PASS INFORMATION

Title	A post-authorization safety study of golimumab in ulcerative colitis using the Spanish ENEIDA registry
Version identifier of the final study report	Version 1.2
Date of last version of the final study report	22-Aug-2023
EU PAS Register number	EUPAS15752
Active substance	L04AB06
Medicinal product	SIMPONI® (golimumab)
Product reference	[redacted]
Procedure number	[redacted]
Marketing authorization holder(s)	Janssen Biologics B.V.
Joint PASS	No
Research question and objectives	This study evaluated whether the use of golimumab (GLM) is associated with risk of colectomy due to intractable disease or advanced colonic neoplasia (ACN) (colorectal cancer [CRC] or high-grade dysplasia [HGD]), in patients with ulcerative colitis (UC) as compared with alternative therapies for similar severity of disease. Primary objectives: 1. Describe the clinical and demographic profile of first-time users of GLM in the treatment of UC compared with the corresponding profile of first-time users of comparator therapies (other anti–tumor necrosis factor alpha [anti-TNFα] agents or thiopurines [TPs]) 2. For patients with UC initiating GLM or other anti-TNFα agents, describe the risk of incident colectomy due to intractable disease 3. For patients with UC initiating GLM, another anti-TNFα agent, or a TP, describe the risk of ACN, which is the composite endpoint of incident CRC or HGD 4. Compare the risk of colectomy due to intractable disease between GLM and other anti-TNFα agents 5. Compare the risk of ACN between GLM and other anti-TNFα agents Secondary objectives 1. For patients with UC initiating GLM, another anti-TNFα agent, or a TP, describe the risk of incident CRC 2. Compare the risk of CRC between GLM and other anti-TNFα agents

	3. If baseline characteristics suggest comparability between cohorts of patients receiving GLM and TPs, compare (1) risk of incident ACN and (2) risk of incident CRC Exploratory objective 1. Describe the incidence of hepatosplenic T-cell lymphoma (HSTCL) in each study cohort.
Country(-ies) of study	Spain
Author	[redacted]
Merck Final Repository (RCAM) Date	

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	Janssen Biologics B.V. Einsteinweg 101; 2333 CB Leiden, The Netherlands
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1 ABSTRACT

Title

A post-authorization safety study of golimumab in ulcerative colitis using the Spanish ENEIDA registry

Marketing Authorization Holder: Janssen Biologics B.V.

Author: [redacted]

Keywords

Golimumab, ulcerative colitis, colectomy, advanced colonic neoplasia, PASS

Rationale and background

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of unknown etiology that may be associated with severe symptoms and impaired quality of life. Ulcerative colitis may affect all ages, and medical treatment depends on disease severity and extent. In the case of intractable disease, colectomy may be indicated. Patients with UC are at increased risk of developing colorectal cancer (CRC) and dysplasia compared with the general population.

SIMPONI® (golimumab [GLM]) received European marketing authorization for treatment of moderately to severely active UC on 19-Sep-2013. This registry-based study provides additional information on colectomy, CRC and dysplasia, and hepatosplenic T-cell lymphoma (HSTCL), as outlined in the risk management plan for SIMPONI® that was approved with authorization of the UC indication.

This study used data from ENEIDA (National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants), a large prospectively maintained registry of patients with IBD in Spain.

Research question and objectives

This study evaluated whether the use of GLM is associated with risk of colectomy due to intractable disease and advanced colonic neoplasia (ACN) CRC or high-grade dysplasia (HGD) in patients with UC as compared with alternative therapies for similar severity of disease. No a priori hypotheses were evaluated. As an exploratory objective, this study also described the incidence of HSTCL in these populations.

Primary objectives:

1. Describe the clinical and demographic profile of first-time users of GLM in the treatment of UC compared with the corresponding profile of first-time users of comparator therapies (other anti-TNFα agents or thiopurines [TPs])
2. For patients with UC initiating GLM or other anti-TNFα agents, describe the risk of incident colectomy due to intractable disease
3. For patients with UC initiating GLM, another anti-TNFα agent, or a TP, describe the risk of ACN, the composite endpoint of incident CRC or HGD

4. Compare the risk of colectomy due to intractable disease between GLM and other anti-TNFα agents
5. Compare the risk of ACN between GLM and other anti-TNFα agents

Secondary objectives

1. For patients with UC initiating GLM, another anti-TNFα agent, or a TP, describe the risk of incident CRC
2. Compare the risk of CRC between GLM and other anti-TNFα agents
3. If baseline characteristics suggest comparability between cohorts of patients receiving GLM and TPs, compare (1) risk of incident ACN and (2) risk of incident CRC

Exploratory objective

1. Describe the incidence of HSTCL in each of the study cohorts

Study design

This long-term, non-interventional observational study used a new-user, bidirectional cohort design with a nested case-control analysis. The cohort study used data that were collected for the Spanish ENEIDA IBD registry, and the nested case-control analysis also used data from retrospective review of selected medical charts. Crude analyses of risk were performed for study outcomes, and multivariable models were fit for the outcomes with sufficient events (eg, colectomy due to intractable disease).

Setting

This non-interventional study was conducted among patients enrolled in the ENEIDA registry who had newly received any of the study drugs as treatments for UC during the study period. The study population was drawn from the ENEIDA centers judged to have research-quality data.

Subjects and study size, including dropouts

Patients were selected into the study if they were aged 18 years or older, diagnosed with UC, had not experienced any of the study outcomes prior to study entry, and initiated therapy with GLM, an anti-TNFα agent other than GLM, or a TP. Initiation of these treatments served to define 3 study cohorts. The enrollment period ran from 19-Sep-2013 (date of European Union approval of GLM for UC) through 31-Dec-2021. Patients were followed through 30-Mar-2022 for assessment of incident study outcomes. Patients were excluded from the study if they were previously exposed to vedolizumab or any novel immunomodulatory agent. The study included 474 patients in the GLM cohort, 1,737 patients in the other anti-TNFα agent cohort, and 1,380 patients in the TP cohort.

Variables and data sources

Exposures

This non-interventional study evaluated drug treatments ("study drugs") that were prescribed in the context of clinical care; the protocol did not direct any choice of therapies. The main exposure of interest was treatment with GLM prescribed for UC. The primary comparator group comprised other anti-TNFα agents prescribed for UC (ie, infliximab and adalimumab, including biosimilars). A secondary comparator group for the neoplasia outcome analysis comprised TP analogs (ie, azathioprine and 6-mercaptopurine) prescribed for UC.

Over time, patients with UC who initiated GLM may have later received comparator treatments in various sequences. Analyses reflected the time-dependent nature of these treatment exposures.

Outcomes

The 2 primary outcomes were incidence of colectomy due to intractable disease and incidence of ACN (a composite of CRC or HGD). The secondary outcome was incidence of CRC; incidence of HSTCL was an exploratory outcome.

Separate exposure risk windows were defined for the colectomy and ACN outcomes. For the colectomy outcome, time at risk started 1 day after cohort entry and continued to 90 days after the end of drug supply (ie, treatment discontinuation). Periods of overlapping exposure were thus possible if one study drug was started shortly after discontinuing the first. Accordingly, the analysis of the colectomy outcome used 3 mutually exclusive exposure categories: (1) GLM only, (2) other anti-TNFα agents only, and (3) overlapping exposure time. Poisson regression was the primary method of analysis for the outcome colectomy due to intractable disease.

A different risk window was used for the analysis of the neoplasia outcome, given that the effect of the study drugs could theoretically last long after the end of exposure. For the GLM and other anti-TNFα agent cohort, the risk window extended to the end of follow-up (ie, occurrence of an outcome or other censoring event). The risk window for TPs extended 6 months after the end of drug supply (ie, treatment discontinuation). Given the length of these risk windows, a patient who switched therapies during the study could simultaneously contribute person-time to more than one exposure category. For the neoplasia outcomes, Cox regression was performed.

Covariates

Among the covariates specified in the protocol, age, sex, duration of UC, and prior treatment of UC with cyclosporine were identified as potential confounders and included in the final analysis.

Source of data

The cohort study used secondary data that were collected for the Spanish ENEIDA IBD registry; the nested case-control analysis also used data from retrospective review of selected medical charts.

Results

Among the study population, 64 cases of colectomy due to intractable disease and 10 cases of ACN were identified during the 8.5-year study period. No cases of HSTCL were observed.

The incidence rates (IRs) of colectomy due to intractable disease were 4.4 (95% confidence interval [CI]: 1.2-11.2) per 1,000 person-years (PY) with GLM-only use, 12.4 (95% CI: 9.1-16.5) per 1,000 PY with other anti-TNFα agents–only use, and 78.6 (95% CI: 16.2-229.7) per 1,000 PY with overlapping exposure to both GLM and other anti-TNFα agents.

Compared with use of only other anti-TNFα agents, GLM-only use was not associated with an increased risk of colectomy in the adjusted Poisson and Cox models (incidence rate ratio [IRR]=0.40; 95% CI: 0.14-1.13 and hazard ratio [HR]=0.41; 95% CI: 0.15-1.15, respectively). Results from the age-adjusted nested case-control study were consistent with the results of the cohort analyses.

The IR of ACN was 1.5 (95% CI: 0.2-5.4) per 1,000 PY in the GLM cohort, 1.3 (95% CI: 0.5-2.8) per 1,000 PY in the other anti-TNFα agent cohort, and 1.0 (95% CI: 0.3-2.6) per 1,000 PY in the TPs cohort.

Compared with use of other anti-TNFα agents, GLM use was not associated with an increased risk of ACN in the adjusted Cox model (adjusted HR=1.09; 95% CI: 0.22-5.44). Compared with use of TPs, GLM use was not associated with an increased risk of ACN (adjusted HR=1.08; 95% CI: 0.19-6.13). The nested case-control study analyses also showed that GLM use was not associated with an increased risk of ACN as compared with use of other anti-TNFα agents or TPs, although findings from the nested case-control analyses were based on a small number of GLM-exposed events.

No events of HSTCL were identified during the conduct of the study.

Discussion

Results from this post-authorization safety study (PASS) do not indicate an increased risk of colectomy due to intractable disease associated with GLM use compared with use of other anti-TNFα agents in a prospectively followed population of patients with UC under routine clinical care in Spain. Results were robust to various analytical methods and sensitivity analyses. This study considered person-time (ie, time at risk) occurring shortly after switching from another anti-TNFα agent to GLM (or vice versa) as a special exposure category when risk windows overlapped. During such time of overlapping exposure (to GLM plus other anti-TNFα agents), patients were at an increased risk of colectomy due to intractable disease, likely owing to the underlying UC severity that prompted the change in therapy. However, this finding was based on sparse events. Results for ACN were based on small numbers of events, but do not suggest an increased risk among users of GLM compared with users of other anti-TNFα agents or users of TPs.

Marketing Authorization Holder(s)

Janssen Biologics B.V.

Names and affiliations of principal investigators

[redacted]

2 LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylic acid
ACN	advanced colonic neoplasia
AE	adverse event
AR	adverse reaction
AEMPS	Spanish Agency of Medicines and Medical Devices [Agencia Española del Medicamentos y Productos Sanitarios]
ATNF	anti–tumor necrosis factor alpha
CI	confidence interval
CRC	colorectal cancer
eCRF	electronic case report form
EMA	European Medicines Agency
ENEIDA	National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants (Spain) [Estudio Nacional en Enfermedad Inflamatoria Intestinal Sobre Determinantes Genéticos y Ambientales]
EU PAS Register	European Union Electronic Register of Post-authorisation Studies
GETECCU	Spanish Working Group on Crohn's Disease and Ulcerative Colitis [Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa]
GLM	golimumab
HGD	high-grade colorectal dysplasia
HOI	health outcome(s) of interest
HR	hazard ratio
HSTCL	hepatosplenic T-cell lymphoma
IBD	inflammatory bowel disease
IR	incidence rate
IRR	incidence rate ratio
JAK	Janus kinase

MSD	Merck Sharp & Dohme, Corp
MySQL	My Structured Query Language
NCC	nested case-control
NE	not estimable
NP	not performed
OR	odds ratio
PASS	post-authorization safety study
PI	principal investigator
PRAC	Pharmacovigilance Risk Assessment Committee (of the European Medicines Agency)
PSC	primary sclerosing cholangitis
PY	person-years
Q1	first quartile
Q3	third quartile
RTI-HS	RTI Health Solutions
S1P	sphingosine-1-phosphate
SAP	statistical analysis plan
SD	standard deviation
TNFα	tumor necrosis factor alpha
TP	thiopurine
UC	ulcerative colitis

3 INVESTIGATORS

RTI Health Solutions (RTI-HS) is responsible for conducting, analyzing, and reporting results from the study and for contracting with the study principal investigators at GETECCU and the participating centers. The core research team is listed below.

Study principal investigators	[redacted]
Coordinating investigator for each country in which the study is to be performed	
Sponsor contacts	[redacted]
Other contacts	[redacted]
Vendor/collaborator	GETECCU (Spanish Working Group on Crohn's Disease and Ulcerative Colitis) [redacted]
Investigators	See stand-alone document listed in Annex 1.

This study was sponsored by Merck Sharp & Dohme LLC (MSD) as part of the agreement with the MAH, Janssen Biologics B.V., to evaluate whether the use of GLM is associated with a risk of colectomy due to intractable disease, ACN, or HSTCL in patients with UC as compared with alternative therapies for similar severity of disease.

This study is a Category 3 PASS and is part of the risk management plan for GLM.

4 OTHER RESPONSIBLE PARTIES

See Section 3.

5 MILESTONES

Milestone	Planned Date	Actual Date	Comments
Endorsement of the protocol by PRAC		[redacted]	
ENEIDA's reference ethics committee approval	[redacted]	[redacted]	
RTI International institutional review board approval	[redacted]	[redacted]	
AEMPS study approval	[redacted]	[redacted]	[redacted]
GETECCU scientific committee approval	[redacted]	[redacted]	
First data transfer from ENEIDA/data lock progress report 1	[redacted]	[redacted]	[redacted]
Registration of protocol in the EU PAS Register	[redacted]	[redacted]	[redacted]
Study progress report 1	[redacted]	[redacted]	[redacted]
Data lock progress report 2	[redacted]	[redacted]	
Study progress report 2	[redacted]	[redacted]	[redacted]
Data lock progress report 3	[redacted]	[redacted]	
Study progress report 3	[redacted]	[redacted]	[redacted]
Data lock progress report 4	[redacted]	[redacted]	
Study progress report 4	[redacted]	[redacted]	[redacted]
Data lock progress report 5	[redacted]	[redacted]	
Study progress report 5	[redacted]	[redacted]	[redacted]
Final SAP	[redacted]	[redacted]	[redacted]

Milestone	Planned Date	Actual Date	Comments
End of data collection	[redacted]	[redacted]	[redacted]
Final report of study results	[redacted]	[redacted]	

Abbreviations: AEMPS, Spanish Agency of Medicines and Medical Devices; ARs, adverse reactions; EMA, European Medicines Agency; ENEIDA, National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants; EU PAS Register, European Union electronic register of post-authorization studies; GETECCU, Spanish Working Group on Crohn's Disease and Ulcerative Colitis; PRAC, Pharmacovigilance Risk Assessment Committee (of the EMA); SAP, statistical analysis plan.

6 RATIONALE AND BACKGROUND

6.1 Rationale

SIMPONI® (golimumab, [GLM]), an anti-TNFα agent, was approved on 01-Oct-2009 in the European Union for the indications of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. Moderately to severely active UC was the second indication for GLM that received European marketing authorization on 19-Sep-2013.[1,2] Since TNFα mediates inflammation and modulates cellular immune responses, the possibility exists for anti-TNFα agents, including GLM, to cause immune suppression affecting host defenses against infections and malignancies. When this study was designed, neither the pivotal registration trials nor any of the other clinical trials in the development program for GLM had suggested an association between the drug and a modified risk of CRC, dysplasia, HSTCL, or colectomy.[1,2] However, as part of the approval of the UC indication, postmarketing follow-up activities were included in the European Union (EU) risk management plan to gather additional information on CRC, colorectal dysplasia, HSTCL, and colectomy in the patient population with moderately to severely active UC in real-world conditions of drug utilization.

To gather this additional information, this Category 3 PASS used data from an ongoing registry of patients with IBD in Spain, ENEIDA (National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants).[3] Due to its widespread nature and participation of main referral hospitals, this registry was expected to capture the majority of GLM treatments prescribed for the treatment of UC in Spain since the date of its market authorization.

6.2 Background

Disease. Ulcerative colitis is a chronic IBD of unknown etiology characterized by inflammation primarily involving the colonic mucosa. The diagnosis of UC peaks between the ages of 15 and 35 years but may affect a person of any age. The symptoms of UC depend on the extent and severity of the disease and may include bloody diarrhea and rectal bleeding, along with systemic symptoms of fever and weight loss. The clinical

course is typically relapsing and remitting, although occasionally it may take an unremitting, continuous course. Anatomically, the inflammation is uniform and continuous, with no intervening areas of normal mucosa. In nearly all cases, inflammation involves the rectum and extends proximally for a variable distance.[4] Approximately 15% of patients may experience an aggressive course of the disease.[5]

Medical therapy. Therapy for UC has evolved in recent years. The text in the next paragraph describes treatment algorithms that were standard practice in 2014-2015 when the current study was designed.

