	Body mass index
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CRP	C-reactive protein
EMA	European Medicines Agency
FCP	Faecal calprotectin
FDA	Food and Drug Administration
GI	Gastrointestinal
GSALT	Gut-selective anti-lymphocyte trafficking
HBI	Harvey-Bradshaw Index
HR	Hazard ratio
IPW	Inverse probability weighting
KM	Kaplan-Meier
MAdCAM-1	Mucosal vascular address in cell adhesion molecule 1
MRI	Magnetic resonance imaging
PNR	Primary non-response
PY	Person year
SAE	Serious adverse event
SD	Standard deviation

<b>SI</b>	Serious infection
<b>SLOR</b>	Secondary loss of response
<b>TNF</b>	Tumour necrosis factor
<b>UC</b>	Ulcerative colitis
<b>UCEIS</b>	Ulcerative Colitis Endoscopic Index of Severity
<b>US</b>	United States

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## ABSTRACT

**Background and aims:** This study aimed to compare real-world clinical effectiveness and safety of vedolizumab, an  $\alpha 4\beta 7$ -integrin inhibitor, and anti-tumour necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) agents in biologic-naïve ulcerative colitis (UC) and Crohn's disease (CD) patients.

**Methods:** This was a 24-month retrospective medical chart study in adult UC and CD patients treated with vedolizumab or anti-TNF $\alpha$  in Canada, Greece and the United States. Inverse probability weighting was used to account for differences between groups. Primary outcomes were cumulative rates of clinical effectiveness (clinical response, clinical remission, mucosal healing) and incidence rates of serious adverse events (SAEs) and serious infections (SIs). Secondary outcomes included cumulative rates of treatment persistence (patients who did not discontinue index treatment during follow-up) and dose escalation and incidence rates of disease exacerbations and disease-related surgeries. Adjusted analyses were performed using inverse probability weighting.

**Results:** A total of 1095 patients (604 UC, 491 CD) were included. By 24 months, rates of clinical effectiveness were similar between groups, but incidence rates of SAEs (HR=0.42 [0.28-0.62]) and SIs (HR=0.40 [0.19-0.85]) were significantly lower in vedolizumab vs anti-TNF $\alpha$  patients. Rates of treatment persistence ( $p < 0.01$ ) by 24 months were higher in vedolizumab patients with UC. Incidence rates of disease exacerbations were lower in vedolizumab patients with UC (HR=0.58 [0.45-0.76]). Other outcomes did not significantly differ between groups.

**Conclusion:** In this real-world setting, first-line biologic therapy in biologic-naïve patients with UC and CD demonstrated that vedolizumab and anti-TNF $\alpha$  treatments were equally effective at controlling disease symptoms, but vedolizumab has a more favourable safety profile.

**Keywords:** vedolizumab, biologic-naïve, real-world effectiveness

## INTRODUCTION

Inflammatory bowel disease (IBD) is a collective term for several conditions manifesting through gastrointestinal tract inflammation and include ulcerative colitis (UC) and Crohn's disease (CD).<sup>1</sup> UC and CD are chronic diseases often requiring life-long treatment and frequent hospitalization, resulting in reduced quality of life and substantial healthcare utilization.<sup>2</sup> Biologic therapies are a class of drugs used in the treatment of moderate-severe IBD. While anti-tumour necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) agents were the first biologics approved for IBD treatment, loss of response to treatment and the systemic nature of anti-TNF $\alpha$  treatments have led to a need to identify inhibitors of alternative signalling pathways.<sup>3</sup>

Vedolizumab is a gut-selective anti-lymphocyte trafficking (GSALT) agent approved for the treatment of moderate-severe UC and CD. It is a humanized monoclonal antibody which selectively antagonizes  $\alpha 4\beta 7$  gastrointestinal integrin receptors, resulting in reduced lymphocyte trafficking into intestinal tissue.<sup>4</sup> In the GEMINI phase III clinical trials, vedolizumab demonstrated greater efficacy in biologic-naïve patients vs those with non-response to anti-TNF $\alpha$  agents.<sup>5, 6</sup> Real-world studies of vedolizumab have shown high rates of clinical effectiveness over 44 weeks<sup>7</sup> (24/35 [68.6%] of biologic-naïve patients in clinical remission) and similar effectiveness to anti-TNF $\alpha$  treatments (12 month clinical remission: vedolizumab 38%, anti-TNF $\alpha$ : 34%) in predominately anti-TNF $\alpha$  exposed patients.<sup>8</sup> In biologic-naïve patients (IBM Explorlys database) greater treatment persistence of vedolizumab versus infliximab (77.6% vs. 64.6%;  $p=0.0005$ ) was observed over 24 months.<sup>9</sup> To guide physician decision making on the most suitable first-line biologic, comparing anti-TNF $\alpha$  to vedolizumab in a real world setting of biologic-naïve patients is critical.

The primary objective of this study was to compare the real-world clinical effectiveness and safety of vedolizumab and anti-TNF $\alpha$  over 24 months post-treatment initiation in biologic-naïve UC and CD patients. Additional objectives over 24 months were to describe treatment patterns associated with first-line biologic use as well as the incidence of IBD-related

surgical procedures and disease exacerbations. This analysis also looked at the clinical effectiveness of first-line biologic anti-TNF $\alpha$  compared to second-line anti-TNF $\alpha$  post-vedolizumab discontinuation over 6 months.

## MATERIALS AND METHODS

### Study Design

This was a multi-country (US, Canada and Greece), multi-center, retrospective cohort study conducted with an eligibility period for initiating first-line biologic vedolizumab or anti-TNF $\alpha$  treatment between May 20, 2014 and July 31, 2017. Eligibility periods were based on approval dates by the Food and Drug Administration (20 May 2014), Health Canada (UC: 19 May 2015, CD: 19 May 2016), and the European Medicines Agency (22 May 2014). Data abstraction occurred September 21, 2017 to December 14, 2018. Adult patients ( $\geq 18$  years) diagnosed with UC or CD, who were biologic naïve and initiated first-line biologic “index treatment” with either vedolizumab or an anti-TNF $\alpha$  (infliximab, infliximab biosimilars, adalimumab, adalimumab biosimilars, golimumab or certolizumab pegol; US and Canada and only) during the eligibility periods, and had  $\geq 6$  months of follow-up data were included in the study. Patients were identified using hospital medical record databases. This study included patients receiving concomitant non-biologic therapies (aminosalicylates, corticosteroids, immunomodulators). While data collection included three CD patients receiving ustekinumab, these patients were not included in the final analysis dataset to focus results on the comparison between vedolizumab and anti-TNF $\alpha$  treatments. In Canada, CD patients were also eligible if they had received vedolizumab prior to approval through a compassionate use access program (n=9). For Greece, only patients who initiated vedolizumab were included into the study. Patients were excluded if their index treatment was administered as part of a clinical trial, if they had initiated treatment as combination therapy with two biologic agents, or if they had received prior treatment with biologic agents.

In the US, patients were randomly selected in order to include similar numbers of vedolizumab and anti-TNF $\alpha$  patients and to minimize the potential for selection bias. Random selection was performed after patients were deemed eligible for the study, prior to data abstraction.

The post-index treatment follow-up period was defined as time between index treatment initiation and the earliest date of chart abstraction initiation, death, last contact with the site, or 6 months post-treatment discontinuation (Canada only). Data was also collected at baseline (index treatment initiation) and prior to treatment initiation, as far back as disease diagnosis.