Medical treatment for UC depends on disease severity and extent. Patients with mild-to-moderate UC are treated initially with oral 5-aminosalicylic acid (5-ASA) medications combined with topical treatment with 5-ASA or steroid suppositories, plus 5-ASA enema or steroid foam preparations. The oral 5-ASA preparations should be continued for maintenance of remission. For patients with moderate to severe UC, oral steroids are used to achieve initial disease control, followed by oral 5-ASA or TPs (6-mercaptopurine or azathioprine) for maintenance in a step-up therapeutic strategy. For patients who do not respond to or are intolerant to TPs, anti-TNFα agents such as infliximab, adalimumab, or GLM may be used. For patients hospitalized with acute severe disease or moderate to severe persistent UC who have not responded to intravenous corticosteroids after 3 to 5 days of treatment, therapeutic choices are either intravenous cyclosporine, an anti-TNFα agent, other novel drugs such as vedolizumab, or colectomy. Compared with first-line and second-line therapies, anti-TNFα agents and other biologics tend to be preferentially prescribed to patients with more severe, treatment-resistant disease.

Since the study began, some new therapies have been introduced to treat moderate to severe UC. Newer biologic agents include the anti-integrin vedolizumab, the anti-interleukin 12/23 antibody ustekinumab, and 2 new small molecules—ozanimod, an oral sphingosine-1-phosphate (S1P) receptor modulator, and tofacitinib, an oral small molecule Janus kinase (JAK) inhibitor. These new drugs have the indication in the EU to treat patients with moderate to severe UC who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or a biologic agent.[6]

Colectomy. When medical therapy fails, colectomy (ie, total or subtotal colectomy) is the surgical therapy of choice. The 5-year and 10-year cumulative risk of colectomy is 10% to 15%, mostly in patients with moderate to severe disease activity.[5] Predictors of an aggressive disease course and colectomy are young age at diagnosis (<40 years old), extensive disease, severe endoscopic activity, presence of extra-intestinal manifestations, early need for corticosteroids, and elevated inflammatory markers.[5] Colectomy is also performed to treat CRC and sometimes HGD. In a Norwegian population-based cohort study, colonic neoplasia accounted for about 10% of colectomies.[7] Less common reasons for colectomy in UC include emergent complications such as toxic megacolon, colonic perforation, massive hemorrhage, and colonic obstruction.

Neoplasia. Compared with the general population, patients with UC are at an increased risk of CRC and colonic dysplasia.[8] Colonic dysplasia is subcategorized into HGD and low-grade dysplasia. Because HGD carries a high probability of progression to CRC, it is typically treated with colectomy unless it arises from a sporadic polyp, in which case polypectomy is the treatment of choice. Low-grade dysplasia is associated with a smaller risk of progression to cancer and only rarely leads to colectomy; it can usually be managed with endoscopic removal of lesions and enhanced surveillance. Professional

society guidelines suggest enhanced surveillance with colonoscopy to monitor for CRC and dysplasia in patients with longstanding UC.[4,9] Screening colonoscopy is generally recommended to start 8 years after the initial diagnosis. In addition to CRC and dysplasia, HSTCL has been identified as a possible adverse event (AE) in patients with IBD treated with anti-TNFα agents. In the IBD population, the disease affects primarily males aged younger than 35 years, and almost all patients who develop HSTCL have also been exposed to TPs.[10] The incidence of HSTCL in the UC population is thought to be extremely rare, although it has not been formally quantified.

7 RESEARCH QUESTION AND OBJECTIVES

This study evaluated the risk of (1) colectomy due to intractable disease and (2) ACN (ie, CRC or HGD) in patients with UC treated with GLM and compared it to the risk associated with the use of alternative therapies (ie, other anti-TNFα agents or TPs) for UC of similar severity. This study also described the incidence of HSTCL in these populations as an exploratory objective. No a priori hypotheses were evaluated.

The primary objectives for the study were as follows:

1. To describe the clinical and demographic profile of first-time users of GLM in the treatment of UC compared with the corresponding profile of first-time users of comparator therapies (other anti-TNFα agents or TPs)
2. For patients with UC initiating GLM or other anti-TNFα agents, describe the risk of incident colectomy due to intractable disease
3. For patients with UC initiating GLM, another anti-TNFα agent, or a TP, describe the risk of ACN (the composite endpoint of incident CRC or HGD)
4. Compare the risk of colectomy due to intractable disease between GLM and other anti-TNFα agents
5. Compare the risk of ACN between GLM and other anti-TNFα agents

The secondary objectives for the overall study were as follows:

1. For patients with UC initiating GLM, another anti-TNFα agent, or a TP, describe the risk of incident CRC
2. Compare the risk of CRC between GLM and other anti-TNFα agents
3. If baseline characteristics suggest comparability between cohorts of patients receiving GLM and TPs, compare (1) risk of incident ACN and (2) risk of incident CRC

As an exploratory objective, the study described the incidence of HSTCL in each study cohort.

The reporting period for this final report is 19-Sep-2013 through 30-Mar-2022.

Results presented in this final report for the cohort analysis were based exclusively on the ENEIDA registry computerized database that contains information routinely collected from practices that contribute data to the registry. Hereafter, the study team refers to this data source as “routine ENEIDA data.” The data lock date was 30-Mar-2022. The nested case-control analysis supplemented the cohort analysis of the routine ENEIDA data with data obtained from the medical charts of patients selected as cases or controls. Adverse

reactions (ARs) attributed to GLM (SIMPONI®) or infliximab originator (Remicade®) that were identified by site investigators during the chart abstraction process were reported.

This final report includes all analyses outlined in the protocol for which a minimum of 10 events were observed for each outcome of interest and followed the rules specified in the statistical analysis plan (SAP) (Mod5.3.6/ENEIDA - Statistical Analysis Plan), as well as the data use agreements for data from the ENEIDA registry and from the medical charts of patients selected for the nested case-control analysis.

8 AMENDMENTS AND UPDATES

The study was registered in the European Union Electronic Register of Post-authorisation Studies (EU PAS Register) on 11-Oct-2016 (EUPAS15752). The redacted protocol was posted on 18-Oct-2016, and the publications section was updated on 23-Nov-2018. Subsequent amendments and updates (key changes) to the study protocol are summarized in Table 1.

Table 1: Amendments or Updates to the Study Protocol

No.	Date	Section(s) of Study Protocol	Amendment or Update	Reason
1	24-Oct-2019	9.2.3.1	Update	To reflect changes in methods as described in fourth progress report
2	23-Nov-2021	9.2.2, 9.2.3.1, 9.3.2, 9.7.2.1	Update	To reflect changes in study design, methods, and outcomes as described in fifth progress report
3	17-Nov-2022	Title Page, 3, 4, 6, 9.2.2, 9.2.3.2, 9.3.3, 9.7, 9.8, 12, Annex 1	Amendment	To reflect administrative and milestone changes and protocol changes inclusive of study design, methods, data analysis, outcomes, and quality control

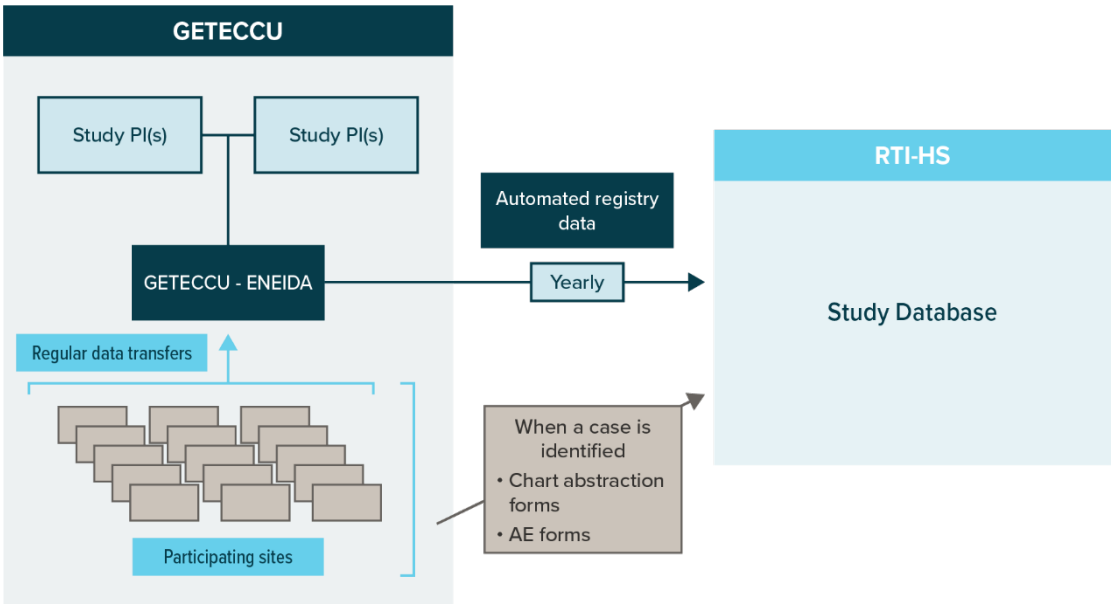
9 RESEARCH METHODS

9.1 Study Design

9.1.1 Overview of Study Design

Study MK-8259-042 was a long-term, non-interventional, observational Category 3 PASS using a new-user, bidirectional cohort design with cohort and nested case-control analyses that evaluated the risks of colectomy, ACN, and HSTCL in patients with UC treated with GLM compared with patients with UC treated with other anti-TNFα agents or TPs. The cohort study used data obtained bidirectionally from the Spanish ENEIDA registry, while the nested case-control analysis also used data from the retrospective review of selected medical charts (Section 9.5.2). Overall, the study used registry data from 30 sites across Spain that qualified as being of research quality in the ENEIDA registry (Section 9.5.1). The general organization of the sources of data, research team, and the flow of information for the study is presented in Figure 1.

Figure 1: Organization and Flow of Study Data



Abbreviations: AE, adverse event; ENEIDA, National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants (Spain); GETECCU, Spanish Working Group on Crohn's Disease and Ulcerative Colitis; PI, principal investigator; RTI-HS, RTI Health Solutions.

9.2 Setting

This non-interventional study was conducted in patients who received any of the study drugs as treatment for UC in a clinical practice setting. The study used data accrued from ENEIDA, a large prospectively maintained registry of patients with IBD in Spain (see Section 9.5.1), plus data abstracted retrospectively from medical charts from 28 participating ENEIDA sites. The study started 19-Sep-2013 and ended on 31-Dec-2021 for inclusion of new study patients and on 30-Mar-2022 for assessment of incident study outcomes. The report also includes ARs attributed to GLM (SIMPONI®) or infliximab originator (Remicade®) that were identified by site investigators during the chart abstraction process from this period if received through 31-May-2022.

9.2.1 Study Cohorts

9.2.1.1 Cohort Analysis

Cohorts of patients with UC who were new users of GLM (the main exposure of interest) or new users of comparator therapies (ie, other anti-TNFα agents or TPs) were identified using data from the ENEIDA registry from research-qualified centers (n=30). Per the protocol, patients who qualified to enter more than 1 cohort based on the inclusion and exclusion criteria were included in each corresponding cohort. Thus, cohorts were not mutually exclusive, and if a patient qualified to enter more than 1 study cohort, they contributed the corresponding person-time at risk to each applicable cohort.

A new user or initiator was defined as a patient having no prior records of prescription of the same drug (or its biosimilar).

The specifications of each cohort were as follows:

- *GLM cohort*: Patients with UC qualified for entry into the GLM cohort if they initiated GLM for the first time on or after 19-Sep-2013; prior use of a different anti-TNFα agent was permitted, as was prior or concurrent use of TPs. The following drug and brand name qualified patients for enrollment in the GLM cohort:
  - Golimumab: SIMPONI®
- *Other anti-TNFα agent cohort*: Patients with UC qualified for entry into this comparator cohort if they initiated an anti-TNFα agent other than GLM (ie, infliximab or adalimumab, including biosimilars) for the first time on or after 19-Sep-2013; prior use of a different anti-TNFα agent was permitted, as was prior or concurrent use of TPs. Biosimilars were considered the same anti-TNFα agent as the originator. This cohort served as the primary reference group for all comparative evaluations. The following drugs and brand names qualified patients for enrollment in the other anti-TNFα agent cohort:
  - Infliximab: REMICADE®, Remsima®, Inflectra®, Flixabi®, Zessly®
  - Adalimumab: Humira®, Yuflyma®, Amsparity®, Idacio®, Hulio®, Hyrimoz®, Hefiya®, Imraldi®, Amgevita®
- *TP cohort*: Patients with UC who initiated a TP for the first time on or after 19-Sep-2013 qualified for entry into the TP cohort if they were naive to both TPs and anti-TNFα agents. This cohort served as a secondary comparator only for the ACN outcome. The following drugs and brand names qualified patients for enrollment in the TP cohort:
  - Azathioprine: Imurel®, Immufalk®
  - 6-Mercaptopurine: Purinethol®, mercaptopurina
  - Thiopurine(s)

9.2.1.2 Nested Case-Control Analysis

In addition to the cohort analysis, nested case-control analyses evaluated the associations between GLM and the 2 main outcomes of interest, colectomy due to intractable disease and ACN. Up to 2 controls (ie, patients enrolled in the study but without a study outcome) were matched to each case for duration of UC, and length of follow-up time at the date of the corresponding case's outcome (see Section 9.3.2). The motivation for the nested case-control approach was 2-fold. First, it allowed for the incorporation of information on potential confounding variables that were not well captured in the routine ENEIDA data, such as systemic steroid use and hospitalization for UC, both of which are potential proxies for disease activity. Second, the nested case-control analysis allowed assessment of the study main objectives on a population with validated information on the study outcomes (date and diagnosis), as well as on some other key dates, such as the date of diagnosis of UC or the date of initiation of the last study drug.

9.2.2 Follow-up

9.2.2.1 Definitions of Follow-up Time

Patient time at risk or follow-up time in each cohort started at the date of cohort entry and extended until the date of end of follow-up within the study period. Date of cohort entry corresponded to the date of first record of one of the cohort-defining medications after other inclusion criteria were met (see Section 9.3.1). The last date of study entry permitted was 31-Dec-2021; however, cohort entry due to switching was allowed until the end of follow-up. The date of end of follow-up for each cohort member was the date of the earliest censoring event encountered (censoring criteria are described in the text that follows.) Some censoring criteria varied by study outcome (details below), but several criteria were shared across all outcomes.

Censoring criteria common to analyses of all outcomes:

- Withdrawal from the registry.
- Death.
- End of study period (30-Mar-2022).
- Loss to follow-up. Based on common clinical practice in Spain, patients receiving anti-TNFα agents or immunomodulatory therapies would be expected to have regular follow-up visits at least every 6 months. Patients who appeared to be receiving study medications (as indicated by date of medication prescription or dispensing) but who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed "lost to follow-up" and censored 6 months after the last follow-up visit.
- Initiation of a novel immunomodulatory drug that was newly marketed during the study period (see list in Section 9.3.1). These agents may have a direct effect on study outcomes and are likely to be preferentially prescribed to patients with UC with more active or severe disease. Therefore, including person-time exposed to these drugs would have very likely led to intractable confounding and uninterpretable results. Because uncontrolled disease activity may prompt therapeutic changes, it is possible that censoring follow-up immediately after switching may mask effects of the drug that preceded the switch. For this reason, the date of censoring was set 90 days after the start of the novel immunomodulatory drug.
- Prescription of 2 anti-TNFα agents on the same date.