There were 37 sites included in this study across three countries (USA: 15 sites; Canada: 13 sites; Greece: 9 sites); sites were comprised of university/academic hospitals and private practice centers and were geographically dispersed and of varied sizes. The study received ethics and any other local approvals in line with country specific requirements.

### **Data Collection and Outcome Measures**

All data were collected retrospectively from patient medical charts. Patient demographics, clinical and treatment history were collected and disease severity at baseline was determined using the closest assessment to treatment initiation (within  $\leq 6$  months prior to index) using a hierarchical algorithm of standard clinical assessments for severity (Supplemental Table 1). Data collected post-index treatment initiation included treatment patterns, clinical effectiveness, disease exacerbations (worsening of symptoms attributed to CD or UC), hospitalizations, surgical procedures, and safety events. Study outcomes of interest for treatment patterns included treatment persistence, defined as patients who did not discontinue their index treatment for any reason during the study follow-up period, and dose escalation, defined as an increase in index treatment frequency (vedolizumab) or dose and/or treatment frequency (anti-TNF $\alpha$ ) for  $\geq 2$  consecutive drug administrations. Due to limited follow-up on the subset of patients on second-line biologic anti-TNF $\alpha$  treatment post-vedolizumab discontinuation, outcomes were assessed up to 6 months after initiating second-line anti-TNF $\alpha$ . Clinical outcomes were assessed, and clinical response, clinical remission and mucosal healing were defined based on a hierarchical algorithm utilizing standard measures of disease activity (definitions below; further detailed in Supplemental Figures 1-10).

### Clinical Outcomes Definitions in Patients with UC

Clinical response was defined as: Mayo overall score: reduction in score of at least three points and a decrease of at least 30% from the baseline score, with a decrease of at least one point on the rectal bleeding subscale OR an absolute rectal bleeding score of 0 or 1, or if unknown, partial Mayo score: reduction in score of at least two points and a decrease of at least 30% from the baseline score, with a decrease of at least one point on the rectal bleeding subscale OR an absolute rectal bleeding score of 0 or 1 or if unknown, treatment response recorded in the medical chart as 'complete response' or 'partial response', or if unknown, physician global assessment: decrease of  $\geq 1$  point (or improvement by  $\geq 1$  category) from baseline.

Clinical remission was defined as Mayo overall score: score  $\leq 2$  points, with no individual sub score  $> 1$ ; or in absence of available subscores patients were classified in remission if the overall score was  $\leq 2$ , or if unknown, Partial Mayo score: score  $\leq 2$  points, with no individual sub score  $> 1$ ; or in absence of available subscores patients were classified in remission if the overall score was  $\leq 2$ , or if unknown, treatment response recorded in the medical chart as 'in remission', or if unknown, Physician global assessment: score of 0 (normal).

Mucosal healing was defined as Endoscopic assessment score = 0 or 1 (i.e., normal or inactive disease or mild disease), or if unknown, one or more endoscopic procedure finding(s) from the CRF drop down list indicating inactive disease (no findings/no active disease, no erosion, no ulcers, no inflammation or inflammatory activity, or no pathological findings), UCEIS score = 0 (i.e., normal or inactive disease or mild disease).

### Clinical Outcomes Definitions in Patients with UC

Clinical response was defined as Crohn's Disease Activity Index (CDAI): positive change in category from baseline (CDAI categories include: score  $< 150$ , score of 151-219, score of 220-450, score  $> 450$ ), or if unknown, Harvey-Bradshaw Index (HBI) Overall: decrease of  $\geq 3$  points from baseline, or if unknown, Modified HBI: This has the same cut-offs and definition as HBI Overall, shown above, or if unknown, Treatment response recorded in the medical chart as 'complete response' or 'partial response'.

Clinical remission was defined as CDAI score of  $< 150$  points, or if unknown, HBI score of  $\leq 4$  points, or if unknown, Modified HBI score of  $\leq 4$  points, or if unknown, Remission status recorded in the medical chart as 'in remission'.

Mucosal healing was defined as endoscopic assessment score = 0 or 1 (i.e., normal or inactive disease or mild disease), or if unknown, SES-CD score of  $< 3$  (not derived but based on CRF documentation of score) [SESCD], Lack of ulceration' defined by one or more of the following endoscopic procedure finding(s) from the CRF drop down list- either selection of 'no ulcers' or free-text indication of 'lack of ulceration', or if unknown, one or more endoscopic procedure finding(s) from the CRF drop down list indicating inactive disease (no findings/no active disease, no erosion, no ulcers, no inflammation or inflammatory activity, or no pathological findings).

### Primary non-response (PNR) and Secondary Loss of Response (SLOR) Definitions

Patients were classified as having PNR or SLOR if they either discontinued their index treatment due to inability to obtain a response or loss of response, if they had a disease exacerbation, a bowel-related surgical procedure, an IBD-related hospitalization (excludes hospitalizations for treatment infusions/injections or diagnostic/evaluation procedures or tests), or a dose escalation for any reason  $\leq 14$  weeks post index treatment initiation (PNR) and  $>14$  weeks post index treatment initiation (SLOR).

### Safety Outcomes

Safety outcomes of interest include serious adverse events (SAE) and serious infections (SI) occurring from treatment initiation up to five half-lives post-treatment discontinuation (see appendix 1) in order to cover the period of time of detectable serum drug levels. Adverse event (AEs) or infections were classified as serious if they were life threatening, required hospital admission, resulted in significant disability/incapacity or were recorded as an important medical event.

### **Statistical Analyses**

Results were conducted separately by disease type and compared by vedolizumab versus anti-TNF $\alpha$ . Unadjusted comparisons were performed using t-tests or non-parametric tests for continuous data and Chi-square tests for categorical data. *P*-values were provided from log-rank tests.

Cumulative rates were calculated for patients with  $\geq 1$  outcome assessment and using Kaplan-Meier analyses. Cumulative rates were calculated by computing the probability of the occurrence of an event (response, remission, etc.) at a time-point and then multiplying by any earlier computed probabilities. Kaplan-Meier figures show the number of patients at risk over time. The number at risk decreases over time from the total number of patients at time zero, as the *n* at risk only includes patients still on treatment and that have clinical outcomes that can still be assessed. At the last timepoint, patients still at risk are those who have not reached the outcome (and have data that can be assessed). Due to variability of real-world clinical assessments, time windows of  $\pm 1.5$  months were used for 12, 18 and 24-month outcomes assessments. Adjusted disease exacerbations, disease-related surgeries, SAEs and SIs were presented as counts of first occurrences using incidence rates (IR) expressed per 100 person-years (100 PYs) of exposure and hazard ratios with 95% CI.