Additional censoring criteria in analyses of specific outcomes:

- Additional censoring criteria for *colectomy due to intractable disease*:
  - Colectomy due to intractable disease
  - Total colectomy due to any cause
  - Other types of colectomy depending on reason for operation, patient characteristics, and timing of any subsequent colectomy, according to the algorithm presented in Figure 2

- Diagnosis of ACN or CRC. These conditions are commonly treated by colectomy (total or partial). According to the study principal investigators (clinical specialists in UC), the amount of residual colon left after a partial colectomy is small enough that the risk of a second colectomy due to intractable UC is greatly reduced. Therefore, the risk in patients who have had a partial colectomy is no longer comparable to the risk among patients with a complete colon. Patients who experience ACN/CRC but who do not have a colectomy performed are most likely too sick to undergo colectomy, in which case, these patients are also unlikely to be at risk for colectomy due to intractable disease

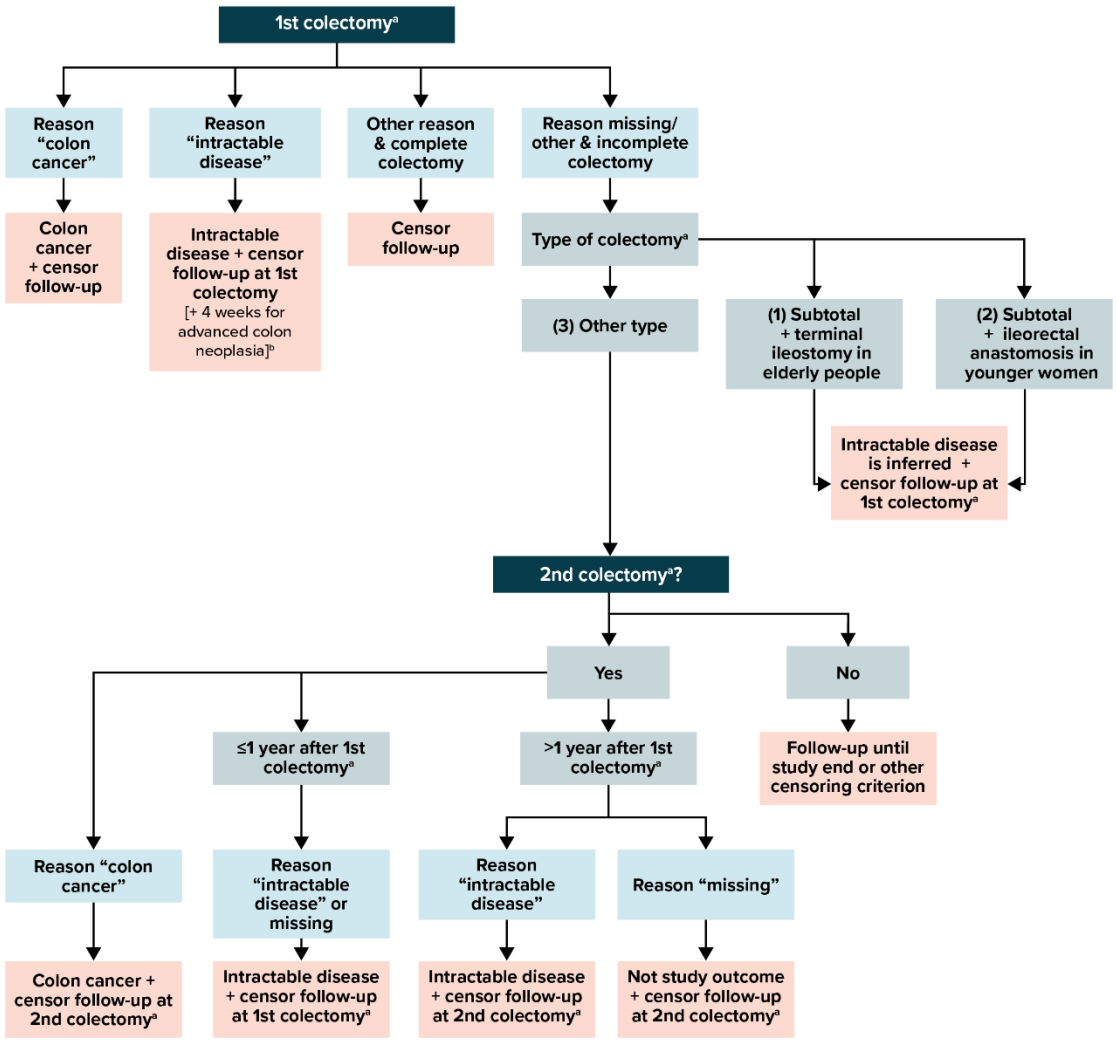
- Additional censoring criteria for *ACN and CRC*:
  - Occurrence of ACN or CRC
  - Total or partial colectomy for any reason. Patients who have undergone a total colectomy have virtually no tissue left in which ACN can develop. The amount of residual colon left after a partial colectomy is small enough that the risk of developing ACN is greatly reduced. Therefore, the risk in patients who have had a partial colectomy is no longer comparable to the risk among patients with a complete colon

- Additional censoring criteria for *HSTCL*:
  - The occurrence of HSTCL censored follow-up for further diagnoses of HSTCL

Criteria that excluded patients from participating in the study are described in Section 9.3.1.

Figure 2 summarizes the censoring of follow-up according to the type of colectomy and patient characteristics.

Figure 2: Patient Follow-up and Type of Colectomy



[a] Operation for colon resection.

[b] To allow inclusion of subclinical advanced colonic neoplasia detected in resected colon.

9.3 Patients

9.3.1 Identification of Patients for the Cohort Analysis

Patients entered the cohort study population if they met the following inclusion criteria:

- Were from a research-quality site that contributed data to the ENEIDA registry (see Section 9.5.1).
- Were aged 18 years or older at the date of study drug initiation.
- Had a diagnosis of UC.
- Initiated therapy with GLM, an anti-TNFα agent other than GLM, or TP starting 19-Sep-2013 (the date of GLM EU approval for UC) through 31-Dec-2021.

- Date of first prescription of cohort-defining drug (index date) occurred within a clinically credible period (<6 months) after the last recorded (ie, most recent) clinic visit in ENEIDA (dates of some index prescriptions do not have corresponding clinic visits). Index dates beyond this range raise concerns that the clinical record for this patient may be incomplete.

Patients were excluded if, before cohort entry:

- They had experienced any of the study outcomes of interest (underwent partial or complete colectomy or received a diagnosis of ACN or HSTCL) before or on the cohort entry date.
- For each of the 3 study cohorts (ie, GLM, other anti-TNFα agents, and TPs), the patient initiated the cohort-defining drug before 19-Sept-2013 (ie, they were prevalent users of that drug at the study start date). However, patients could enter the study later based on subsequent initiation of other cohort-defining drugs.
- Patients had initiated a novel biological or immunomodulator agent before cohort entry:
  - Vedolizumab: Entyvio®
  - Natalizumab: Tysabri®, Antegren®
  - Visilizumab: Nuvion®
  - Denosumab: Prolia®, Xgeva®
  - Etrolizumab: Raptiva®
  - Tocilizumab: Actemra®, RoActemra®
  - Ustekinumab: Stelara®
  - Certolizumab: Cimzia®
  - Tofacitinib: Xeljanz®

  This list defines the drugs referred to as "vedolizumab and other novel immunomodulators" mentioned in the protocol and covers drugs that would likely be prescribed to patients with more severe UC and that are potentially related to the study outcomes. The list has been expanded since study design to include drugs becoming newly available to treat UC or its complications.
- The indication for which a study drug was prescribed was not UC.

9.3.1.1 Definition of Risk Windows for the Cohort Analyses

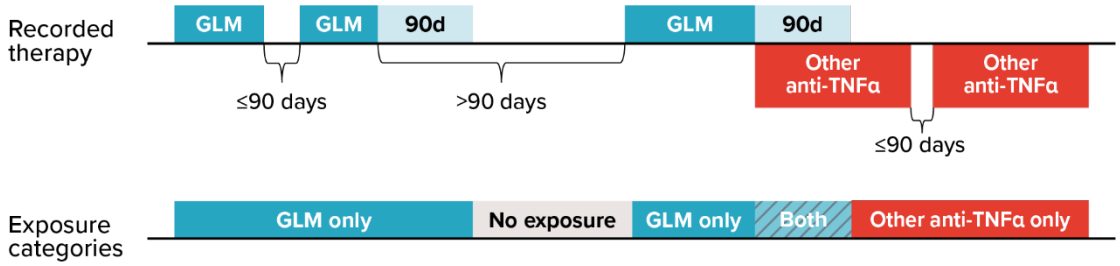
This study used outcome-specific risk windows for the outcomes of colectomy due to intractable disease and neoplasia (eg, ACN and HSTCL). Because the theoretical risk of cancer after exposure to biological therapies has an unknown latency, the risk window for neoplasia outcomes for both GLM and other anti-TNFα agents was "once exposed, always at risk."[11-13] In contrast, for the outcome *colectomy due to intractable disease,* the risk window for all exposures of interest (including GLM and other anti-TNFα agents) started 1 day after drug initiation through 90 days after the last treatment or until one of the triggers for end of follow-up occurred, whichever came first.

Due to the observational nature of this study, patients could start, stop, restart, and/or switch therapies during follow-up. Study cohorts were therefore not mutually exclusive, and a more detailed definition of risk windows reflected these possible exposure patterns and scenarios.

Colectomy due to intractable disease was attributable to a study exposure category if the date of the outcome occurred during the person-time at risk for that study exposure category. For this outcome, the following study exposure categories were possible: (1) GLM only, (2) other anti-TNFα agents only, (3) both GLM and other anti-TNFα agents, and (4) no exposure to either GLM or other anti-TNFα agents. If a patient stopped a study therapy and then restarted the same therapy (or a therapy belonging to the same exposure group) within 90 days, it was treated as a single continuous episode of exposure with no gaps. If a patient had a gap in therapy longer than 90 days, then his or her person-time after those 90 days was categorized as having no exposure to this study drug (until a new start of a study therapy or the occurrence of the outcome or censoring event). If a patient switched study therapies, then the 90-day period after the stop of the first study therapy had an exposure category of being exposed to both study drugs (switchers).

Figure 3 shows an example of the exposure categories for the colectomy outcome also considering the effect of gaps between exposure to the study drugs.

Figure 3: Example of Exposure Category Definitions for the Outcome Colectomy Due to Intractable Disease



Abbreviations: *n*d, number of days; GLM, golimumab; TNFα, tumor necrosis factor alpha.

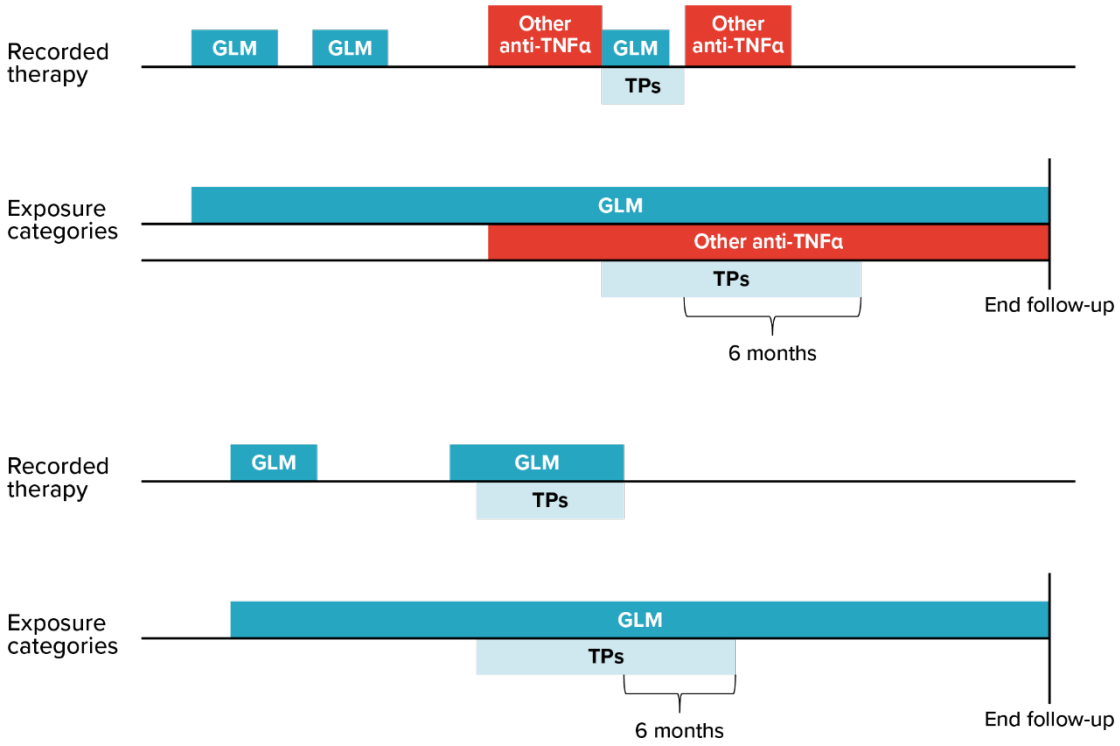
Additionally, a descriptive analysis of IRs of colectomy due to intractable disease was conducted with an "ever exposed, always at risk" alternative risk window that accounted for person-time for each study drug summed over the entire follow-up period.[5,11,12] The alternative risk window started 1 day after drug initiation and continued through the end of follow-up, regardless of any subsequent switch in treatment.

For the neoplasia outcomes (ACN and HSTCL): These outcomes were attributable to a treatment exposure if the date of the outcome occurred during the person-time at risk for that exposure category. For this outcome, the following exposure categories were possible: (1) GLM, (2) other anti-TNFα agents, and (3) TPs. For anti-TNFα agents, the potential effect on risk of neoplasia outcomes may persist after discontinuation of the anti-TNFα agent. As has been the practice in other studies of risk of cancer associated with the anti-TNFα agents, the primary risk window for these exposures is "once exposed, always at risk."[11-13] Patients accumulated person-time from the date of qualification for each applicable cohort until the date of outcome or censoring event, regardless of stopping, restarting, or switching therapies.

However, for TP use, the risk window began at the start of treatment with TP and continued until the end of follow-up or 6 months after drug discontinuation, whichever occurred first. Patients who switched from azathioprine to mercaptopurine (or vice versa) were considered to have continuous exposure to TPs, provided that the gap between the end of azathioprine and the start of mercaptopurine was less than 6 months (or vice versa). Patients exposed to both TPs and anti-TNFα agents accrued person-time to each cohort analogously to the situation depicted in Figure 4. Thus, a patient could contribute time at risk to more than 1 drug (GLM) or drug class (anti-TNFα agents or TPs) simultaneously.

If the patient experienced a neoplasia outcome after exposure to more than one exposure of interest, then the outcome was attributed to each applicable exposure category using the corresponding person-time at risk. Figure 4 illustrates risk windows for neoplasia outcomes for each exposure category.

Figure 4: Example of Exposure Category Definitions for Neoplasia Outcomes



Abbreviations: GLM, golimumab; TNFα, tumor necrosis factor alpha; TPs, thiopurines.

Because the actual biologic risk window for neoplasia outcomes is not known, the study team also planned to evaluate alternative definitions of the risk window that lagged the start of time at risk and varied the potential period at risk after discontinuation of exposure, as follows:

- Sensitivity analysis 1: For all study exposures, the risk window began 6 months after the start of current exposure and ended 6 months after discontinuation of exposure or at the end of follow-up, whichever occurred first.

- Sensitivity analysis 2: For all study exposures, the risk window began 6 months after the start of current exposure and ended 2 years after discontinuation of exposure or at the end of follow-up, whichever occurred first.

Thiopurines were not used as a comparator for the outcome colectomy due to intractable disease.

9.3.2 Identification of Cases and Controls for the Nested Case-Control Analyses

Among patients included in the study cohorts, routine ENEIDA data were used to identify cases of colectomy due to intractable disease and ACN arising from the study cohorts. Up to 2 controls (ie, patients without a study outcome) were selected and matched to each case. For cases, the reference date was defined as the date when the patient experienced the outcome of interest. The same date was assigned as the reference date to the matched control(s).

Looking backward in time from the reference date, it was determined whether the reference date fell within a risk window of a study drug. To focus the chart abstraction efforts on informative patients, the case-control analysis included only those cases with exposure to a relevant study medication within the applicable risk window leading to the reference date (ie, within 90 days prior to the reference date for colectomy or any date prior to the reference date for ACN or CRC outcomes). Potential control patients were identified from risk sets assembled using incidence density sampling, matching on time since initial UC diagnosis and calendar time of the outcome date.[14] Potential controls were assigned a reference date equivalent to the outcome date of their matched case. Similar to what was done for cases, only controls whose reference date fell within the exposure risk window of a study drug were eligible.

Controls were eligible if, on the reference date, they

- Were alive, under observation, and had not yet experienced the outcome.
- Had been exposed to a relevant study medication within the applicable risk window leading to the reference date (ie, within 90 days prior to the reference date for colectomy; any date prior to the reference date for ACN or CRC outcomes) (see Section 9.2.2.1).
- Had a duration of UC similar to that of the corresponding case (ie, within ±12 months).
- Had a length of follow-up time in the study similar to that of the corresponding case (ie, within ±3 months).

Each case was matched with up to 2 controls. If more than 2 potential controls were eligible to be selected for a given case, then 2 were selected at random. If a control was selected and his or her chart could not be obtained, another eligible control was randomly selected, if available. It is important to note that a patient who eventually became a case could be eligible to be a control for another patient, as long as he or she had not yet experienced the outcome on the applicable reference date. Furthermore, it was possible for a patient to be a control for multiple cases. If a case had no eligible controls for

matching, some of the matching criteria were relaxed (ie, expanded time windows for UC duration and/or length of follow-up time).

9.3.3 Ethics Approval

The study protocol was reviewed and approved by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) (the scientific society maintaining the ENEIDA registry), the study's reference ethics committee (Hospital Universitario de La Princesa, Madrid), and the Spanish Agency for Medicines and Medical Devices (AEMPS).

To be enrolled in the ENEIDA registry, patients need to sign an informed consent form to allow inclusion of their health information in the registry and its use for research purposes. No study-specific informed consent form was required for use of the routine ENEIDA data. However, this study included a nested case-control analysis involving medical chart abstraction that required specific additional institutional review board reviews. At all participating sites, institutional review boards considered that the ENEIDA registry informed consent also covered the chart review portion of the study because all requested variables were within the scope of information collected by the registry.

Identifiable patient-level data remained entirely within the ENEIDA environment, and RTI-HS personnel had access only to the deidentified ENEIDA data necessary to conduct the study and to the deidentified data abstracted from medical charts. Only aggregated analysis results and study reports were shared with the Sponsor.

9.4 Variables

Data for the study were ascertained by using readily available ENEIDA data, which included the diagnosis of UC, study drug exposure, study outcomes, patient demographics, and covariates of interest. Additionally, for the nested case-control analyses, data for selected variables were sought from review of the medical charts of case and control patients. The investigators from the 28 sites participating in the chart abstraction component of the study reviewed medical charts and completed a specific questionnaire (see Section 9.5.2 and the stand-alone questionnaire, which is listed in Annex 1).

9.4.1 Exposure

The main exposures of interest in this study were treatment with GLM, other anti-TNFα agents, and TPs. Drug data included information on indication, start date, and discontinuation date of each treatment course of the study drugs.

The following drugs defined the exposures of interest:

- GLM cohort:
  - Golimumab: SIMPONI®
- Other anti-TNFα agent cohort:
  - Infliximab: REMICADE®, Remsima®, Inflectra®, Flixabi®, Zessly®
  - Adalimumab: Humira®, Yuflyma®, Amsparity®, Idacio®, Hulio®, Hyrimoz®, Hefiya®, Imraldi®, Amgevita®

- TP cohort:
  - Azathioprine: Imurel®, Immufalk®
  - 6-Mercaptopurine: Purinethol®, mercaptopurina
  - TPs

9.4.2 Outcomes

The study outcomes were colectomy due to intractable disease, ACN (a composite of CRC and HGD), CRC, and HSTCL. Only incident diagnoses (those with an onset after cohort entry) qualified as outcomes.