To account for differences in baseline characteristics between groups, all adjusted analyses were performed using inverse probability weighting (IPW).<sup>10</sup> Baseline covariates included in the model were: age, sex, disease location, disease duration ( $\leq 2$  years, 2-5 years, 5-10 years,  $> 10$  years, unknown), disease-related hospitalizations, disease severity, steroid dependency status, fistula status (for CD only) and a composite biochemical marker (fecal calprotectin [FCP], C-reactive protein [CRP], albumin). See supplemental tables 2 and 3 for additional information on the IPW adjustments and supplemental figures 11 and 12 for the distribution of propensity scores before and after weighting. IPW weights were not trimmed for this analysis. A *p*-value below 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

## RESULTS

### Patient Population

A total of 1466 patients were screened with 1095 patients (598 vedolizumab [380 UC, 218 CD] and 497 anti-TNF $\alpha$  [224 UC, 273 CD]) included in the final dataset. Three-hundred and seventy-one patients were excluded for: not meeting eligibility criteria (161 patients), not being randomly selected (USA only; 183 patients), incomplete data abstraction (24 patients), or were a screen failure post-study enrolment (3 patients) (Figure 1).

### Baseline and Clinical Characteristics

#### Ulcerative Colitis

##### Unadjusted Comparisons

A total of 604 patients with UC were included, 380 (62.9%) were treated with vedolizumab and 224 (37.1%) with an anti-TNF $\alpha$  (62 adalimumab, 24 golimumab, 137 infliximab, 1 infliximab-abda). At baseline, 59.5% of vedolizumab-treated patients and 48.7% of anti-TNF $\alpha$  treated patients were male ( $p=0.01$ ), had a mean (SD) age of 45.7 (17.4) vs 39.6 (15.7) years ( $p<0.01$ ), and had a greater proportion of patients in the longer disease duration categories ( $p<0.01$ ). A larger proportion of anti-TNF $\alpha$  patients had moderate to severe disease (82.7% vs 72.4%;  $p<0.01$ ) (Table 1).

##### Adjusted Comparisons

A total of 597 patients were included, 376 (63.0%) were treated vedolizumab and 221(37.0%) an anti-TNF $\alpha$  agent (62 adalimumab, 24 golimumab, 134 infliximab, 1 infliximab-abda). None of the covariates adjusted for in the IPW model were different between cohorts (Supplemental Table 2 and 4).

#### Crohn's Disease

##### Unadjusted Comparisons

A total of 491 patients with CD were included, 218 (44.4%) were treated with vedolizumab and 273 (55.6%) with an anti-TNF $\alpha$  (144 adalimumab, 120 infliximab, 2 infliximab-abda, 3 infliximab-dyyb, 4 certolizumab pegol). At baseline, approximately half of CD patients treated with vedolizumab (52.3%) or anti-TNF $\alpha$  (50.9%) were male, had a median age of 51.7 (16.8) vs 39.7 (14.8) years ( $p<0.01$ ), and had a greater proportion of patients in the longer disease duration categories ( $p<0.01$ ). A substantially larger proportion of anti-TNF $\alpha$  patients had moderate to severe disease (64.7% vs 55.3%;  $p=0.01$ ) (Table 1).

## Adjusted Comparisons

A total of 481 patients with CD were included and of these patients, 215 (44.7%) initiated treatment with vedolizumab and 266 (55.3%) initiated treatment with an anti-TNF $\alpha$  (142 adalimumab, 115 infliximab, 2 infliximab-abda, 3 infliximab-dyyb, 4 certolizumab pegol). None of the covariates adjusted for in the IPW model were different between cohorts (Supplemental Table 3 and 4).

## **PRIMARY OUTCOMES**

### **Clinical Effectiveness (Clinical Response, Clinical Remission and Mucosal Healing)**

#### **Ulcerative Colitis**

In the adjusted cumulative analyses, there were similar rates of response (vedolizumab: 88.3%; anti-TNF $\alpha$ : 86.2%,  $p=0.64$ ), remission (vedolizumab: 65.9%; anti-TNF $\alpha$ : 48.6%;  $p=0.09$ ; Figure 2) and mucosal healing (vedolizumab: 86.6%; anti-TNF $\alpha$ : 80.6%;  $p=0.66$ ; Figure 2) between cohorts over 24 months. Unadjusted analyses are shown in Supplemental Figure 13. See the statistical analysis section in the methods for further description of which patients are included in the n at risk.

#### **Crohn's Disease**

In the adjusted analyses, there were similar rates of response (vedolizumab: 84.0%; anti-TNF $\alpha$ : 72.1%;  $p=0.27$ ), remission (vedolizumab: 76.6%; anti-TNF $\alpha$ : 68.5%;  $p=0.10$ ; Figure 3) and mucosal healing (vedolizumab: 100%; anti-TNF $\alpha$ : 90.4%;  $p=0.12$ ; Figure 3) between cohorts over 24 months. As stated in the statistical analyses section of the methods, rates are based on the n at risk, and thus, rates of 90%-100% does not mean that 90%-100% of all CD patients reached this outcome. See the statistical analysis section in the methods for further description of which patients are included in the n at risk.

### **Safety in Unadjusted and Adjusted Populations**

#### **Inflammatory Bowel Disease**

Adjusted results from the combined UC and CD populations showed that vedolizumab patients were less likely to experience SAEs (HR=0.42 [0.28-0.62]) and SIs (HR=0.40 [0.19-0.85]).

#### Ulcerative Colitis

Unadjusted results in the UC population showed that overall, SAEs occurred in 6.8% and 19.2% of patients in the vedolizumab and anti-TNF $\alpha$  cohorts, respectively. See supplemental Tables 5 and 7 for most frequent SAEs and SIs.

Adjusted results found that vedolizumab patients were less likely to experience SAEs (HR= 0.37 [0.21-0.63]), but not SIs (HR= 0.56 [0.21-1.51]) (Figure 4A).

### Crohn's Disease

Unadjusted results showed that overall, SAEs occurred in 8.3 % of vedolizumab and 19.0% of anti-TNF $\alpha$  patients respectively. See supplemental Tables 6 and 8 for most frequent SAEs and SIs.

Adjusted results found that vedolizumab patients were less likely to experience SAEs (HR= 0.49 [0.28-0.86]) and SIs (HR= 0.26 [0.08-0.87]) (Figure 4B).

## **SECONDARY OUTCOMES**

### **Treatment Patterns**

#### **Ulcerative Colitis**

Adjusted results showed the estimated cumulative probability of treatment persistence was significantly higher for vedolizumab compared with anti-TNF $\alpha$  patients ( $p < 0.01$ , Figure 5). The primary reasons for treatment discontinuation were PNR (vedolizumab: 37/376 [9.8%]; anti-TNF $\alpha$ : 38/221 [17.2%]) and SLOR (vedolizumab: 24/376 [6.4%]; anti-TNF $\alpha$ : 21/221 [9.5%]). One vedolizumab (0.3%) and 5 anti-TNF $\alpha$  (2.3%) patients discontinued due to SAEs (vedolizumab: drug-induced lupus; anti-TNF $\alpha$ : fever/chills, severe shortness of breath, lupus-like reaction, pain [chest pain]). The cumulative probability of dose escalation was significantly less for vedolizumab compared to anti-TNF $\alpha$  patients ( $p < 0.01$ ). Primary reasons for dose escalation are shown in Appendix 2.

#### **Crohn's Disease**

In adjusted analyses, the probability of treatment persistence was similar between vedolizumab and anti-TNF $\alpha$  patient cohorts over 24 months ( $p = 0.25$ ) (Figure 5). The primary reasons for discontinuation were PNR (vedolizumab: 19/215 [8.8%]; anti-TNF $\alpha$ : 13/266 [4.9%]) and SLOR (vedolizumab: 9/215 [4.2%]; anti-TNF $\alpha$ : 10/266 [3.8%]). Three (1.4%) vedolizumab and 7 (2.6%) anti-TNF $\alpha$  patients discontinued treatment due to SAEs (vedolizumab: Bell's palsy, recurrent respiratory tract infections, carcinoid tumour; anti-TNF $\alpha$ : rash, basal cell carcinoma, allergic reaction, autoimmune hepatitis, pelvic abscess, lupus like reaction). The cumulative probability of dose escalation was similar for vedolizumab and anti-TNF $\alpha$  patients ( $p = 0.18$ ). Primary reasons for dose escalation are shown in Appendix 2.

## **Disease Exacerbations and Disease-related Surgeries**

### **Ulcerative Colitis**

Vedolizumab patients were significantly less likely to experience a disease exacerbation (HR= 0.58 [0.45-0.76]). Vedolizumab patients had 0 colectomies and anti-TNF patients had 1, so a HR was not calculated (Figure 4A).

### **Crohn's Disease**

Rates of disease exacerbations (HR= 0.84 [0.59-1.19]) and disease-related surgeries (HR= 1.00 [0.27-3.72]) were not different between cohorts (Figure 4B).

## **Treatment Persistence, Clinical Response and Clinical Remission of First-line**

### **Biologic and Second-line Biologic Anti-TNF $\alpha$ by 3 and 6 months**

Adjusted analyses were not performed due to small sample size.

### **Ulcerative Colitis**

The unadjusted rates of treatment persistence, clinical response and clinical remission at 6 months for first-line biologic anti-TNF $\alpha$  patients was similar to second-line biologic anti-TNF $\alpha$  patients (Supplemental Figure 15)

### **Crohn's Disease**

The unadjusted cumulative rates of treatment persistence and clinical response were similar between first-line biologic anti-TNF $\alpha$  patients and second-line biologic anti-TNF $\alpha$  patients at 6 months (Supplemental Figure 14). The rate of clinical remission was significantly higher in patients on second-line biologic anti-TNF $\alpha$  compared to first-line (Supplemental Figure 16; first-line [n at risk=136]: 36.2%; second-line [n at risk=1]: 74.6%,  $p<0.01$ ).

## **DISCUSSION**

This long-term (24-month), comparative real-world study in UC and CD patients fills an important evidence gap, comparing the effectiveness and safety of vedolizumab and anti-TNF $\alpha$  agents in biologic-naïve patients. Retrospective data from >1000 IBD patients demonstrated that the vedolizumab cohort had similar rates of clinical effectiveness and were significantly less likely to experience SAEs or SIs compared to the anti-TNF $\alpha$  cohort up to 2 years post-treatment initiation. Results support the long-term effectiveness and safety of vedolizumab as a first-line biologic treatment in IBD patients.

Treatment persistence, hypothesized to be related to treatment effectiveness and safety, was similar to a retrospective vedolizumab study with a median follow-up of 17 months (58% persistence; biologic-naïve patients/patients with prior anti-TNF $\alpha$ )<sup>11</sup> and to a database study

(the IBM Explorys database) by 24 months (77.6%; biologic-naïve patients).<sup>9</sup> However, as rates of clinical response and remission were not different between treatment cohorts in the current study, it is possible that treatment persistence in vedolizumab treated patients with UC reflects other reasons for persistence (i.e. safety or other reasons).

Rates of dose escalation are in line with current literature (4-60%<sup>12</sup> over 12 months), with lower rates observed for patients on vedolizumab compared to those on anti-TNF $\alpha$  treatments.<sup>13</sup> Though research supports dose escalations being used to recapture response following SLOR,<sup>14</sup> rates of escalation for this study may have been impacted by the bias that vedolizumab treatment labels did not include escalation instructions (in US or Canada). In real-world practice, prescribing behavior can vary across sites, so it is possible data doesn't fully align with approved labels.

Effectiveness comparisons between first-line biologic anti-TNF $\alpha$  and second-line biologic anti-TNF $\alpha$  treatment cohorts suggest that anti-TNF $\alpha$  effectiveness may not be compromised by prior vedolizumab exposure. This finding aligns with literature showing 75% (9/12) of UC patients who failed first line vedolizumab had improved clinical symptoms 3 months post-second-line anti-TNF $\alpha$  initiation.<sup>15</sup> However, sample sizes were small and larger investigations are needed. Previously, the GEMINI trials<sup>5,6</sup> (biologic-naïve remission rates, UC: 47%; CD: 49%,) and the VICTORY consortium (database of outcomes for IBD patients from a multi-center research group)<sup>21</sup> (biologic-naïve: 61%) showed remission rates similar to the current study. It is common for patients to be switched between a variety of treatments until clinical symptoms improve,<sup>16</sup> so it is important to consider how a given treatment affects subsequent-line clinical effectiveness. Vedolizumab may fit both criteria as a first-line biologic that is clinically effective and does not reduce effectiveness of second-line treatments. Results need to be confirmed by a larger sample of patients.

Rates of mucosal healing were similar between vedolizumab and anti-TNF $\alpha$  patients. Results at 12 months (vedolizumab: 55.0% [UC]) may be similar to the VICTORY consortium at 12 months (biologic-naïve patients: 51%).<sup>17</sup> Results differ from the recent VARSITY trial at week 52 (vedolizumab: 39.7%; adalimumab:27.7%; p=0.0005)<sup>18</sup> potentially due to real-world study design or the current study not focusing on one specific anti-TNF $\alpha$ . Due to sample size and data availability limitations, it was not possible to assess relationships between mucosal healing and clinical remission.

This study showed that UC patients treated with vedolizumab were less likely to experience exacerbations, which suggests that their disease may be better controlled long-term. It is also the first study to demonstrate a more favourable tolerability profile of vedolizumab compared to anti-TNF $\alpha$  treatments in a population that is solely bio-naïve IBD patients.

Safety results are in line with other studies, including the VICTORY consortium<sup>17</sup> and the GEMINI 1 trial<sup>5</sup>, which showed low incidence of SAEs (VICTORY: 6%, GEMINI 1 [biologic-naïve patients]: 9%) and SIs (VICTORY: 4%, GEMINI 1 [biologic-naïve patients]: 1%) on

vedolizumab.<sup>19</sup> Further, systematic reviews showed vedolizumab treatment associated with low rates of AEs, SAEs and SIs,<sup>20</sup> whilst anti-TNF $\alpha$  treatments associated with increased SIs and postoperative complications.<sup>6, 21</sup> These findings may be explained by differences in mechanisms of action between anti-TNF $\alpha$  and vedolizumab treatments. However, as SAEs and SIs were reported in the current study irrespective of relationship to treatment, incidences may not reflect those directly related to treatments.

This real-world study had several limitations. Due to the retrospective design, data were limited to what was in patient medical charts and data quality varied by site; however rigorous data quality control was undertaken. There were differences in some of the unadjusted baseline characteristics between vedolizumab and anti-TNF $\alpha$  cohorts, which is why weighted analyses were performed. Also, individual comparisons of anti-TNF $\alpha$  treatments versus vedolizumab were not performed. For clinical effectiveness, sample sizes were smaller by 24 months and patients may also have achieved outcomes before the event being recorded in the chart, which may affect the Kaplan Meier estimates. There may be factors not measured (e.g. patient decision, reimbursement) that impacted rates of treatment persistence. The anti-TNF $\alpha$  second-line cohort had a small sample size, short follow-up time and results that were unadjusted, which may decrease generalizability of findings. In Greece, only vedolizumab patients were included; not collecting anti-TNF $\alpha$  patients from all sites is a comparative analysis limitation. Nine (4.1%) CD patients treated with vedolizumab in Canada received treatment as part of a compassionate use access program prior to approval, though it is not expected that any bias affected study results. Lastly, though the composite biochemical marker was designed based on clinical cut-offs from the literature that may differentiate inactive from active disease, it is not a validated algorithm.