- *Total or partial colectomy due to intractable disease*. Information about bowel surgery is considered mandatory data in ENEIDA. Categories available include: "intractable disease" ("refractoriness to medical treatment"), "stenosis," "perforation," "hemorrhage," "dysplasia or cancer," and "other." The date of colectomy is also available in the ENEIDA database. Based on consultation with the study principal investigators (clinical specialists in IBD) and clinical guidelines,[15] the following scenarios were deemed to meet the definition of colectomy due to intractable disease when no other reasons for colectomy were indicated:
  - Subtotal colectomy with terminal ileostomy among patients aged 65 years or older (ie, elderly)
  - Subtotal colectomy with ileorectal anastomosis among women aged up to 50 years (ie, women of childbearing age)
    In these 2 specific subpopulations (elderly and women of childbearing age), the conservative approach consisting of a partial colectomy is the currently preferred surgical approach to treat resistant UC
- *ACN* (a composite endpoint that includes both CRC and HGD). The rationale for using a composite endpoint was that both constituents represent different phases of the same disease pathway. Current understanding of CRC is that all such cancers go through a dysplastic phase before malignant transformation. Patients with HGD have a high probability of progressing to CRC, and like patients with CRC, they are typically treated with colectomy.[9]
- *HSTCL*. Information about HSTCL was ascertained from the ENEIDA registry. However, cases of HSTCL may be difficult to capture because these rare lymphoid malignancies can conceivably be classified as lymphomas without further specification in the ENEIDA registry. To ensure that all reported cases of HSTCL in the ENEIDA registry were captured, registry data managers performed a sensitive search for lymphoma-related diagnoses in the registry free-text fields on a yearly basis to identify potential cases. Any identified patients were further evaluated by the investigators at the corresponding hospitals to confirm or rule out a diagnosis of HSTCL.

9.4.3 Covariates

The covariates assessed for this study were age, sex, calendar year of study entry, UC maximum extent and duration, prior treatment with corticosteroids or cyclosporine, prior hospitalization for UC, prior diagnosis with primary sclerosing cholangitis (PSC), number

of screening colonoscopies, number of previous types of anti-TNFα agents used, recent switcher after short-term use of another anti-TNFα agent (ie, during the 90-day period after starting a new anti-TNFα agent following discontinuation of another anti-TNFα agent that was used for 3 months or less), and recent switcher after longer-term use of another anti-TNFα agent (ie, during the 90-day period after starting a new anti-TNFα agent following discontinuation of another anti-TNFα agent that was used for more than 3 months). Section 9.8 presents additional information about ascertainment windows for the covariates.

9.4.4 Adverse Reactions

As specified in the study protocol, all serious ARs, nonserious ARs, and health outcomes of interest (HOIs) related to the Sponsor's products (ie, SIMPONI® and REMICADE®), as well as special situations (ie, pregnancy exposure, overdose, off-label use, and the suspected transmission of an infectious agent via the medicinal product), were reported to the Sponsor if encountered during the review of the medical charts for the nested case-control study. All reported ARs to the Sponsor's products that were received by RTI-HS were entered into the study database and are shown in Table 25 in Section 10.6 if they were received on or before 31-May-2022.

9.5 Data Sources and Measurement

9.5.1 The ENEIDA Registry

ENEIDA is a large, prospectively maintained registry of patients with IBD in Spain. It is conducted under the auspices of GETECCU, a national scientific society devoted to the study of IBD.[16] Data in the ENEIDA registry come from a network of more than 90 academic and community gastroenterology practices across Spain that have an interest in IBD. As of 30-Mar-2022, the registry's entire census of patients with UC was 35,708. Participation in the registry is voluntary for both physicians and patients, and physicians who contribute data to ENEIDA receive no payment for this registry work. ENEIDA has its own data managers. The ENEIDA registry is stored in a password-protected MySQL database that is maintained in a secure server facility. The investigator or qualified designee at each contributing practice is responsible for verifying the accuracy of patient data as data are entered into the ENEIDA database.

Practices that participate in the ENEIDA registry enter data into an electronic case report form (eCRF) that is immediately uploaded in the central ENEIDA database. Data in ENEIDA comprise a predefined set of clinical variables. The registry mandates completion of a limited number of fields on the eCRF, while completion of other fields is optional. Contributing practices are judged to be of research quality based on the percentage of patients with IBD in each practice enrolled in ENEIDA and on the percentage of completion of mandatory data fields. Section 9.5.1.1 describes the criteria used to determine the research quality of data from contributing practices.

9.5.1.1 List of Mandatory Variables and Calculation of Variable Completeness

ENEIDA practices are expected to complete a set of mandatory variables for each registered patient. On a monthly basis, ENEIDA assesses the completeness of data for each ENEIDA practice for all registry patients, not just the patients seen in the practice

that month. Practices with low data completion are asked, but not compelled, to be more thorough.

The mandatory variables are grouped into the following categories:

- Demographic data: name, family name, date of birth, sex, date of inclusion in the registry, date of the last visit.
- Clinical data: date of the first diagnosis of UC, current diagnosis (in case the IBD diagnosis changed since presentation), and disease location.
- Immunosuppressive therapy (yes or no): drug type, date of drug initiation, continuation of treatment (yes/no), drug indication, AEs (including type and whether it was necessary to stop the drug).
- Biologic therapy (yes or no): drug name, date of drug initiation, continuation of treatment (yes/no), drug indication, secondary loss of response, AEs (including type and if it was necessary to stop the drug).
- Surgical therapy (yes or no): details of surgical therapy: date of surgery, type (urgent/programmed), type of surgery (abdominal or perianal), indication for surgery.
- Risk factors: family history, smoking habit (at last visit and at the moment of UC diagnosis).

Calculations of percentage of data completeness include all patients registered within a site, except for sections on details of treatments that refer only to patients who received the corresponding therapies (ie, 3, 4, and 5 from the list above). Note that if a single variable in a specific section was missing, the entire section was considered to be incomplete. Each site then received scores for completeness for each section of mandatory data.

The population for this study was drawn from the ENEIDA practices judged to have research-quality data. Practices that satisfied the following 2 criteria at the start of the study qualified as research quality: (1) enrolled at least 75% of their patients with IBD into the registry (a self-reported variable) and (2) entered at least 75% of the mandatory variables on the eCRFs, based on monthly audit of cumulative site data. Research-quality practices did not change during the conduct of the study.

9.5.2 Medical Charts

In addition to the data collected by the ENEIDA registry, the study also included data obtained through abstraction of medical charts for the nested case-control analysis. Specifically, the chart abstraction questionnaire (see stand-alone document, which is listed in Annex 1) obtained information on the following variables:

- Number of types of anti-TNFα agents previously used to treat UC since the diagnosis of UC.
  - Infliximab, adalimumab, GLM, and other anti-TNFα agents were considered different types
  - Biosimilars were treated as the same anti-TNFα agent as the originator drug

- Reason for starting, stopping, or changing any of the study therapies (GLM, other anti-TNFα agents, TP) or combination of study therapies (only for the switches closest to the index date).
- Type of study outcome and date.
- First exposure to each of the 3 study drugs (ie, GLM, other anti-TNFα agents, and TPs).
- Number of screening colonoscopies since diagnosis of UC.
- Prior diagnosis of PSC ever before index date.

In addition, 4 variables were ascertained twice, in 2 different ascertainment periods: period 1—in first year after UC diagnosis (hereafter "first year after diagnosis"), which was truncated if the first prescription of a study drug occurred before a full year elapsed, and period 2—in the year before the last episode of a study drug commenced, looking backward from the date of study outcome (or an equivalent date among the controls)—this period could extend back only as far as the date of the first UC diagnosis, and thus could be truncated.

- Number of hospitalizations for UC.
- Maximum extent of UC that was documented. Collection of this information from the medical charts was informative because the ENEIDA registry includes only 1 value for the maximum extent of UC, which is not date stamped; prior information is overwritten when a higher extent is reached.
- Prescription of corticosteroids, with route and cumulative duration of use.
- Prescription of cyclosporine, with cumulative duration of use.

The chart abstraction process was limited to patients from the 28 practices that agreed to participate in the nested case-control analysis. Moreover, only patients whose reference date (outcome date for cases and equivalent date for matched controls) fell within a risk window of one of the study drugs were included in the nested case-control analysis and were thus selected for chart abstraction. For the variables listed above, the nested case-control analysis relied on data ascertained from chart abstraction, rather than the corresponding data from the routine ENEIDA data.

An exploratory analysis was conducted to examine the agreement between the data elements from the ENEIDA registry and data on the same variables obtained from chart abstraction. The following variables were evaluated:

- Date of first diagnosis of the study outcome.
- Date of first GLM use.
- Number of previous types of anti-TNFα agents used for the treatment of UC since the diagnosis date.
- Date of UC diagnosis.

- Date of maximum extent of UC during the first year after diagnosis.
- Date of maximum extent of UC before initiation of the last episode of the last study drug before the reference date.

The medical charts were also the source of data used to identify potential ARs to the Sponsor's study drugs (see Section 9.4.4).

9.5.3 Study Procedures

This study involved a secondary analysis of data from the routine ENEIDA database, which documents patient care in a usual care setting. Accordingly, no study-specific procedures were required for this PASS.

For the nested case-control analysis, eligible patients were identified yearly in the ENEIDA data, and chart abstraction was requested at the corresponding hospitals. Prior to abstracting chart data, the investigators at the corresponding practices conducted an initial training and yearly refresher trainings on the specific aims and procedures of the chart abstraction process and reporting of ARs. During the conduct of the study, 2 practices opted out of the chart abstraction component due to (1) the local ethics committee not providing approval for the chart abstraction component of the study and (2) not having adequate research personnel availability to participate. Cases and controls for which medical chart data had already been obtained at the time of their practice opting out of the study were retained for the nested case-control analysis.

9.6 Bias

The study had potential for several types of bias.

Potential for information bias. The readily available ENEIDA data may not contain complete information on all relevant study variables. Many fields are not mandatory for ENEIDA sites to complete, and based on pilot work, it was expected that the true frequencies of certain medical events (eg, corticosteroid use and hospitalizations) were underestimated. However, the pilot study also indicated that capture of the main study outcomes was reasonably complete.[17] Chart review was planned for all cases and a sample of controls to augment capture of information on potential confounding variables in the nested case-control analyses.

Potential for confounding by severity of disease. This is a concern in any observational safety study. Disease activity cannot be directly ascertained from the registry data and is not systematically recorded in medical records. However, proxies for chronic inflammatory burden, such as disease duration, disease extent, and history of prior UC therapies, are systematically recorded in the registry data. Moreover, other markers of disease activity, such as steroid treatment history and hospitalization for UC, were sought from medical records for the nested case-control analysis.

Potential for bias in longitudinal variables. In addition, the structure of the database limited the ability to address certain study questions. Disease extent is not stored as a time-dependent variable; rather, it is continually updated and at any point reflects the maximal disease extent ever observed in a given patient. As a consequence, analyses based on registry data may exaggerate the maximal disease extent at the time of cohort

entry. As part of the case-control study, the maximal disease extent at the time of cohort entry (the index date) was ascertained from medical records. Similarly, dates of clinic visits are not stored in a longitudinal fashion. The registry tracks only the date of the latest clinic visit; as a result, the ability to address the completeness of follow-up care was constrained.

Potential for selection bias. Based on pilot study data, loss to follow-up was anticipated to be approximately 10% per year. If loss to follow-up differed by exposure status, it could introduce selection bias. To evaluate this possibility, baseline characteristics of patients who were lost to follow-up and those who were not lost to follow-up were tabulated.

Potential for residual confounding and random error. This may occur because of incomplete information on potential confounding variables and because of the rarity of some study outcomes. This situation limited the ability to perform multivariable statistical adjustment and resulted in IRs and IRRs with limited precision.

Finally, because the background incidence of HSTCL is so low (approximately 1 case per million PY), it was already anticipated during the design phase of the present study that few if any cases of HSTCL would be encountered during this study.

9.7 Study Size

The cohort study used all available data from qualified ENEIDA sites for patients with UC who met all entry criteria and initiated GLM, other anti-TNFα agents, or TPs during the study period.

Protocol Section 9.5, Study Size, contemplated study size for cohort analyses of colectomy due to intractable disease and for ACN separately. The protocol expressed study size expectations in a number of ways. First, it predicted 996 patients initiating any anti-TNFα agent across the study period. The current study enrolled substantially more: 474 patients initiated GLM and 1,737 patients initiated other anti-TNFα agents (Analysis Table 1). The protocol scenarios that estimated the detectable relative risk of colectomy also assumed study size in terms of person-time at risk across all anti-TNFα agents (1,700 PY), varying assumptions about the proportion of person-time from GLM use from 15% to 40%. In the current study, overall person-time across all anti-TNFα use was 4,742.4 PY, of which 912.3 PY (19.2%) were accrued from GLM-only exposure (Analysis Table 6.1.1).

For the ACN outcome, the protocol assumed 3,150 PY at risk across all anti-TNFα agent use, again varying the proportion due to GLM use from 15% to 40%. In the current study, overall person-time at risk across all anti-TNFα agent use was 5,985 PY, of which 1,347.8 (22.5%) accrued from GLM exposure (Analysis Table 6.1.2).

In summary, the current study met or exceeded expectations for study size outlined in the protocol.

9.8 Data Transformation

For the cohort analyses, all covariates were ascertained from registry data on the date of cohort entry and were updated each time the patient changed exposure categories.

- Age (continuous and categorized as follows: 18-34 years, 35 to 64 years vs ≥65 years).
- Sex (male vs female).
- Calendar year of cohort entry (for description by each year and for analysis grouped as 2013-2015, 2016-2018 vs 2019-2021).
- UC disease duration was defined as the time between the date of diagnosis and date of cohort entry and handled as a continuous variable for descriptive analyses. For comparative analyses, duration was categorized based on tertile as follows: <33rd percentile value, 33rd to <67th percentile, or ≥67th percentile).
- Medication use: systemic steroids and cyclosporine.
  - Yes if use was recorded any time before cohort entry.
- Hospitalization for UC.
  - Yes if it was documented any time before cohort entry.
- Diagnosis with PSC ever before cohort entry (yes/no).
- Screening colonoscopy any time before cohort entry (yes/no).
- Number of previous anti-TNFα agents any time before cohort entry (0 or 1 vs 2).
- Recent switcher after use of another anti-TNFα agent (short-term use [≤3 months], long-term use [>3 months] vs did not switch). Recent switcher refers to starting a new anti-TNFα agent within 90 days following discontinuation of another anti-TNFα agent.

For the nested case-control analyses:

- Except for the variables noted immediately below, covariates listed in Section 9.5.2 were evaluated from the medical charts at the last change in exposure category (ie, the one leading to the outcome in cases or equivalent date for the controls)
- The following 4 variables were evaluated during 2 ascertainment windows, as noted in Section 9.5.2:
  - Number of hospitalizations for UC.
  - Maximum extent of UC documented according to the following categories: extensive, left sided, proctitis, not recorded.
  - Prescription of corticosteroids (yes/no).
  - Prescription of cyclosporine (yes/no).

9.8.1 Data Management

This study involved a secondary analysis of routine ENEIDA data, previously described in Sections 9.5.1 and 9.5.2. The readily available routine ENEIDA data are maintained and managed in a password-protected MySQL database on a server in a secure facility. The clinical investigator or qualified designee is responsible for verifying the accuracy of patient data as it is entered into the ENEIDA database.

A separate database was created for this study, details of which are included in a stand-alone data management plan, which also includes the procedures used for contacting sites for chart reviews and describes the flow of abstracted clinical data into the study database. It also includes the chart abstraction questionnaire, which was piloted during the first phase of the study and was modified to improve clarity of questions based on the chart reviewers' feedback, as specified in the study's 2018 progress report. The study database incorporated routine ENEIDA data and data collected via chart abstraction for selected cases and controls (see Section 9.3.2).

9.9 Statistical Methods

All analyses were performed in SAS version 9.4 or higher (Cary, North Carolina: SAS Institute; 2013) and follow the SAP dated 25-Jun-2020 (Mod5.3.6/ENEIDA - Statistical Analysis Plan).

Among the patients who met all the criteria for inclusion in the analysis, the number of patients who qualified for each cohort (GLM, other anti-TNFα, and TPs) was generated. Patients could enter more than 1 cohort as long as the corresponding inclusion and exclusion criteria were met.

As planned a priori, the cohort analyses relied only on automated routine ENEIDA data. The nested case-control analyses used information that had been abstracted from review of medical charts for all but the following 3 variables: date of birth, sex, and recent switcher status (defined in Section 9.8).

9.9.1 Main Summary Measures

Descriptive statistics were generated for patient characteristics at the time of cohort entry for each cohort. Duration of follow-up for each cohort and reasons for end of follow-up by study outcome were summarized with descriptive statistics and by year of cohort entry. Finally, patterns of persistence and changing of study medications over time were summarized by study outcome. For continuous variables, descriptive statistics comprised the number of nonmissing values, mean, standard deviation, median, first quartile, third quartile, minimum value, and maximum value. For categorical variables, descriptive statistics comprised frequencies and percentages.

Outcome descriptive statistics consisted of the incidence of each outcome (ie, colectomy due to intractable disease, ACN, CRC, and HSTCL), total PY of follow-up considering the applicable outcome-specific risk window, IR (ie, the number of outcomes divided by the PY at risk) per 1,000 PY, and the 95% CI as derived from the Poisson distribution. Outcome diagnoses were accepted as provided by the ENEIDA registry.