This study also had multiple strengths as this is the first large-scale, long-term study to assess and compare treatment outcomes in biologic naïve “real life” IBD populations. IPW preserves sample size and adjusted for multiple covariates to balance the baseline characteristics between the treatment cohorts. The utilization of data from medical records allowed for the data capture as occurring in real-world practice.

In conclusion, results from this real-world study of patients with IBD suggest that first-line vedolizumab and anti-TNF $\alpha$  treatments yield similar rates of clinical effectiveness up to 2 years post treatment initiation, and that vedolizumab has a more favourable safety profile compared to anti-TNF $\alpha$  treatments. These real-world data suggest vedolizumab may have a favourable benefit: risk profile as a first-line biologic treatment for patients with IBD.

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## **ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

The study was approved by the local ethics committee at each participating site. Patients alive at the time of chart abstraction (99% of patients) signed an informed consent form prior to participation in this study, if there was no waiver of informed consent.

## **CONSENT FOR PUBLICATION**

Not applicable.

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## FIGURE LEGENDS

**Figure 1. Patient Screening and Analysis Flowchart**

**Figure 2. Adjusted Cumulative Rates of Clinical Remission and Mucosal Healing in Ulcerative Colitis Patients**

**Figure 3. Adjusted Cumulative Rates of Clinical Remission and Mucosal Healing in Crohn's Disease Patients**

**Figure 4. The Adjusted First Incidence of Disease Exacerbations, Disease-related Surgeries, Serious Adverse Events and Serious Infections of Patients with Ulcerative Colitis (panel A) and Crohn's Disease (panel B)**

**Figure 5. Adjusted Cumulative Rates of Treatment Persistence, in Ulcerative Colitis and Crohn's Disease Patients**

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## TABLES

**Table 1. Unadjusted Baseline Demographics and Clinical Characteristics of Biologic Naïve Ulcerative Colitis and Crohn's Disease Patients Treated with Vedolizumab or Anti-TNF $\alpha$  Therapy**

Baseline Characteristics	Ulcerative Colitis			Crohn's Disease		
	Vedolizumab N=380	Anti-TNF $\alpha$ N=224	<i>p</i> -value	Vedolizumab N=218	Anti-TNF $\alpha$ N=273	<i>p</i> -value
<b>Demographics</b>						
Mean (SD) age	45.7 (17.4)	39.6 (15.7)	<b>&lt;0.01</b>	51.7 (16.8)	39.7 (14.8)	<b>&lt; 0.01</b>
Sex [male], n (%)	226 (59.5)	109 (48.7)	<b>0.01</b>	114 (52.3)	139 (50.9)	0.76
BMI, n with available data (%)	227 (59.7)	129 (57.6)	0.20	135 (61.9)	178 (65.2)	0.07
< 18.5 (underweight), n (%)	4 (1.8)	4 (3.1)		4 (3.0)	5 (2.8)	
18.5- 24.9 (normal), n (%)	93 (41.0)	60 (46.5)		46 (34.1)	68 (38.2)	
25.0- 29.9 (overweight), n (%)	74 (32.6)	35 (27.1)		53 (39.3)	41 (23.0)	
$\geq$ 30 (obese), n (%)	56 (24.7)	30 (23.2)		32 (23.7)	64 (36.0)	

Baseline Characteristics	Ulcerative Colitis			Crohn's Disease		
	Vedolizumab N=380	Anti-TNF $\alpha$ N=224	<i>p-value</i>	Vedolizumab N=218	Anti-TNF $\alpha$ N=273	<i>p-value</i>
Smoking status, n with available data (%)	314 (82.6)	195 (87.1)	0.04	189 (86.7)	234 (85.7)	0.39
Current, n (%)	23 (7.3)	15 (7.7)		32 (16.9)	35 (15.0)	
Former, n (%)	95 (30.3)	40 (20.5)		39 (20.6)	65 (27.8)	
Never smoked, n (%)	196 (62.4)	140 (71.8)		118 (62.4)	134 (57.3)	
<b>Clinical characteristics</b>						
Disease duration, n with available data (%)	320 (84.2)	181 (80.8)	<b>&lt;0.01</b>	176 (80.7)	220 (80.6)	<b>&lt;0.01</b>
< 2 years, n (%)	86 (26.9)	90 (49.7)		50 (28.4)	111 (50.5)	
2- < 5 years, n (%)	72 (22.5)	39 (21.5)		32 (18.2)	30 (13.6)	
$\geq$ 5 years, n (%)	162 (50.6)	52 (28.7)		94 (53.4)	79 (35.9)	
Median (min-max) observation period, (months)	16.4 (3.0–47.0)	21.3 (3.5–51.1)	0.48	15.7 (4.2–45.9)	19.3 (6.0–51.0)	<b>&lt;0.01</b>
Ulcerative colitis disease location at index, n with available data (%)	339 (89.2)	196 (87.5)	0.07	-	-	
Extensive colitis (proximal to hepatic flexure), n (%)	155 (45.7)	107 (54.6)		-	-	
Left sided (distal to splenic flexure), n (%)	160 (47.2)	72 (36.7)		-	-	
Ulcerative proctitis, n (%)	24 (7.1)	17 (8.7)		-	-	
Crohn's disease location at index, n with available data (%)	-	-		196 (89.9)	230 (84.2)	<b>0.01</b>
Colonic with/without upper GI disease, n (%)	-	-		42 (21.4)	67 (29.1)	
Ileal with/without upper GI disease, n (%)	-	-		85 (43.4)	71 (30.9)	

Baseline Characteristics	Ulcerative Colitis			Crohn's Disease		
	Vedolizumab N=380	Anti-TNF $\alpha$ N=224	<i>p</i> -value	Vedolizumab N=218	Anti-TNF $\alpha$ N=273	<i>p</i> -value
Ileocolonic with/without upper GI disease, n (%)	-	-		69 (35.2)	92 (40.0)	
Disease severity at index, n with available data (%)	323 (85.0)	190 (84.8)	<b>&lt;0.01</b>	180 (82.6)	220 (80.6)	<b>0.01</b>
Moderate, n (%)	178 (55.1)	86 (45.3)		84 (46.7)	93 (42.3)	
Severe, n (%)	56 (17.3)	71 (37.4)		17 (9.4)	50 (22.7)	
Disease behaviour, n with available data (%)	-	-		154 (70.6)	178 (65.2)	0.64
Non-stricturing, non-penetrating, with or without perianal disease, n (%)	-	-		92 (59.7)	105 (59.0)	
Penetrating, with or without perianal disease, n (%)	-	-		17 (11.0)	21 (11.8)	
Stricturing, with or without perianal disease, n (%)	-	-		45 (29.2)	52 (29.2)	
Active Fistula at index, n with available data (%)	-	-		189 (86.7)	239 (87.5)	<b>&lt; 0.001</b>
Active fistula, n (%)	-	-		8 (4.2)	40 (16.7)	
Prior non-biologic therapy, n with available data (%)	371 (97.6)	218 (97.3)	0.40	176 (80.7)	238 (87.2)	0.05
Most common types of prior non-biologic therapy						
Prednisone (CS), n (%)	215 (58.0)	152 (69.7)		65 (36.9)	132 (55.5)	
Mesalazine (5-ASA), n (%)	316 (85.1)	177 (81.2)		78 (44.4)	100 (42.0)	
Azathioprine (5-ASA), n (%)	104 (28.0)	59 (27.1)		61 (34.7)	80 (33.6)	
CS bridging therapy*, n with available data (%)	70 (18.4)	60 (26.8)	0.17	37 (17.0)	57 (20.9)	0.43
n (%)	18 (25.7)	20 (33.3)		10 (27.0)	18 (31.6)	

Baseline Characteristics	Ulcerative Colitis			Crohn's Disease		
	Vedolizumab N=380	Anti-TNF $\alpha$ N=224	<i>p-value</i>	Vedolizumab N=218	Anti-TNF $\alpha$ N=273	<i>p-value</i>
Steroid-dependent, n with available data (%)	380	224	0.27	218	273	0.63
n (%)	116 (30.5)	78 (34.8)		32 (14.7)	36 (13.2)	
Composite biochemical marker, n with available data (%)	286 (75.2)	172 (76.8)	0.04	158 (72.5)	194 (71.1)	0.07
Within normal range, n (%)	78 (27.3)	32 (18.6)		41 (25.9)	35 (18.0)	
Outside normal range, n (%)	208 (72.7)	140 (81.4)		117 (74.1)	159 (82.0)	
Prior UC or CD-related surgeries (since diagnosis), n (%)	1 (0.3)	1 (0.5)	1.00	10 (4.6)	16 (5.9)	0.53
UC or CD-related hospitalizations (12 months prior), n (%)	25 (6.6)	40 (17.9)	<b>&lt;0.01</b>	22 (10.1)	35 (12.8)	0.35

Abbreviations: ASA=aminosalicylate; BMI=body mass index; CD=Crohn's disease; GI=gastrointestinal; SD=standard deviation; TNF=tumor necrosis factor; UC=ulcerative colitis. \*Patients were classified as having CS bridging therapy at index treatment initiation if CS started  $\leq$  1 month ( $\leq$ 30.5 days) prior to index AND was ongoing at index initiation AND was discontinued within 3 months ( $\leq$  91 days) following index treatment initiation.

Figure 1.