Figures were generated to graphically display the cumulative incidence of the study outcomes by exposure category whenever numbers allowed.

9.9.2 Main Statistical Methods

9.9.2.1 Descriptive Analyses

The present final report includes the descriptive analyses using the complete data set for the study (ie, using data from 19-Sep-2013 through 30-Mar-2022). The previously submitted progress reports included descriptive analyses as conducted in an incremental fashion.

The study cohort assembly process for the GLM, other anti-TNFα agents, and TP cohorts is outlined in attrition tables and figures. The number of patients in the ENEIDA registry eligible to be included in the analysis is provided after the application of each successive entry criterion in hierarchical order.

Descriptive statistics were generated for patient characteristics at the time of cohort entry for each study cohort. Individual patients could contribute to more than 1 cohort if they were qualified users of more than 1 study drug.

Duration of follow-up for each study cohort was calculated for following outcomes: ACN, Colectomy due to intractable disease, and HSTCL. For each year of cohort entry, descriptive statistics were generated for the total months of follow-up time for each study cohort. This follow-up time was calculated based on the risk windows described in Section 9.3.1.1 and censoring events (Section 9.2.2).

For each study cohort, the frequency of each reason for ending follow-up for each outcome was tabulated for patients who entered the cohort during each study calendar year. Additionally, a summary table combining data across all calendar years was generated.

Given that patients could change therapy after study cohort entry, descriptive statistics of the overall exposure time to GLM, exposure time to any other anti-TNFα agent, and exposure time to a TP were generated for each study cohort. Additionally, to characterize further the patterns of persistence and changing of study medication over time, the time to first change of therapy after cohort entry for all outcomes was summarized for each study cohort. Change of therapy was defined as the addition or subtraction of a study medication (GLM, other anti-TNFα agents, or TP) from the patient's regimen at the date of cohort entry. Time at risk, that is, time of exposure considering the corresponding risk windows, was summarized separately as time at risk to each exposure category for each study outcome.

Crude IRs were estimated for the study outcomes by exposure category, considering the corresponding risk windows (as described in Section 9.2.2). Crude IRs were also estimated stratified by the potential confounders listed in Section 9.4.3. Cumulative incidence function plots were generated for each study outcome by study treatment exposure category. Cumulative incidences accounted for only outcome-specific person-time at risk, which was accrued as described in Section 9.3.1.1. Accordingly for the outcome of colectomy due to intractable disease, the cumulative incidence function of each curve displayed began at the time of cohort entry and allowed for short gaps in

treatment, but it excluded person-time for gaps in treatment longer than 90 days. When gaps of 90 days or longer occurred, the person-time before and after the gap was concatenated into one continuous episode. An equivalent approach was used to calculate IRs, Poisson models, and Cox models for the colectomy outcome. In contrast, for all analyses of neoplasia outcomes, time after cohort entry was considered person-time at risk regardless of any treatment gaps (see Figure 4).

The cumulative incidence function for an outcome of interest at a particular point in time was defined as the probability that the outcome occurred at or before the particular point in time. The value of the cumulative incidence function estimates was derived from nonparametric methods to account for the risks of competing events specific to each study outcome.[18,19] In these cumulative incidence analyses, death, ACN, and total or partial colectomy for other reasons were considered competing events for colectomy due to intractable disease; any total or partial colectomy (for any reason) and death were considered competing events for ACN. Death was a competing event for HSTCL.

9.9.2.2 Comparative Analyses: Cohort Approach

For all comparative analyses, outcomes that occurred within the applicable risk window (as defined in Section 9.3.1.1) were used.

Because colectomy due to intractable disease had a risk window that extended 90 days beyond the end of the treatments under study, it was possible for a patient to experience this study outcome while not being exposed to any study therapy (eg, if a patient stopped a therapy for more than 90 days, experienced the outcome, then started a new therapy). In a time-to-event approach (eg, Cox regression), patients must be followed until the occurrence of the study outcome or a censoring event, thus incorporating any periods of nonexposure to study therapies. However, in Poisson regression, these periods of nonexposure to study therapies—which were not of primary interest for the study—do not necessarily need to be incorporated into analysis, as follow-up time while exposed can be the main unit of analysis. Therefore, Poisson regression (considering only periods at risk associated with exposures of interest) was the primary method of analysis for the outcome colectomy due to intractable disease, while Cox regression was used as a secondary analytic method for this outcome. However, for the neoplasia outcomes, only Cox regression was performed.

Crude analysis. For the outcome colectomy due to intractable disease, a univariable Poisson regression model with log-time offset was generated where the occurrence of the outcome was modeled as a function of study exposure category only (modeled as a multilevel categorical variable). Additionally, a univariable Cox regression model was generated where all possible exposure categories to the drugs of interest were considered (Section 9.4.1, Exposure). For both Poisson and Cox regression models, the exposure category was modeled as a time-varying variable for all analyses when applicable. Crude IRRs and HRs from the Poisson and Cox regression models, respectively, were calculated for the outcome of colectomy due to intractable disease. The Cox regression models were repeated for ACN and CRC. The corresponding table for HSTCL was not generated due to the absence of HSTCL events. The corresponding 95% CIs were calculated using robust estimations to account for repeated patients.

Adjusted analysis. Only variables associated with the outcome, regardless of association with exposure (which facilitates the discarding of instrumental variables), were included

in the adjusted models. To identify which covariates should be considered in the multivariable model for colectomy due to intractable disease, a separate Poisson regression model was generated for each candidate variable of interest, where the incidence of colectomy during time at risk was modeled as a function of the candidate variable only. The resulting IRR and 95% CI for the candidate variable was reported. To be considered for inclusion into the multivariable model, variables needed to exhibit an IRR greater than 1.25 or less than its inverse (ie, 0.80). Additionally, other variables could be forced into the model if deemed clinically important. In the event that the number of variables that qualified based on these cutoffs was larger than could be supported in the multivariable adjustment model (ie, it would not converge), additional considerations were applied to build a more parsimonious model. These included strength of association in the screening model and perceived clinical importance.

Nonetheless, to evaluate the potential confounding effect of each candidate variable, stratified analyses were undertaken, evaluating the effect of main exposures overall (crude associations) as compared with Mantel-Haenszel adjusted IRRs. Bivariate Poisson regression models where the occurrence of the outcomes was modeled as a function of study exposure category and each candidate confounding variable, one at a time, were generated.

Candidate covariates were evaluated for the Cox regression analyses for ACN but not for CRC or HSTCL since the small number of identified outcomes (n<10) would not allow the inclusion of even one adjustment variable in the models. The SAP (Mod5.3.6/ENEIDA - Statistical Analysis Plan) indicated that multivariable models with fewer than 10 outcomes across all cohorts would not be conducted.

Multivariable Poisson regression was the primary method of analysis for the outcome colectomy due to intractable disease. All covariates selected from the candidate variable screening process were measured at baseline (ie, first study drug use within the study period) and were updated at each relevant change in exposure during follow-up (ie, GLM, other anti-TNFα agents, and periods of overlapping exposure resulting from the switch to GLM from other anti-TNFα agents or vice versa). The resulting IRRs and 95% CIs for the treatment exposure effect and for each included covariate were estimated and reported. Cox regression (considering all follow-up time regardless of exposure to study therapies) was employed as a secondary analysis of colectomy due to intractable disease, updating covariate information (as with the Poisson model) at any change in exposure category. The analyses of ACN were based on an adjusted Cox regression model. All 95% CIs were calculated using robust estimations to account for repeated measures.

For colectomy due to intractable disease, these multivariable regression models were regenerated for the comparison of study treatment exposure categories by the subgroups of interest. Finally, an alternative risk window of exposure through the end of follow-up (ie, “once exposed, always at risk”) was applied. Several multivariable sensitivity analyses planned for the outcome ACN were not conducted due to the small number of observed ACN events, consistent with plans in the SAP (Mod5.3.6/ENEIDA - Statistical Analysis Plan).

To explore the possibility of competing risks between the 2 outcomes (colectomy due to intractable disease and ACN) influencing the comparative analyses, a multivariable Cox regression model was generated using a composite outcome that assessed time to the earliest of colectomy due to intractable disease, ACN, or death.

In this study, all evaluations of exposure-outcome associations involved more than 2 exposure categories (eg, GLM, other anti-TNFα agents, and TP). All Poisson and Cox models that evaluated such exposure-outcome associations included all exposures in a single model.

9.9.2.3 Comparative Analyses: Nested Case-Control Approach

Separate nested case-control analyses were planned to evaluate the association between study exposures and the outcomes: colectomy due to intractable disease and the neoplasia outcomes (ACN/CRC). Cases and controls were characterized on the date of the last change in exposure with respect to exposures and covariates of interest, obtained from medical chart abstraction. Crude odds ratios (ORs) were estimated along with corresponding 95% CIs, using a univariable conditional logistic regression model in which the occurrence of the outcomes was modeled as a function of study exposure category only (modeled as a multilevel categorical variable).

Several variables were evaluated as potential confounders, including age, sex, UC duration, maximum extent of disease, prior treatment with steroids, prior treatment with cyclosporine, previous hospitalization for UC, prior diagnosis with PSC, prior screening colonoscopy, number of previous anti-TNFα agents, and recent switch after use of another anti-TNFα agent.

Similar to the variable screening process in the cohort analysis, a separate conditional logistic regression model, where the occurrence of each outcome was a function of the candidate variable only, was generated for each candidate variable of interest. In the event that the number of variables that qualified based on the cutoffs was larger than could be supported in the multivariable adjustment model (ie, it would not converge), additional considerations were applied to build a more parsimonious model. (Similar to the cohort analyses, the screening thresholds were IRR greater than 1.25 or less than its inverse (ie, 0.80)). These included strength of association in the screening model and perceived clinical importance. After the covariates for adjustment were determined, a multivariable logistic regression model, conditional on matching, was generated where the occurrence of colectomy due to intractable disease was modeled as a function of study therapy exposure group and selected covariates determined from the candidate variable screening process. Using this approach, adjusted ORs and 95% CIs for the study therapy exposure effect on colectomy due to intractable disease were estimated. Similar methods were planned to estimate the adjusted ORs in the case-control analyses for ACN but were not performed due to the sparsity of outcomes.

9.9.3 Missing Values

As in most database analyses, the absence of information on a given diagnosis, such as an outpatient diagnosis, was classified as the absence of the condition. This approach is further justified given that the data were generated during the course of specialized patient care. All patients without a recorded diagnosis were considered to not have the condition.

For all variables, the frequency of missing information is shown in the descriptive analyses. Imputation of missing data was not performed.

9.9.4 Sensitivity Analyses

For colectomy due to intractable disease, an alternative risk window of exposure through the end of follow-up (ie, "ever exposed, always at risk") was applied (Analysis Table 11.1).

To explore the possibility of competing risks between the outcomes of colectomy due to intractable disease and ACN, a multivariable Cox regression model was generated using the composite outcome (time to the earliest of colectomy due to intractable disease, ACN, or death) in an "ever exposed, always at risk" approach (Analysis Table 11.5.1 and Analysis Table 11.5.2).

9.9.5 Other Analyses

Exploratory Evaluation of Agreement Between ENEIDA Registry Data and Medical Charts

To better understand how closely the ENEIDA registry replicates the information present in the participating patient's medical charts, the agreement between the routine ENEIDA data and that of the medical charts was described for a number of selected variables. Agreement of the following variables was evaluated: date of UC diagnosis, date of colectomy due to intractable disease, date of first recording of GLM use, and number of prior anti-TNFα agents used for the treatment of UC. This evaluation of agreement between ENEIDA registry data and medical charts was planned after the SAP (Mod5.3.6/ENEIDA - Statistical Analysis Plan) was finalized. Results appear in Annex 2.

9.9.6 Amendments to the Statistical Analysis Plan

Analyses presented in the report follow the SAP dated 25-Jun-2020 with the exception of the changes described in Table 2.

Table 2: Changes to the Statistical Analysis Plan

Change From the Planned Analyses	Timing and Reason for Change	Anticipated Implications for the Interpretation of the Study
Analysis added to gauge agreement between selected variables in ENEIDA data and corresponding variables in medical charts (see Section 9.9.5).	Added to the study analysis in Jul-2018 to provide perspective on how closely the ENEIDA registry replicates the information present in the medical charts of participating patients.	Potential to strengthen credibility of results based on automated data.
Changed specification of 3 covariates that had been measured in 2 time periods (≤1 year before and >1 year before study entry) to ever before cohort entry. The 3 covariates were hospitalization for UC, use of systemic steroids, and use of cyclosporine.	Mar-2022, data were too sparse to use as originally specified.	None.

Table 2: Changes to the Statistical Analysis Plan

Change From the Planned Analyses	Timing and Reason for Change	Anticipated Implications for the Interpretation of the Study
Added descriptive analyses of IRs of colectomy and ACN outcomes by exposure category, stratified by potential confounding factors one at a time (Analysis Table 8.1.1 and Analysis Table 8.2.1).	05-Sep-2022, to provide potential insight into patterns of confounding and effect modification.	May augment understanding of confounding and effect modification.
Added comparative analyses of IRRs and HRs of colectomy and ACN outcomes stratified by potential confounding factors one at a time (Analysis Table 8.1.2 and Analysis Table 8.2.2).	05-Sep-2022, to provide potential insight into patterns of confounding in the data.	May augment understanding of confounding in comparisons across exposure categories.
The SAP indicated that separate models would be developed to evaluate exposure-ACN associations for comparisons of GLM with other anti-TNFα agents and with TP. Only one model was used to evaluate exposure-ACN associations (Analysis Tables 9.2.1 and 9.2.2 in the SAP were collapsed into one: Analysis Table 9.2). Similarly, Analysis Tables 15.2.1 and 15.2.2 in the SAP were collapsed into a single Analysis Table 15.2 to report results of the adjusted case-control analysis of ACN. Ultimately, the adjusted case-control analysis of ACN could not be conducted.	Mar-2022. Because bivariate analyses (Analysis Table 8.2.2) did not suggest different patterns of confounding in each comparison, and because outcomes were sparse, it was reasonable to evaluate all exposures in one model. By including all exposures in one model, the single model included more outcomes than 2 separate models would have included. A greater number of outcomes could potentially support more adjustment factors than 2 separate models might have. Lack of sufficient events prevented the conduct of the planned adjusted case-control analysis for ACN.	May have improved confounding adjustment.
Sensitivity analyses that were planned to repeat case-control analyses using only data from the ENEIDA registry (instead of using data from charts) were not conducted.	05-Sep-2022, analyses were infeasible or uninterpretable because outcomes were sparse.	None. The observed consistency of results from cohort and case-control analyses argues for robustness of findings.

Abbreviations: ACN, advanced colonic neoplasia; ENEIDA, National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants (Spain); GLM, golimumab; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio; SAP, statistical analysis plan; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

9.10 Quality Control

Data from the ENEIDA registry were securely transferred and have been housed on an RTI-HS encrypted server.

Data from the ENEIDA registry were analyzed without any systematic attempt to clean the data specifically for the analyses. Processes are in place during data collection at the ENEIDA registry to limit the extent of errors in data entry. For example, several variables in the ENEIDA registry are subject to logic checks at the time of data entry, and forms cannot be saved if they include implausible values. Additionally, all dates must fall between 01-Jan-1900 and the current date. Several range checks exist for variables that are represented as integers; acceptable values depend on the clinical context.

During the preparation of the analytic file for this study, additional quality-control measures included the following checks for legitimate values for each categorical variable and logic checks for dates.

- Duration of UC was defined as the date of cohort entry minus the date of UC diagnosis. In situations where the date of UC diagnosis occurred after the date of cohort entry, UC duration was set equal to 0.
- In alignment with the protocol, if either lost to follow-up or death were indicated and if neither a lost to follow-up date nor a death date was present, then the patient was censored 6 months after the date of his or her last visit or at the ENEIDA data lock (30-Mar-2022), whichever came first.
- Patients whose date of cohort entry was later than their date of last visit plus 6 months were excluded from analyses.
- Patient ages greater than 100 years were set to missing.

10 RESULTS

Throughout the report, in-text tables are referred to as “Table,” while tables in Annex 3 are referred to as “Analysis Table” and follow the structure of the table shells outlined in the study SAP. A similar naming convention applies to figures, where in-text figures are referred to as “Figure” and figures in Annex 4 as “Analysis Figure.”

10.1 Participants

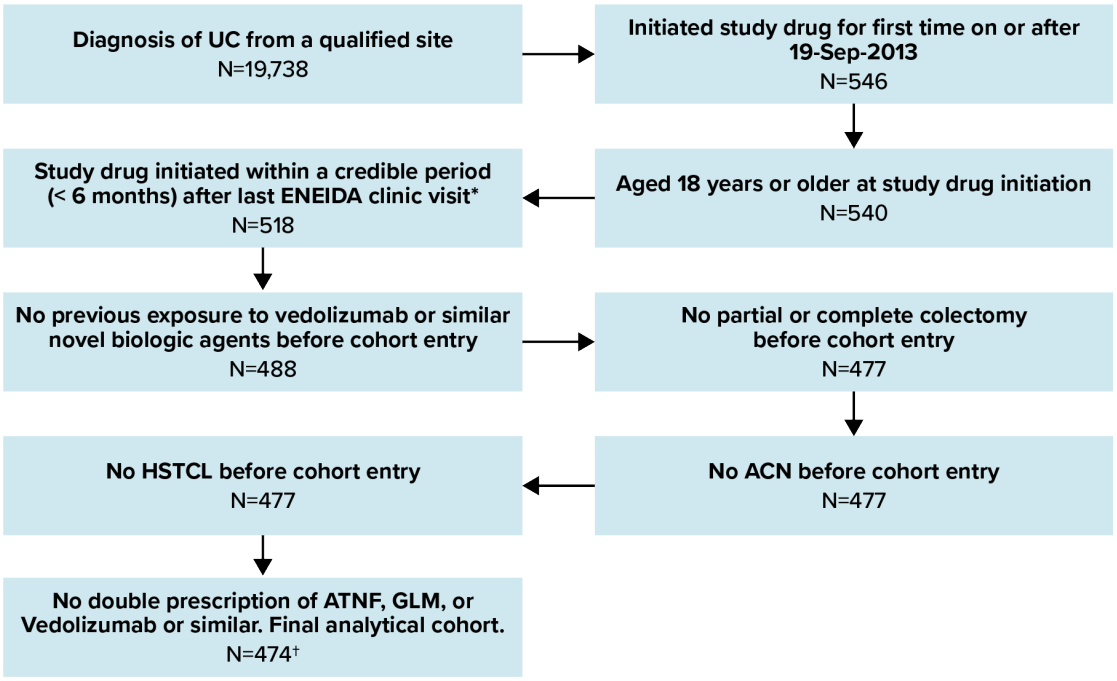
Importantly, throughout the report, the number of patients reported in each cohort corresponds to the number of patients contributing person-time to that specific cohort. Since patients were allowed to switch between study drugs, some patients contributed person-time to more than 1 cohort

10.1.1 Patient Disposition Information

The total number of patients in the ENEIDA registry with a diagnosis of UC was 35,708 as of 30-Mar-2022; of these, 19,738 patients with UC were from the 30 research-quality ENEIDA sites selected as described in Section 9.5.1.1 (28 of these sites participated in the medical chart abstraction component for the nested case-control study). All research-quality sites provided patients for the 3 study cohorts (ie, GLM, other anti-TNFα agents, and TP cohorts). The final number of patients who met the inclusion and exclusion criteria for each cohort is shown in Figure 5, GLM cohort; Figure 6, other anti-TNFα agent cohort; and Figure 7, TP cohort (see also Analysis Table 1). The impact of each inclusion and exclusion criterion on the patient disposition is also shown. Overall, the

study included 474 patients in the GLM cohort, 1,737 patients in the other anti-TNFα agent cohort, and 1,380 patients in the TP cohort.

Figure 5: Assembly of GLM Cohort [19-Sep-2013 Through 31-Dec-2021]

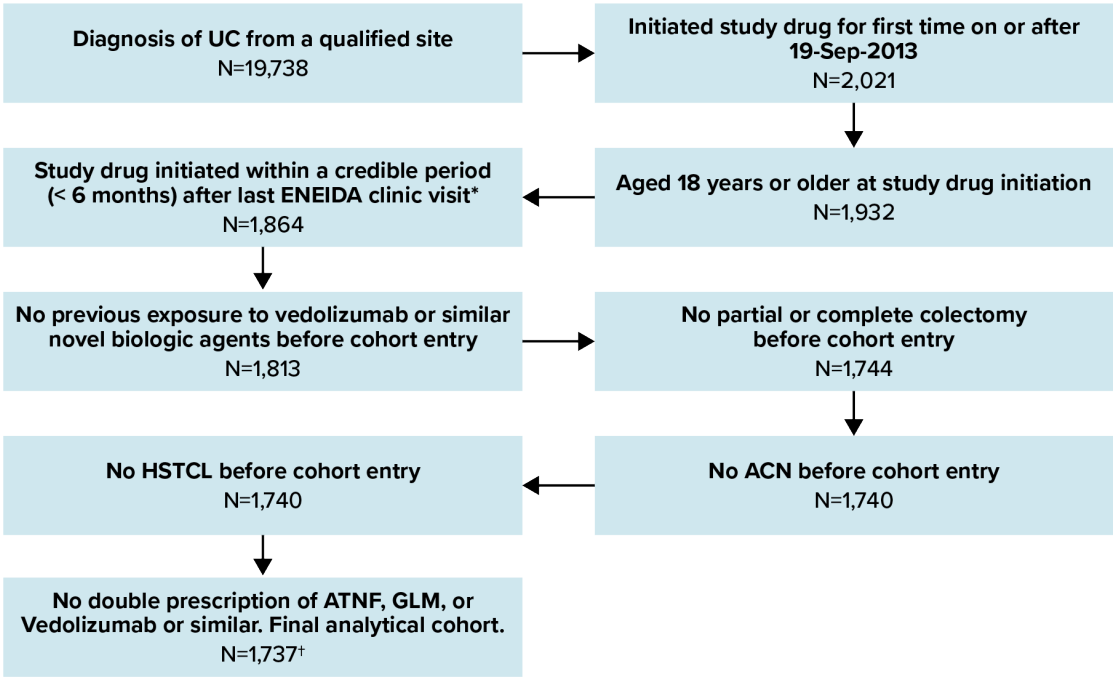


Abbreviations: ACN, advanced colonic neoplasia; ATNF, other anti–tumor necrosis factor alpha agent; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

* Dates of some initial study drug prescriptions did not have corresponding clinic visits (n=22).

† Overall, 3 patients were excluded for having prescriptions for 2 different anti-TNFα agents on the same date. Because coprescription of more than 1 anti-TNFα agent is highly atypical, these patients were excluded out of concern about their data quality.

Figure 6: Assembly of Other Anti-TNFα Agent Cohort [19-Sep-2013 Through 31-Dec-2021]

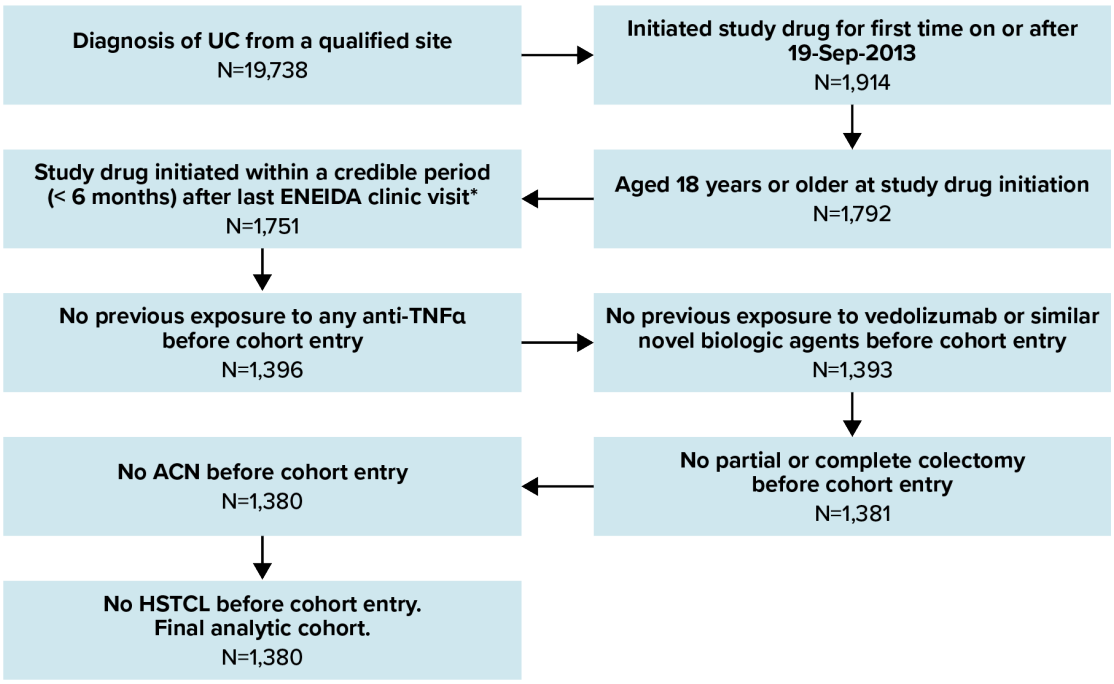


Abbreviations: ACN, advanced colonic neoplasia; ATNF, other anti–tumor necrosis factor alpha agent; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

* Dates of some initial study drug prescriptions did not have corresponding clinic visits (n=68).

† Overall, 3 patients were excluded for having prescriptions for 2 different anti-TNFα agents on the same date. Because coprescription of more than 1 anti-TNFα agents is highly atypical, these patients were excluded out of concern about their data quality.

Figure 7: Assembly of TP Cohort [19-Sep-2013 Through 31-Dec-2021]



Abbreviations: ACN, advanced colonic neoplasia; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

* Dates of some initial study drug prescriptions did not have corresponding clinic visits (n=41).

10.1.2 Protection of Human Subjects

Pseudonymized data from the patients meeting the study inclusion and exclusion criteria were transferred to RTI-HS for analysis in accordance with the informed consent that patients signed when joining the ENEIDA registry. All disaggregated data remained on servers in the EU at all times, and only aggregated results were shared outside the EU.

10.1.3 Chart Abstraction Process for the Nested Case-Control Analysis

In addition to using routinely collected data from the ENEIDA registry, the study collected information on the subset of individuals identified for inclusion in the nested case-control analysis (see Section 9.5.2, Medical Charts). Of the 30 ENEIDA centers that contributed data to the cohort analysis, 28 agreed to participate in the chart abstraction process. Of 191 chart abstractions requested, 178 completed questionnaires were obtained (response rate of 93%).

To ensure that every case of colectomy due to intractable disease had at least one control, it was necessary to relax the caliper for matching on UC duration to ±56 months (instead of ±12 months) and to relax the caliper for matching on the length of follow-up to ±8 months (instead of ±3 months) for 8 of the 41 cases. To ensure that every case of ACN had at least 1 control, it was necessary to relax the caliper for matching on UC duration to ±24 months (instead of ±12 months) for 2 of the 9 cases.

Matching controls were identified for every case, but 3 cases of colectomy due to intractable disease were not included in the analysis because chart abstraction information on their controls was not received by the data lock date for this study (31-May-2022).

The assessment of agreement between automated data and chart abstraction for selected variables appears in Annex 2.

10.2 Descriptive Data

Table 3 describes patient characteristics at the time of entry into each study cohort (ie, at the time of study drug initiation) (see also Analysis Table 2). Median age at entry into the 3 study cohorts was similar (44 years for the GLM and other anti-TNFα agent cohorts and 42 years for the TP cohort). During years 2014 through 2019, GLM represented about 15% of new study drug use, whereas during the last 2 years of the study (2020-2021), GLM initiation tended to become progressively less common (10.8% and 8.8%, respectively, of new study drug use), and new use of other anti-TNFα agents became more prevalent. Patients in the GLM cohort tended to have the longest duration of UC (median, 6.6 years vs 4.1 and 2.5 years, respectively, for the other anti-TNFα agents and TP cohorts). Maximum extent of UC, prior use of corticosteroids, and prior use of cyclosporine were similar across cohorts at the time of first use of each study drug. Past hospitalization for UC was somewhat less common among users of TPs than among users of GLM or of other anti-TNFα agents (14.6% vs 19.8% and 21.8%, respectively). Users of GLM were more likely to have had a prior screening colonoscopy than users of other anti-TNFα agents or TPs (23.4% vs 17.0% vs 13.5%, respectively). Users of GLM were more likely than users of other anti-TNFα agents to have previously used 1 or more anti-TNFα agents (35.2% vs 13.5%). Finally, users of GLM were more likely than users of other anti-TNFα agents to have recently switched after use of another anti-TNFα agent after short-term use (initiated within the past 3 months) (23% for GLM vs 9.5%) and after long-term use (>3 months) (10.5% for GLM vs 2.8%). It is important to reiterate that the cohorts were not mutually exclusive (that is, 42% of the GLM cohort had another exposure, which could have been other anti-TNFα or TP; 34% of the other anti-TNFα cohort had another exposure, which could have been GLM or TP) since patients could qualify as new users of each study drug during the study period and thus be described at each drug initiation. Therefore, any comparison of cohorts is not necessarily a comparison of unique patients.

Table 3: Patient Characteristics at Cohort Entry

Characteristic	Study Cohort		
	GLM (N=474)	Other Anti-TNFα Agents (N=1,737)	TP (N=1,380)
Age in years			
n	474	1,737	1,380
Mean (SD)	45.1 (14.1)	44.2 (153)	43.1 (14.8)
Median (Q1, Q3)	44.0 (36.0,55.0)	44.0 (33.0,55.0)	42.0 (31.0,54.0)
Min, Max	18.0, 87.0	18.0, 98.0	18.0, 92.0
Age group, n (%)			
18 to <35 years	114 (24.1)	510 (29.4)	422 (30.6)
35 to <65 years	319 (67.3)	1,047 (60.3)	839 (60.8)
≥65 years	41 (8.6)	180 (10.4)	119 (8.6)
Sex, n (%)			
Male	236 (49.8)	910 (52.4)	740 (53.6)
Female	238 (50.2)	827 (47.6)	640 (46.4)
Calendar year of cohort entry, n (% over total new use of the drugs [column%] / % over total yearly new use of study drugs [row%])			
2013	2 (0.4 / 1.6)	64 (3.7 / 51.2)	59 (4.3 / 47.2)
2014	77 (16.2 / 15.0)	203 (11.7 / 39.6)	233 (16.9 / 45.4)
2015	67 (14.1 / 12.1)	238 (13.7 / 43.1)	247 (17.9 / 44.7)
2016	71 (15.0 / 13.7)	232 (13.4 / 44.9)	214 (15.5 / 41.4)
2017	75 (15.8 / 15.8)	232 (13.4 / 48.7)	169 (12.2 / 35.5)
2018	63 (13.3 / 16.0)	196 (11.3 / 49.7)	135 (9.8 / 34.3)
2019	58 (12.2 / 14.8)	202 (11.6 / 51.4)	133 (9.6 / 33.8)
2020	35 (7.4 / 10.8)	188 (10.8 / 58.0)	101 (7.3 / 31.2)
2021	26 (5.5 / 8.8)	182 (10.5 / 61.3)	89 (6.4 / 30.0)
UC duration in years[a]			
n	474	1,737	1,380
Mean (SD)	8.9 (8.1)	7.2 (7.8)	5.4 (6.7)
Median (Q1, Q3)	6.6 (2.2,13.1)	4.1 (1.2,11.0)	2.5 (0.7,8.0)
Min, Max	0.0, 41.0	0.0, 42.6	0.0, 39.4
Maximum extent of disease, n (%)[b]			
Extensive	232 (48.9)	899 (51.8)	672 (48.7)
Left side only	190 (40.1)	633 (36.4)	549 (39.8)
Proctitis	29 (6.1)	109 (6.3)	101 (7.3)
Not recorded	23 (4.9)	96 (5.5)	58 (4.2)

Table 3: Patient Characteristics at Cohort Entry

Characteristic	Study Cohort		
	GLM (N=474)	Other Anti-TNFα Agents (N=1,737)	TP (N=1,380)
Prior treatment with steroids[d], n (%)			
No	197 (41.6)	635 (36.6)	527 (38.2)
Yes	277 (58.4)	1,102 (63.4)	853 (61.8)
Prior treatment with cyclosporine[d], n (%)			
No	449 (94.7)	1,628 (93.7)	1,317 (95.4)
Yes	25 (5.3)	109 (6.3)	63 (4.6)
Hospitalized for UC[d], n (%)			
No	380 (80.2)	1,358 (78.2)	1,178 (85.4)
Yes	94 (19.8)	379 (21.8)	202 (14.6)
Prior diagnosis with PSC[e], n (%)			
No	177 (37.3)	469 (27.0)	261 (18.9)
Yes	5 (1.1)	19 (1.1)	20 (1.4)
Unknown/missing	292 (61.6)	1,249 (71.9)	1,099 (79.6)
Prior screening colonoscopy[d], n (%)			
No	363 (76.6)	1,442 (83.0)	1,194 (86.5)
Yes	111 (23.4)	295 (17.0)	186 (13.5)
Number of previous other anti-TNFα agents[d], n (%)			
0	307 (64.8)	1,503 (86.5)	1,380 (100)
1	113 (23.8)	227 (13.1)	0 (0)
2	54 (11.4)	7 (0.4)	0 (0)

Table 3: Patient Characteristics at Cohort Entry

Characteristic	Study Cohort		
	GLM (N=474)	Other Anti-TNFα Agents (N=1,737)	TP (N=1,380)
Recent switcher after use of another anti-TNFα agent, n (%)[c]			
After short-term use (≤3 months)	109 (23.0)	165 (9.5)	0 (0)
After long-term use (>3 months)	50 (10.5)	49 (2.8)	0 (0)
Did not switch	315 (66.5)	1,523 (87.7)	0 (0)

Abbreviations: ENEIDA, National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants (Spain); GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] UC duration was the time between the date of UC diagnosis and cohort entry date.

[b] Maximum extent of disease reflects the value for this patient ascertained on 30-Mar-2022, when data extraction occurred. This value may not reflect the actual maximal disease extent at the time of cohort entry. In ENEIDA data, there is only 1 value of this variable per patient; this variable is not date stamped and is subject to continual updating to reflect the maximum extent of disease reached.

[c] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

[d] During the period from UC diagnosis to the cohort entry date.

[e] Ever before the cohort entry date.

Table 4 shows the duration of follow-up in each study cohort for the colectomy analyses. Overall, the mean follow-up for patients in the GLM cohort (23 months) was similar to the other anti-TNFα agents cohort (26 months). Mean follow-up varied for patients enrolled in different study years (see also Analysis Table 3.2).