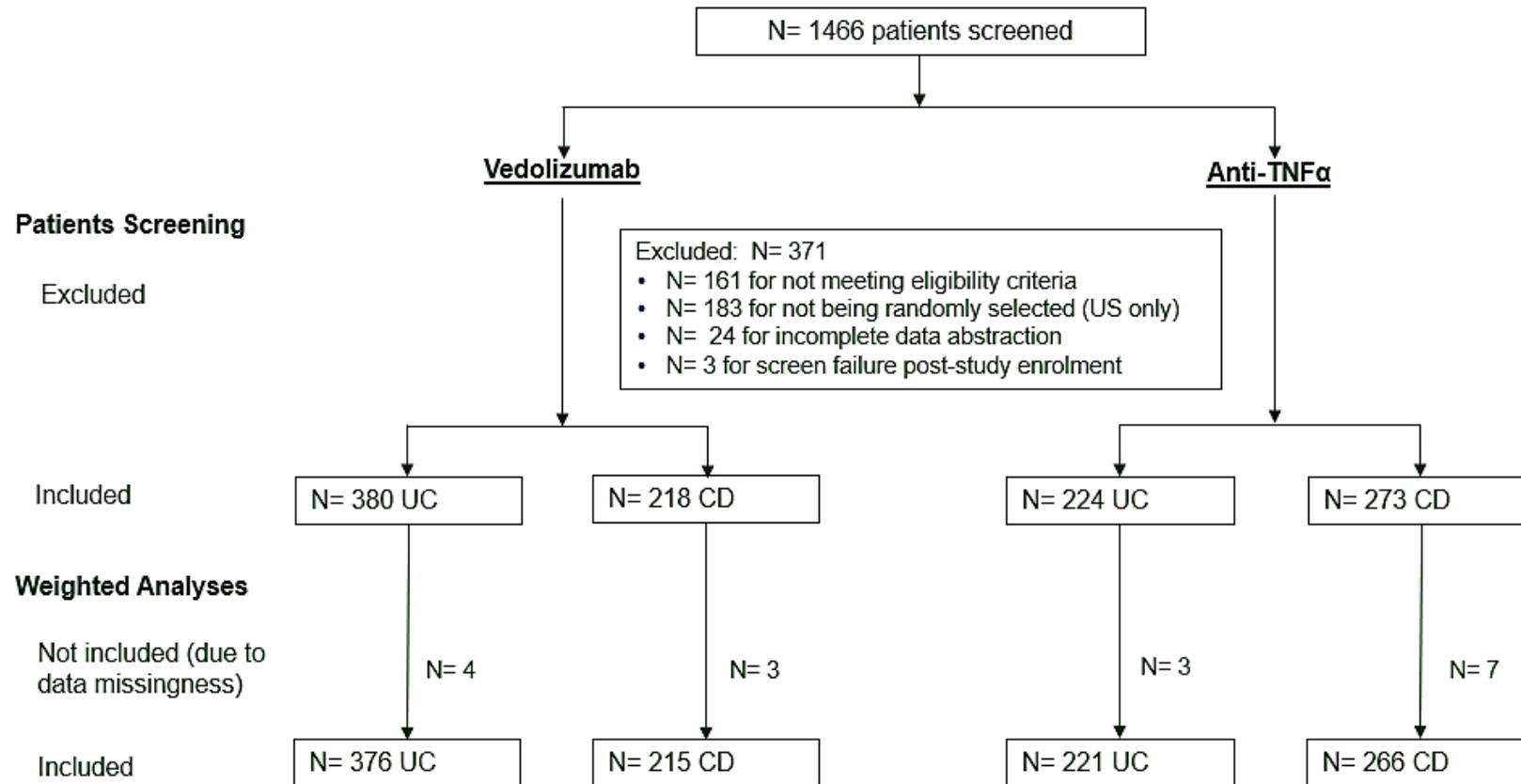
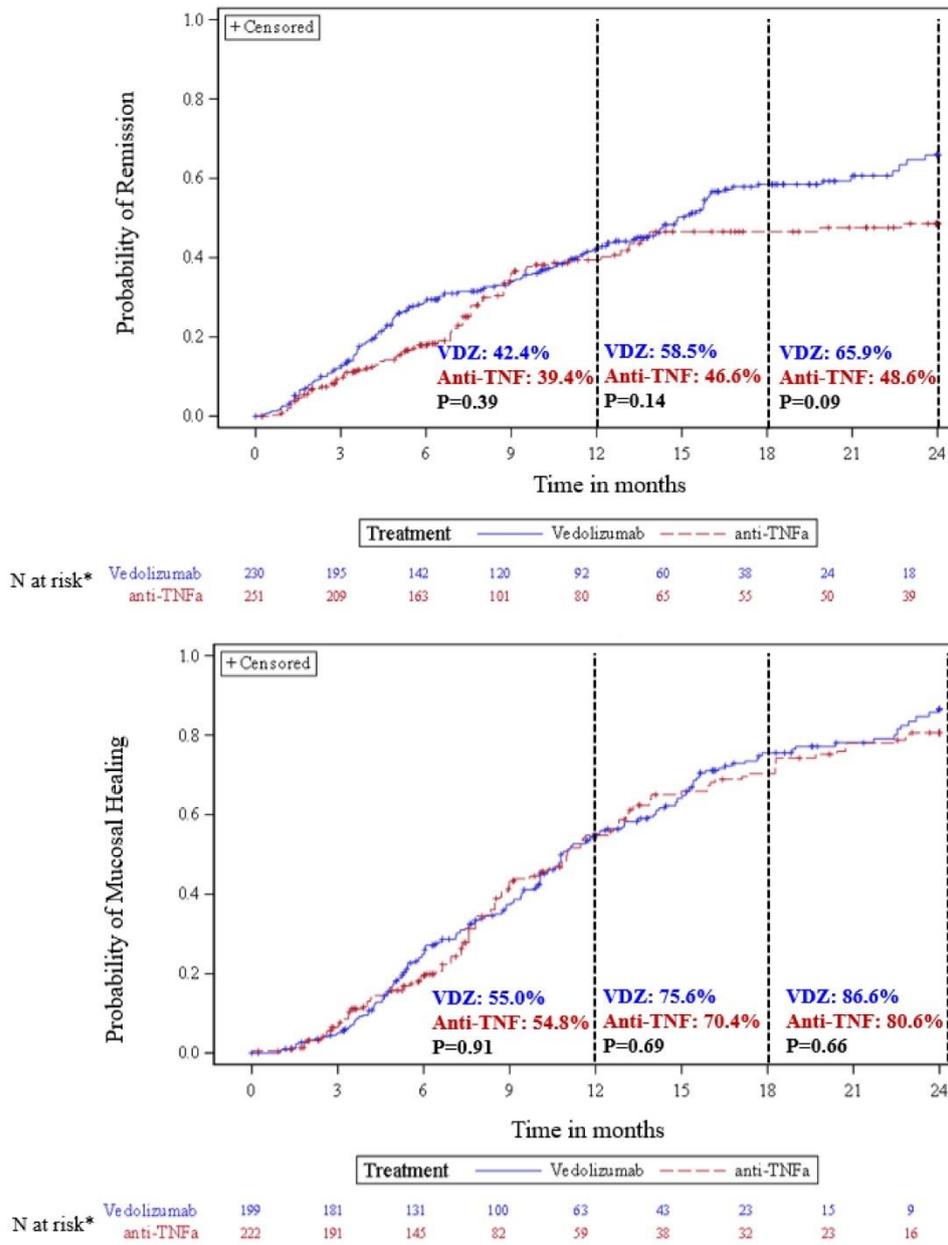
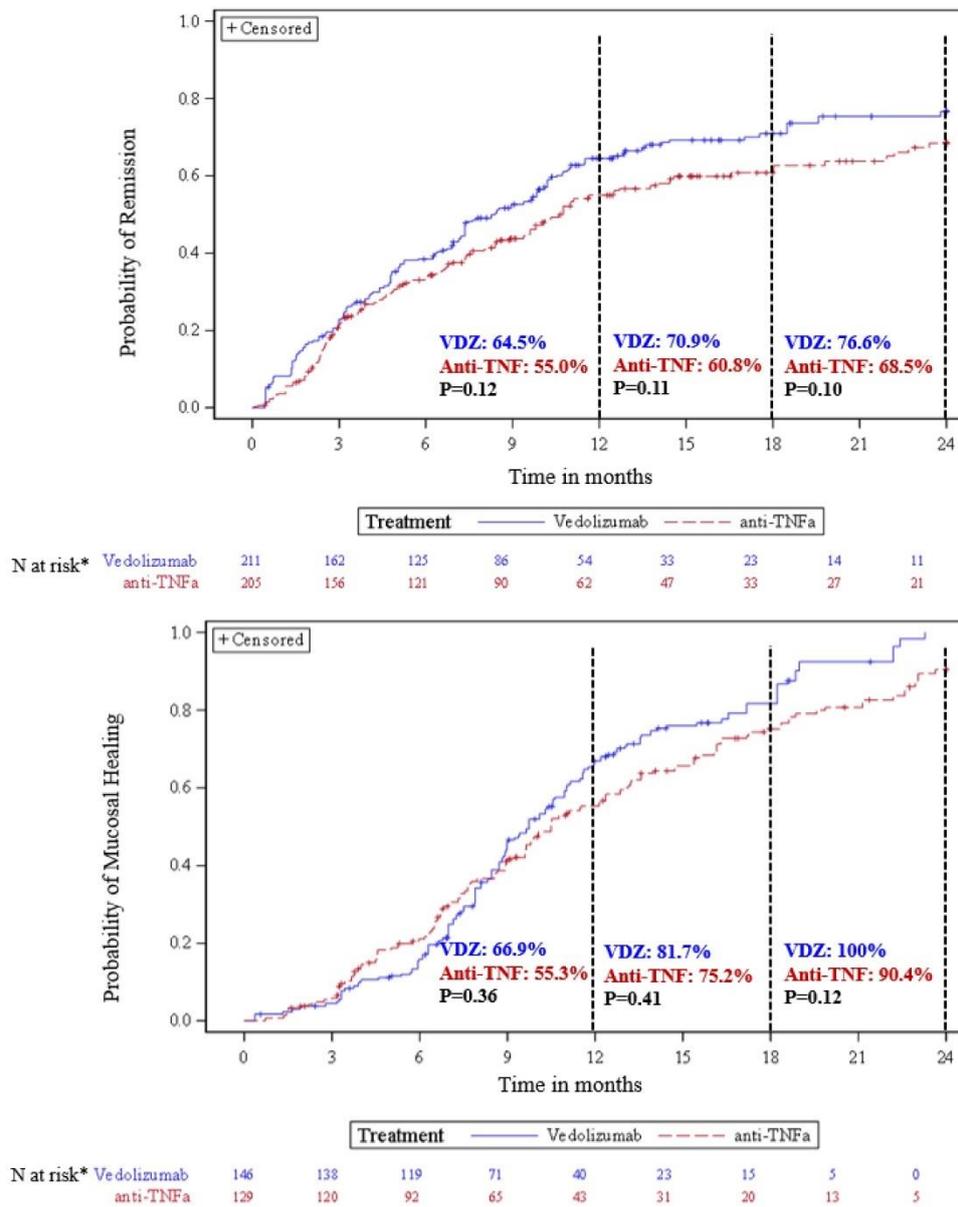


Figure 2.