Table 4: Duration of Follow-up by Cohort for the Colectomy Analyses

Characteristic	Cohort	
	GLM[a]	Other Anti-TNFα Agents[a]
	N=471	N=1,734
Months of follow-up[b]		
Mean (SD)	23 (23.5)	26 (24.0)
Median (Q1, Q3)	13 (5.9, 32.9)	17 (7.6, 38.4)
Min, Max	0.0, 94.1	0.0, 101.8

Abbreviations: GLM, golimumab; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha.

[a] This table includes only those patients who contributed at least some person-time to the GLM-only exposure group or to the other anti-TNFα agent–only exposure group after cohort entry. This table does not include the follow-up time of 6 patients who, during all follow-up time, were exposed exclusively to GLM in combination with other anti-TNFα agents (3 patients in the GLM cohort and 3 patients in the other anti-TNFα agent cohort), although that person-time is included in the comparative analyses in the overlapping (ie, combined) exposure group.

[b] Follow-up for the colectomy analyses includes a 90-day extension period of the risk window after discontinuation (ie, stop date) of the evaluated treatments.

Table 5 shows the duration of follow-up in each study cohort for the ACN analyses. Overall, the mean follow-up for patients in the GLM cohort (34 months) was similar to that of the other anti-TNFα agents cohort (32 months) and the TP cohort (34 months). Mean follow-up tended to be longer in patients who were enrolled earlier in the study (see also Analysis Table 3.1).

Table 5: Duration of Follow-up by Cohort for the ACN Analyses

Characteristic	Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Months of follow-up[a]			
Mean (SD)	34 (26.1)	32 (26.3)	34 (26.6)
Median (Q1, Q3)	27 (12.0, 51.7)	23 (9.9, 51.3)	25 (9.9, 54.1)
Min, Max	0.8, 95.0	0.1, 101.9	0.6, 102.3

Abbreviations: ACN, advanced colonic neoplasia; GLM, golimumab; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine.

[a] Follow-up for ACN used an “ever exposed, always at risk” approach.

The duration of follow-up for the HSTCL analyses is shown in Analysis Table 3.3. Overall, the mean follow-up for patients in the GLM cohort (35 months) was similar to that of the other anti-TNFα agent cohort (33 months) and the TP cohort (34 months). As expected, mean follow-up was longer in patients who were enrolled earlier in the study.

Table 6 shows the reasons triggering the end of follow-up (censoring) during the study for the colectomy and ACN analyses (Analysis Table 4.1.1 through Analysis Table 4.1.10). Censoring due to withdrawal from the registry, death, end of study period, ACN diagnosis, and prescription of 2 anti-TNFα agents at the same time occurred similarly in all 3 cohorts. Total or partial colectomy was more common as a reason to end follow-up in the other anti-TNFα cohort than in the TP cohort. Loss to follow-up (see note a under Table 6) occurred in 50% of patients in the TP cohort and in 34.6% and 37.3% of patients in the GLM and in the other anti-TNFα agents cohorts, respectively. Use of novel biologic agents (eg, vedolizumab) was more common in the GLM cohort, followed by the other anti-TNFα agents cohort and the TP cohort.

The reasons for ending follow-up during the study for the HSTCL analyses appear in Analysis Table 4.2.1 through Analysis Table 4.2.10.

Table 6: Reasons for End of Follow-up for All Outcomes Except HSTCL, 2013-2022

Reason	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Withdrawal from registry, n (%)	12 (2.5)	47 (2.7)	50 (3.6)
Death, n (%)	2 (0.4)	11 (0.6)	14 (1.0)
End of study period, n (%)	129 (27.2)	459 (26.4)	368 (26.7)
Total or partial colectomy for any cause, n (%)	11 (2.3)	60 (3.5)	18 (1.3)
ACN or CRC diagnosis, n (%)	2 (0.4)	6 (0.3)	4 (0.3)
Lost to follow-up[a], n (%)	164 (34.6)	647 (37.3)	690 (50.0)
Initiation of vedolizumab or other novel biologic agents, n (%)	154 (32.5)	507 (29.2)	235 (17.0)
Prescription of 2 anti-TNFα agents on the same date, n (%)	0 (0.0)	0 (0.0)	1 (0.1)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria. The outcomes include colectomy due to intractable disease, ACN, and CRC.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored at the 6 months after the last follow-up visit.

Analysis Table 2.1 and Analysis Table 2.2 show the characteristics of patients according to reason for end of follow-up ("lost to follow-up" vs for other reasons), stratified by cohort. Patterns were generally similar across cohorts. However, only among GLM users, patients lost to follow-up had a shorter UC duration than those with other reasons for censoring (including end of study period).

The utilization patterns of the drugs that qualified for cohort entry are described in Analysis Table 5.1 (for the analyses of the outcomes ACN and colectomy due to intractable disease) and Analysis Table 5.2 (for the HSTCL outcome). Both tables show patterns of persistence and change of study medications; the study population was categorized according to the study drug that first qualified for study entry.

10.3 Outcome Data

Before presenting outcome data, it is useful to review concepts about risk windows that were presented earlier in Section 9.3.1.1. Because the potential biologic effect of study drugs on the outcomes may differ over time, separate exposure risk windows were defined for the colectomy and ACN outcomes. Analysis of the colectomy outcome used 3 mutually exclusive exposure categories: GLM only, other anti-TNFα agents only, and overlapping exposure time. To simplify reporting, the formulation "[exposure category]-only use" (eg, "GLM-only use") is used to refer to person-time associated with its risk window.

A different risk window was used for the analysis of ACN, given that the effect of the study drugs could theoretically last long after the end of exposure. Given the length of these risk windows, a patient who changed therapies during the study could simultaneously contribute person-time to more than one exposure category. Because exposure categories were not mutually exclusive in the analyses of ACN, the risk associated with each cohort-defining exposure is reported in terms of the cohort's name or using the short-hand "[exposure] use" (eg, "GLM use").

The incidence of each study outcome is reported in the Main Results section.

10.4 Main Results

10.4.1 Colectomy Due to Intractable Disease

10.4.1.1 Cohort Analysis

Table 7 shows the crude IRs for colectomy due to intractable disease by mutually exclusive exposure categories (see also Analysis Table 6.1.1). The IR of colectomy was lowest during exposure exclusively to GLM (4.4 per 1,000 PY) and highest during overlapping exposure to both GLM and other anti-TNFα agents (78.6 per 1,000 PY). It should be noted that the latter estimate was based on a total of 3 events that occurred across 38.2 PYs, with a correspondingly wide CI. Across all exposure categories, there was a total of 64 colectomies, each representing a unique event (ie, exposure categories were mutually exclusive).

Table 7: Crude Incidence Rates for Colectomy Due to Intractable Disease, by Mutually Exclusive Exposure Category

Statistic	Exposure Category			
	GLM Only	Other Anti-TNFα Agents Only	GLM+Other Anti-TNFα Agents	No Anti-TNFα Agent Exposure[a]
n	4	47	3	10
PY	912.3	3,791.9	38.2	770.2
IR per 1,000 PY	4.4	12.4	78.6	13.0
95% CI	1.2-11.2	9.1-16.5	16.2-229.7	6.3-23.9

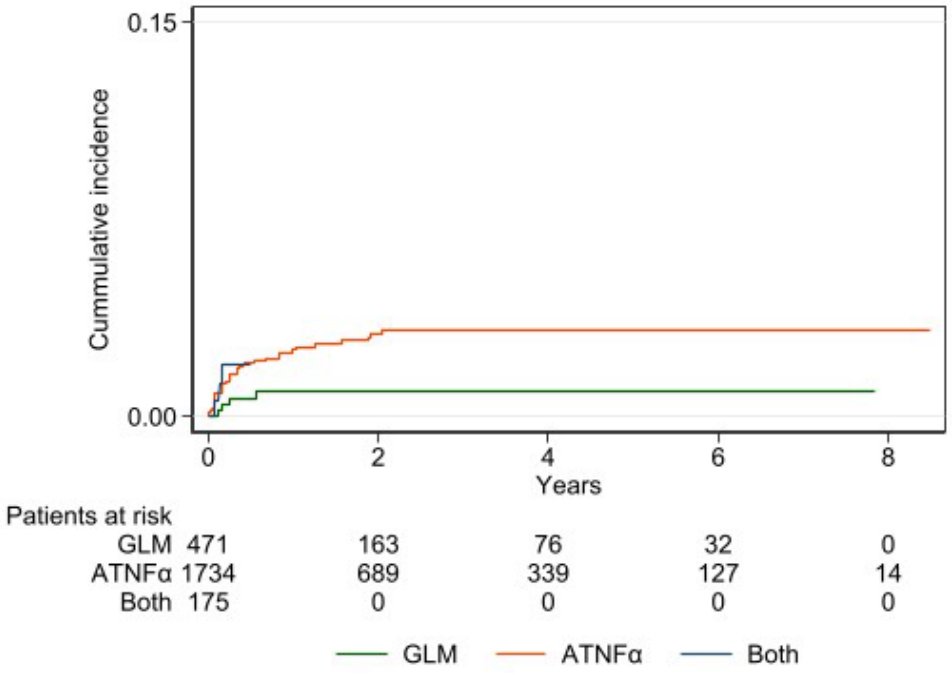
Abbreviations: CI, confidence interval; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha.

Notes: PY were calculated based on the risk window described in Section 9.3.1.1. Because patients may have changed therapy during the study, patients may have contributed to more than 1 exposure category during follow-up.

[a] Refers to person-time when there was no exposure to GLM or other anti-TNFα agents between episodes of GLM or other anti-TNFα agent use.

Figure 8 shows graphically the cumulative incidence of colectomies due to intractable disease among the different exposure categories.

Figure 8: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category



Abbreviations: ATNFα, other anti–tumor necrosis factor alpha agents; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

Note: Colectomies due to intractable disease were identified during the period up to 90 days after each drug discontinuation, as explained in Section 9.3.1.1.

Source: Analysis Figure 1.1.

Analysis Table 8.1.1 shows the crude IRs of colectomy due to intractable disease, stratified by potential confounding variables evaluated one at a time. Given the sparsity of outcomes in the exposure categories GLM-only and overlapping exposure (GLM+other anti-TNFα agents), it is not possible to draw any inferences about effect modification by the stratification factors evaluated.

Table 8 shows the crude IRRs and HRs of colectomy due to intractable disease among patients exposed to the study drugs of interest (see also Analysis Table 7.1). The relative risk estimates comparing GLM-only use with other anti-TNFα agents–only use were not elevated in the crude Poisson and Cox models (IRR=0.35 [95% CI: 0.13-0.98]; HR=0.37 [95% CI: 0.13-1.02]). Based on a small number of events, overlapping exposure of GLM and other anti-TNFα agents showed a greater risk of colectomy than GLM-only use, other anti-TNFα agents–only use, or periods of nonuse of either anti-TNFα agent exposure group.

Table 8: Crude Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease

Comparison	Poisson Model	Cox Model
	Crude IRR (95% CI)	Crude HR (95% CI)
GLM only vs other anti-TNFα agents only	0.35 (0.13-0.98)	0.37 (0.13-1.02)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	6.34 (1.97-20.37)	5.33 (1.64-17.34)
GLM only vs (GLM+other anti-TNFα agents)	0.06 (0.01-0.25)	0.07 (0.02-0.31)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; TNFα, tumor necrosis factor alpha.

Notes: Statistics are by study exposure and use the applicable risk window of follow-up time specific to the outcome. Incidence rate ratios and 95% CIs were derived from a single univariable Poisson regression with log-time offset considering only time exposed to at least 1 study drug. Hazard ratios and 95% CIs were derived from a single univariable Cox regression model. Only exposure categories present in the data were included in regression models.

Analysis Table 8.1.2 shows the adjusted IRRs of colectomy due to intractable disease, stratified by each potential confounding variable one at a time. These IRRs are Mantel-Haenszel estimates based on a Poisson model that include 3 exposure categories, GLM only, other anti-TNFα agents only, and overlapping GLM+other anti-TNFα agents. In each comparison of GLM-only use with other anti-TNFα agent–only use, the crude and adjusted IRRs were very similar, suggesting that results were not confounded by any of the factors under consideration.

Several prespecified variables were included as potential confounders, including age, sex, calendar year of cohort entry, UC duration in years, maximum extent of disease, prior treatment with steroids, prior treatment with cyclosporine, hospitalization for UC, prior diagnosis with PSC, prior screening colonoscopy, number of previous anti-TNFα agents, and recent switch after use of another anti-TNFα agent. These variables were evaluated as potential confounders to include in multivariable adjustment by examining the strength of the covariate-outcome associations. Table 9 shows the univariate association of the candidate variables with colectomy due to intractable disease in the Poisson and Cox

models (see also Analysis Table 8.1). The strongest associations seen in both models were with advanced age (≥65 years vs 18 to <35 years) and prior treatment with cyclosporine (during study planning, cyclosporine was considered to be a proxy for treatment-resistant disease).

Table 9: Candidate Variable Screening for Inclusion in a Multivariable Model Based on Univariable Association With Colectomy Due to Intractable Disease

Candidate Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Age group		
35 to <65 years vs 18 to <35 years	1.10 (0.57-2.11)	0.94 (0.52-1.67)
≥65 years vs 18 to <35 years	2.32 (0.97-5.54)	2.12 (1.01-4.45)
Sex (male vs female)	1.56 (0.89-2.73)	1.37 (0.83-2.26)
Calendar year of cohort entry		
2013-2015 vs 2019-2021	0.65 (0.32-1.34)	1.59 (0.82-3.05)
2016-2018 vs 2019-2021	0.72 (0.35-1.48)	1.16 (0.60-2.27)
UC duration in years[a]		
≥67th percentile vs <33rd percentile	0.50 (0.26-0.95)	0.55 (0.31-0.99)
33rd to <67th percentile vs <33rd percentile	0.48 (0.24-0.93)	0.45 (0.24-0.84)
Maximum extent of disease		
Extensive vs left side only	1.41 (0.78-2.57)	1.61 (0.92-2.81)
Proctitis vs left side only	0.39 (0.05-2.95)	0.70 (0.16-3.00)
Not recorded vs left side only	1.86 (0.61-5.63)	1.60 (0.54-4.72)
Prior treatment with steroids (yes vs no)	1.38 (0.77-2.47)	1.56 (0.90-2.69)
Prior treatment with cyclosporine (yes vs no)	3.46 (1.72-6.98)	3.66 (1.99-6.73)
Hospitalized for UC (yes vs no)	1.44 (0.79-2.63)	1.27 (0.73-2.21)
Prior diagnosis with PSC (yes vs no)	0.50 (0.21-1.19)	NE
Prior screening colonoscopy (yes vs no)	NE	0.62 (0.30-1.31)
Number of previous anti-TNFα agents		
1 vs 0	NE	2.14 (1.16-3.96)
2 vs 0	NE	NE

Table 9: Candidate Variable Screening for Inclusion in a Multivariable Model Based on Univariable Association With Colectomy Due to Intractable Disease

Candidate Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Recent switcher after use of another anti-TNFα agent[b]		
After short-term use (≤3 months) vs did not switch	NE	3.74 (0.51-27.51)
After long-term use (>3 months) vs did not switch	6.04 (1.47-24.86)	6.71 (1.60-28.26)

Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; NE, not estimable; PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Each row represents a separate univariable model assessing the association of each candidate variable with the outcome of interest. Incidence rate ratios and 95% CIs were derived from Poisson regression models with log-time offset. Hazard ratios and 95% CIs were derived from a Cox regression model.

[a] Duration of UC was continually updated, as described in Section 9.8. At the start of the treatment (ie, at baseline), the 33rd percentile for UC duration was 2.0 years, and the 67th percentile was 8.6 years.

[b] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

The number of candidate variables that qualified for consideration in the multivariable adjustment models (ie, exhibiting an IRR greater than 1.25 or less than 0.80; see Section 9.9.2.2 comparative analyses: cohort approach) was greater than could be accommodated given the limited number of outcomes (eg, only 4 cases occurred during the GLM risk window; see Table 9). A general rule of thumb is that one needs approximately 10 outcomes in a multivariable model to support a single explanatory variable. With 54 outcomes across the 3 exposure groups of main interest (Table 9), one expects that a Poisson model would support approximately 5 to 6 variables, 2 of which involve the exposures.

Three variables (age group, UC duration, and prior treatment with cyclosporine) were ultimately selected for the multivariable model for the following reasons. Age group satisfied the screening threshold for association and is clinically reasonable; age is conventionally one of the first variables for which epidemiological studies adjust, and it could be a proxy for other unmeasured factors that could themselves be risk factors for colectomy. UC duration satisfied the screening threshold and is also clinically reasonable; some patients with longer-term disease may opt to undergo elective colectomy because of dissatisfaction with the effectiveness of chronic drug treatment or its tolerability. Several markers of difficult-to-control disease were considered in the list of candidate variables, including maximum disease extent; hospitalization for UC; treatment history with anti-TNFα agents; and prior treatment with cyclosporine, a drug typically reserved for treatment-resistant disease. Of these variables, treatment with cyclosporine had the strongest association with colectomy due to intractable disease (IRR=3.46 in the Poisson model and HR=3.66 in the Cox model) and, as a dichotomous variable, would be less likely to threaten model convergence than the other, multilevel markers of difficult-to-control disease. For similar reasons, in the multivariable model, age group was collapsed into a 2-level variable as aged >65 years vs ≤65 years, because the oldest age category

showed a substantial association with the outcome (IRR=2.32, HR=2.12), while the middle age category (35 to <65 years) did not.

In addition, sex was selected as a relevant variable because of its perceived clinical relevance for the colectomy due to intractable disease even if its association did not reach the statistical threshold pre-established. Sex is conventionally one of the first factors included, along with age, as adjustment variables in epidemiological analyses.