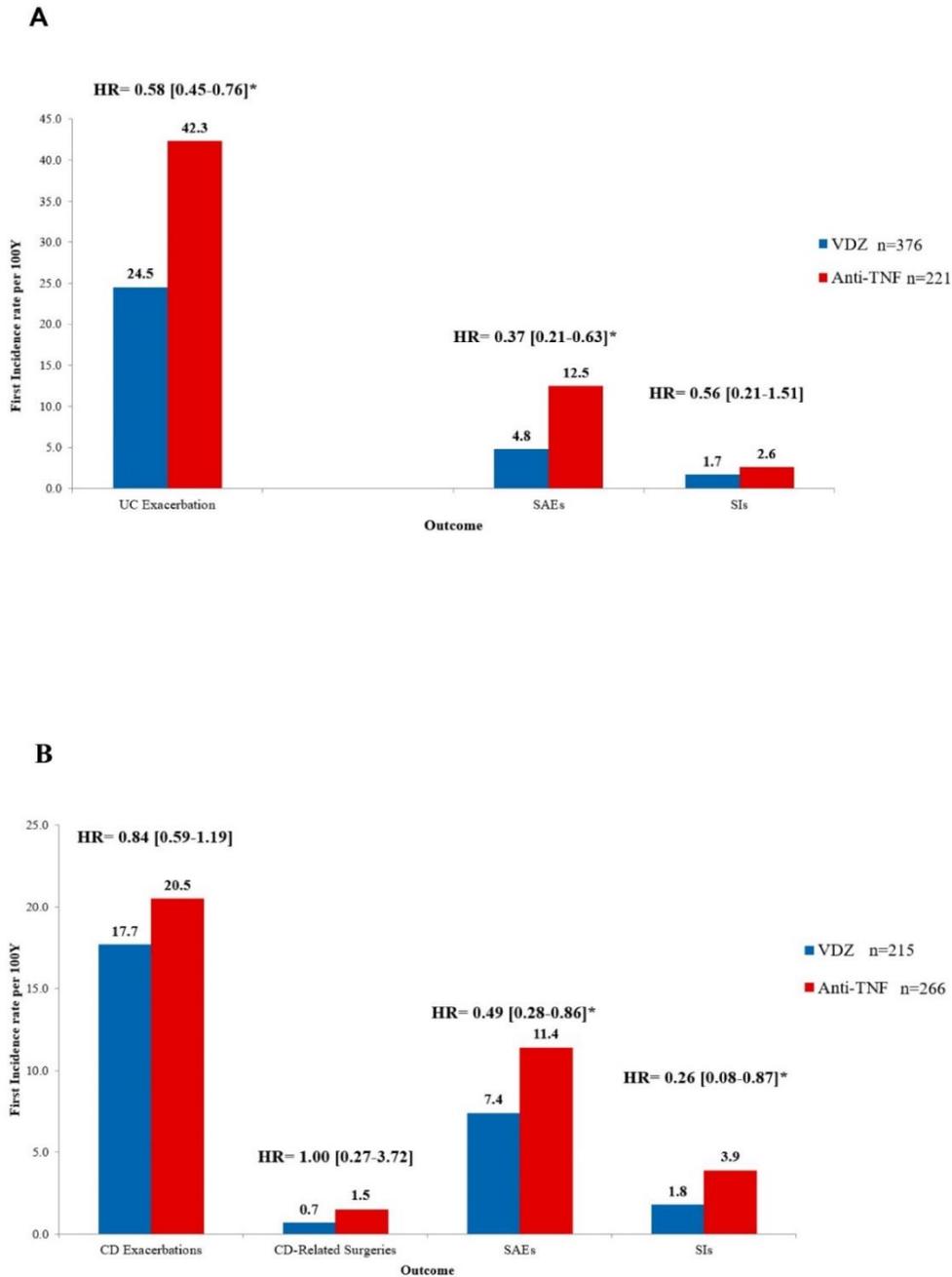
\* The sum of the patient weights for each group still on treatment at and clinical outcome can still be assessed. P-values are unadjusted log-rank. Annotated data are the rates at each time point as indicated by the dashed line.

Figure 3.



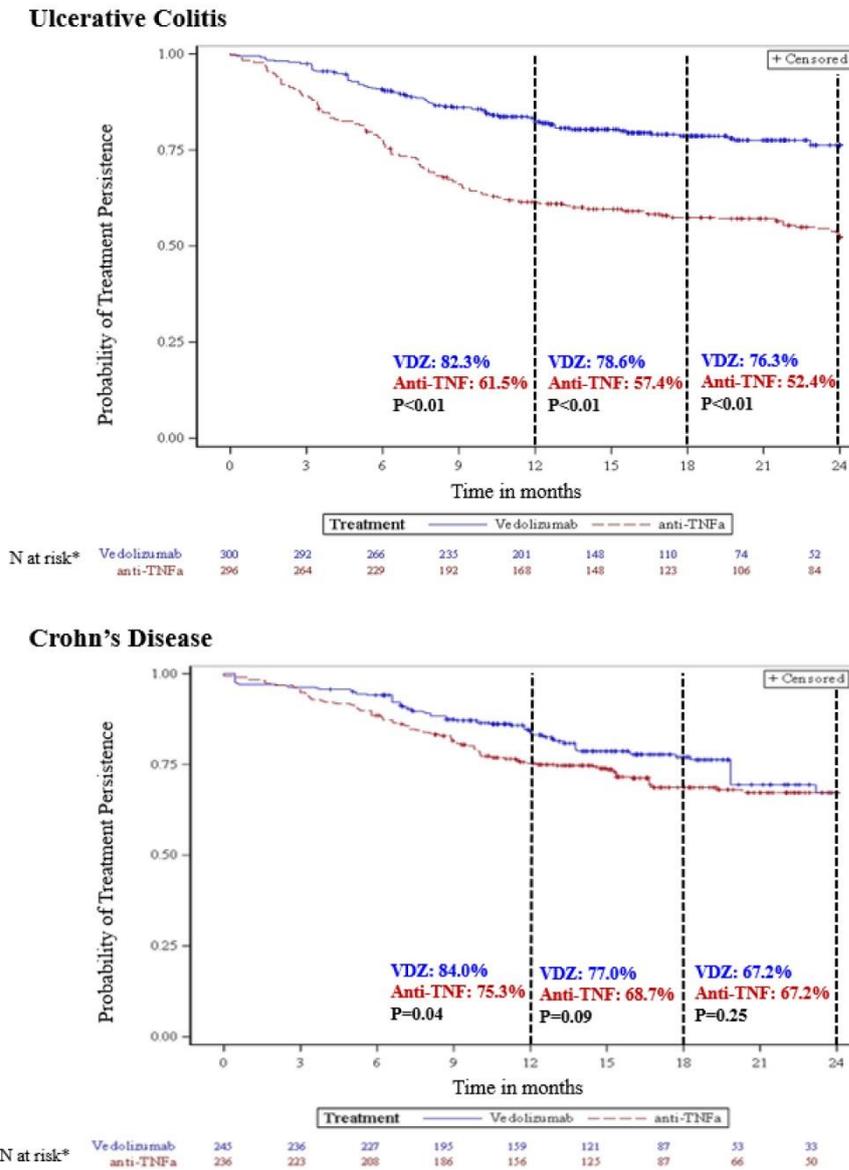
\* The sum of the patient weights for each group still on treatment at and clinical outcome can still be assessed. Annotated data are the rates at each time point as indicated by the dashed line. P-values are unadjusted log-rank.

Figure 4.



Hazard ratios are from adjusted Cox models (number of patients experiencing an AE of interest/ time in years patients were at risk, multiplied by 100). SAE: Serious adverse event, SI: Serious infection. No UC-related surgeries are shown as the vedolizumab cohort had none.

Figure 5.



\* The sum of the patient weights for each group still on treatment at and clinical outcome can still be assessed.