The variable "Recent switcher after use of another anti-TNFα agent" was not included in the model due to its collinearity with the exposure category of interest "GLM+other anti-TNFα agents"; that is, person-time of exposure to both GLM and other anti-TNFα agents. Analysis Table 8.3 shows the collinearity of both variables in a dichotomous fashion. In effect, both variables were measuring the same concept. Moreover, one of the variable categories (switch after short-term use) could not be estimated in the Poisson model.

Because prior screening colonoscopy exhibited considerable collinearity with duration of disease, it was also not selected.

Table 10 shows the multivariable analyses using the Poisson and Cox models adjusting for age group, UC duration, prior treatment with cyclosporine, and sex. See also Analysis Table 9.1. In both models, use of GLM only as compared with use of other anti-TNFα agents only was not associated with an increased risk of colectomy (IRR=0.40 [95% CI: 0.14-1.13]; HR=0.41 [95% CI: 0.15-1.15]). As was seen in the unadjusted analysis, based on 3 colectomy events, overlapping exposure to both GLM and other anti-TNFα agents was associated with a greater risk of colectomy than either GLM-only use or other anti-TNFα agents–only use. Due to the limited number of events, not all covariates (including proxies for disease activity) could be included in the models.

Table 10: Adjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Multivariable Poisson and Cox Regression Models

Comparison	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
GLM only vs other anti-TNFα agents only	0.40 (0.14-1.13)	0.41 (0.15-1.15)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	6.78 (2.08-22.13)	4.95 (1.52-16.08)
GLM only vs (GLM+other anti-TNFα agents)	0.06 (0.01-0.26)	0.08 (0.02-0.38)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Results are from 1 multivariable Poisson model and 1 multivariable Cox model, both of which included multiple exposure categories. Models were adjusted for age group, UC duration in years, prior treatment with cyclosporine, and sex.

10.4.1.2 Nested Case-Control Analysis

The nested case-control analysis was performed among patients with colectomy due to intractable disease. A random selection of matched control individuals with UC for whom medical charts were available was abstracted. Table 11 describes the characteristics of cases (n=41) and controls (n=70) at the time of colectomy or an equivalent date for the controls (see Analysis Table 12.1 and Section 10.1.3). All cases and controls were selected among those that had exposure to GLM or other anti-TNFα agents at the time of the colectomy or the equivalent date for the controls (ie, among informative patients). The variables "maximum extent of disease," "prior use of steroids," "prior screening colonoscopy," and "prior use of cyclosporine" were categorized as described in Section 9.8, Data Transformation.

Overall, 41 patients with a colectomy due to intractable disease and 70 matched UC controls without a colectomy were included in the case-control analysis. Exposure to GLM only at the reference date was less common among cases than controls (7.3% and 27.1%, respectively). Compared with controls, cases were somewhat older (median age, 52 vs 47 years), and in the year before starting the most recent study drug (period 2) had a greater prevalence of extensive disease (56.4% vs 41.8%), treatment with cyclosporine (22.0% vs 3.0%), and hospitalization for UC (70.0% vs 41.2%). The prevalence of the other potential confounding variables was generally similar in cases and controls, although most were based on small numbers.

Table 11: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Colectomy Due to Intractable Disease

	Cases N=41	Controls N=70
Exposure category, n (%)		
GLM only	3 (7.3)	19 (27.1)
Other anti-TNFα agents only	35 (85.4)	49 (70.0)
GLM+other anti-TNFα agents	3 (7.3)	2 (2.9)
Age (years)		
n	41	70
Mean (SD)	49.7 (18.2)	46.3 (17.1)
Median (Q1, Q3)	52.0 (35.0,64.0)	47.0 (33.0,57.0)
Min, Max	19.0, 82.0	19.0, 84.0
Age group, n (%)		
18 to <35 years	10 (24.4)	22 (31.4)
35 to <65 years	21 (51.2)	37 (52.9)
≥65 years	10 (24.4)	11 (15.7)
Sex, n (%)		
Male	28 (68.3)	39 (55.7)
Female	13 (31.7)	31 (44.3)

Table 11: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Colectomy Due to Intractable Disease

	Cases N=41	Controls N=70
Calendar year of reference date, n (%)		
2013	2 (4.9)	3 (4.3)
2014	6 (14.6)	11 (15.7)
2015	8 (19.5)	14 (20.0)
2016	12 (29.3)	22 (31.4)
2017	8 (19.5)	12 (17.1)
2018	3 (7.3)	5 (7.1)
2019	2 (4.9)	3 (4.3)
2020	0 (0)	0 (0)
2021	0 (0)	0 (0)
UC duration in years		
n	41	69
Mean (SD)	7.9 (9.3)	7.2 (8.8)
Median (Q1, Q3)	4.6 (1.0,10.6)	4.4 (1.1,9.3)
Min, Max	0.0, 38.9	0.1, 43.0
Maximum extent of disease period 1, n (%)[a]		
Extensive	14 (43.8)	26 (47.3)
Left sided only	12 (37.5)	18 (32.7)
Other	0 (0.0)	3 (5.5)
Proctitis	6 (18.8)	8 (14.5)
Maximum extent of disease period 2, n (%)[a]		
Extensive	22 (56.4)	23 (41.8)
Left sided only	9 (23.1)	22 (40.0)
Other	2 (5.1)	2 (3.6)
Proctitis	6 (15.4)	8 (14.5)
Treatment with steroids period 1, n (%)[a]		
Yes	29 (70.7)	49 (70.0)
Treatment with steroids period 2, n (%)[a]		
Yes	33 (80.5)	51 (72.9)
Treatment with cyclosporine period 1, n (%)[a]		
Yes	5 (12.5)	0 (0.0)
Treatment with cyclosporine period 2, n (%)[a]		
Yes	9 (22.0)	2 (3.0)
Number of hospitalizations for UC period 1, n (%)[a]		
0	17 (48.6)	43 (67.2)
1 or 2	16 (45.7)	17 (26.6)
3 or more	2 (5.7)	4 (6.3)

Table 11: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Colectomy Due to Intractable Disease

	Cases N=41	Controls N=70
Number of hospitalizations for UC period 2, n (%)[a]		
0	12 (30.0)	40 (58.8)
1 or 2	27 (67.5)	25 (36.8)
3 or more	1 (2.5)	3 (4.4)
Prior diagnosis with PSC, n (%)		
Yes	0 (0)	2 (2.9)
Prior screening colonoscopy period 2, n (%)[a]		
Yes	11 (28.2)	21 (32.3)
Number of previous anti-TNFα agents, n (%)		
0	0 (0)	4 (5.9)
1-2	39 (95.1)	59 (86.8)
3 or more	2 (4.9)	5 (7.4)
Recent switcher after use of another anti-TNFα agent, n (%)[b]		
After short-term use (≤3 months)	6 (14.6)	12 (17.1)
After long-term use (>3 months)	3 (7.3)	4 (5.7)
Did not switch	32 (78.0)	54 (77.1)

Abbreviations: GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurines; UC, ulcerative colitis.

Notes: The reference date for a case was the date that the patient experienced the outcome, while the reference date for a control was the date that their corresponding case experienced the outcome. For the colectomy due to intractable disease outcome, TP was not considered an exposure per the protocol. For the colectomy outcome, the exposure period of interest was anytime within 90 days before the reference date. Information on some variables sought in chart review was not always documented in the medical record. In such situations, the sum of patients across all categories of that variable may be less than the sum of case and control patients.

[a] Period 1: the first year after UC diagnosis, or until cohort entry (whichever occurred first). Period 2: the year before the last episode of a study drug commenced, looking backward from the date of study outcome (or an equivalent date among the controls)—this period could extend back only as far as the date of the first UC diagnosis, and thus could be truncated.

[b] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Table 12 shows the crude ORs of colectomy due to intractable disease for the different exposure categories at the reference date (ie, date of colectomy or equivalent date among the controls). See Analysis Table 13.1. Compared with patients exposed only to other anti-TNFα agents, patients exposed to GLM only were at a decreased risk of colectomy (crude OR=0.17; 95% CI: 0.04-0.78), although this estimate was based on only 3 cases exposed to GLM only. Compared with patients exposed only to GLM or only to other anti-TNFα agents, exposure to both GLM and other anti-TNFα agents was associated with an increased risk of colectomy, although this result was based on 3 cases exposed to both GLM and other anti-TNFα agents. Confidence intervals were wide, and the upper confidence limit could not be estimated. (In Table 12, the association between exposure to GLM and exposure to both GLM and other anti-TNFα agents is shown as the reciprocal association where exposure to both drugs is the reference category; ie, a protective effect of exposure to GLM only.)

Table 12: Nested Case-Control Study: Crude Odds Ratios for Colectomy Due to Intractable Disease

Comparison	Crude OR (95% CI)
GLM only vs other anti-TNFα agents only	0.17 (0.04-0.78)
GLM only vs (GLM+other anti-TNFα agents)	0.04 (0.00-NE)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	4.03 (0.40-NE)

Abbreviations: CI, confidence interval; GLM, golimumab; NE, not estimable; OR, odds ratio; TNFα, tumor necrosis factor alpha.

Notes: Each OR (95% CI) was derived from a univariable conditional logistic regression model, conditional on matching.

Table 13 shows the association of candidate variables with colectomy due to intractable disease in a univariate model for covariate selection and use in an adjusted model in the nested case-control analysis. See Analysis Table 14.1. Only prior hospitalization for UC appeared to be significantly associated with an increased risk of colectomy due to intractable disease, consistent with clinical expectations.

Table 13: Candidate Variable Screening for Inclusion in Multivariable Model in Nested Case-Control Analysis Based on Univariable Association With Colectomy Due to Intractable Disease

Candidate Variable	OR (95% CI)
Age group	
35 to <65 years vs 18 to <35 years	1.28 (0.50-3.32)
≥65 years vs 18 to <35 years	2.10 (0.61-7.24)
Sex (male vs female)	1.54 (0.67-3.54)
UC duration in years[a]	
≥67th percentile vs <33rd percentile	NE
33rd to <67th percentile vs <33rd percentile	NE

Table 13: Candidate Variable Screening for Inclusion in Multivariable Model in Nested Case-Control Analysis Based on Univariable Association With Colectomy Due to Intractable Disease

Candidate Variable	OR (95% CI)
Maximum extent of disease period 1[b]	
Proctitis vs extensive	1.57 (0.39-6.36)
Left sided only vs extensive	1.23 (0.38-3.95)
Not recorded vs extensive	NE
Maximum extent of disease period 2[b]	
Proctitis vs extensive	0.72 (0.20-2.55)
Left sided only vs extensive	0.39 (0.13-1.13)
Not recorded vs extensive	1.08 (0.15-7.75)
Prior treatment with steroids period 1[b] (yes vs no)	1.09 (0.40-2.97)
Prior treatment with steroids period 2[b] (yes vs no)	0.67 (0.26-1.72)
Prior treatment with cyclosporine period 1[b] (yes vs no)	NE
Prior treatment with cyclosporine period 2[b] (yes vs no)	0.14 (0.03-0.65)
Number of hospitalizations for UC period 1[b]	
1 or 2 vs 0	2.30 (0.86-6.16)
≥3 vs 0	1.35 (0.19-9.45)
Number of hospitalizations for UC period 2[b]	
1 or 2 vs 0	3.88 (1.52-9.92)
≥3 vs 0	1.63 (0.15-17.63)
Prior diagnosis with PSC (yes vs no)	NE
Prior screening colonoscopy (yes vs no)	0.66 (0.23-1.89)
Number of previous anti-TNFα agents	
1-2 vs 0	NE
3 or more vs 0	NE
Recent switcher after use of another anti-TNFα agent[c]	
After short-term use (≤3 months) vs did not switch	0.88 (0.30-2.63)
After long-term use (>3 months) vs did not switch	1.18 (0.25-5.53)

Abbreviations: CI, confidence interval; NE, not estimable; OR, odds ratio; PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Each row represents a separate univariable regression model assessing the association of each candidate variable with the outcome. Odds ratios and 95% CIs were derived from conditional logistic regression models.

[a] Duration of UC was ascertained on the date of the event or the corresponding reference date for control patients. The 33rd percentile was 2.6 years, and the 67th percentile was 8.3 years.

[b] Period 1: the first year after UC diagnosis, or until cohort entry (whichever occurred first). Period 2: the year before the last episode of a study drug commenced, looking backward from the date of study outcome (or an equivalent date among the controls)—this period could extend back only as far as the date of the first UC diagnosis, and thus could be truncated.

[c] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Table 14 shows the adjusted conditional logistic regression analysis assessing the risk of colectomy among patients treated with the study drugs. See Analysis Table 15.1. Analyses were adjusted for age (dichotomized ≥35 years vs <35 years), any hospitalization in period 2, cyclosporine use in period 2, and sex. Use of GLM only was not associated with an increased risk of colectomy when compared with use of other anti-TNFα agents only (OR=0.16; 95% CI: 0.02-1.08). However, overlapping exposure to GLM and other anti-TNFα agents compared with exposure to (1) other anti-TNFα agents only or (2) GLM only was associated with an increased risk of colectomy based on 3 cases exposed to both GLM and other anti-TNFα agents. This finding was consistent with the decrease in risk when comparing use of GLM only with use of GLM and other anti-TNFα agents. (In Table 14, the association between exposure to GLM only and exposure to both GLM and other anti-TNFα agents is shown as the reciprocal association where exposure to both drugs is the reference category; ie, a protective effect of exposure to GLM only.)

Table 14: Nested Case-Control Study: Adjusted Conditional Logistic Regression Model; Outcome: Colectomy Due to Intractable Disease

Comparison	OR (95% CI)
GLM only vs other anti-TNFα agents only	0.16 (0.02-1.08)
GLM only vs (GLM+other anti-TNFα agents)	0.02 (0.00-0.50)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	8.69 (0.60-124.90)

Abbreviations: CI, confidence interval; GLM, golimumab; OR, odds ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Results are based on one conditional logistic model, adjusted for age (dichotomized ≥35 and <35 years), number of hospitalizations for UC in period 2, prior treatment with cyclosporine use in period 2, and sex.

10.4.2 Advanced Colonic Neoplasia, Colorectal Cancer, and HSTCL

10.4.2.1 Cohort Analysis

Analyses for all neoplasia outcomes used the exposure risk windows that extended long after actual exposure (see Section 9.2.2.1). Because these risk windows could overlap, the same outcome could be attributed to more than one exposure category. Comparative analyses of neoplasia outcomes compared GLM use primarily with use of other anti-TNFα agents and secondarily with use of TP. The protocol stipulated that the comparison with TP would proceed only if baseline characteristics of the GLM and TP cohorts were sufficiently comparable. On average, patients in the TP cohort had, as expected, UC of shorter duration and less severity than that of patients included in the GLM and other anti-TNFα agents cohorts. However, the study team considered that the differences were not excessively large and that they could be appropriately controlled for in the analysis.

Table 15 shows the crude IRs for all neoplasia outcomes by exposure category. See also Analysis Table 6.1.2. There were 10 unique events of ACN; for 2 affected patients, the ACN occurred during risk windows attributable to more than one exposure category. There were 6 unique events of CRC; CRC occurred in 1 patient during risk windows attributable to more than one exposure category. Two events of ACN occurred in patients exposed to both GLM and other anti-TNFα agents (in an “ever exposed, always at risk”

exposure framework) and are therefore repeated in the corresponding exposure categories in Table 15, bringing the total number of ACN events in Table 15 to 12. The IR of ACN ranged from 1.0 to 1.5 per 1,000 PY. The IR of CRC ranged from 0.4 to 1.5 per 1,000 PY. Among those exposed to GLM, there were 2 cases of ACN for an IR of 1.5 (95% CI: 0.2-5.4) per 1,000 PY; both cases of ACN were CRC. Among patients exposed to other anti-TNFα agents, there were 6 cases of ACN for an IR of 1.3 (95% CI: 0.5-2.8) per 1,000 PY; of these, 2 cases were CRC, for an IR of 0.4 (95% CI: 0.1-1.6) per 1,000 PY. For TPs, there were 4 cases of ACN for an IR of 1.0 (95% CI: 0.3-2.6) per 1,000 PY; of these, 3 cases were CRC, for an IR of 0.8 (95% CI: 0.2-2.3) per 1,000 PY.

No cases of HSTCL were identified during the study.

Table 15: Crude Incidence Rates for Neoplasia Outcomes, by Exposure Category

Outcome	Exposure Category		
	GLM	Other Anti-TNFα Agents	TP
Advanced colorectal neoplasia			
n[a]	2	6	4
PY	1,347.8	4,637.2	3,871.8
IR per 1,000 PY	1.5	1.3	1.0
95% CI	0.2, 5.4	0.5, 2.8	0.3, 2.6
Colorectal cancer			
n[b]	2	2	3
PY	1,347.8	4,637.2	3,871.8
IR per 1,000 PY	1.5	0.4	0.8
95% CI	0.2, 5.4	0.1, 1.6	0.2, 2.3
Hepatosplenic T-cell lymphoma			
n	0	0	0
PY	1,393.2	4,798.9	3,892.0
IR per 1,000 PY	0.0	0.0	0.0
95% CI	0.0, 2.6	0.0, 0.8	0.0, 0.9

Abbreviations: ACN, advanced colonic neoplasia; CI, confidence interval; CRC, colorectal cancer; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: PY at risk were specific to each outcome and based on the applicable risk window for each outcome. Patients could have been exposed to more than 1 study drug during the course of follow-up; because risk windows could overlap, a single outcome could be attributed to more than 1 exposure category.

[a] Across all exposure categories, there were 10 unique occurrences of ACN.

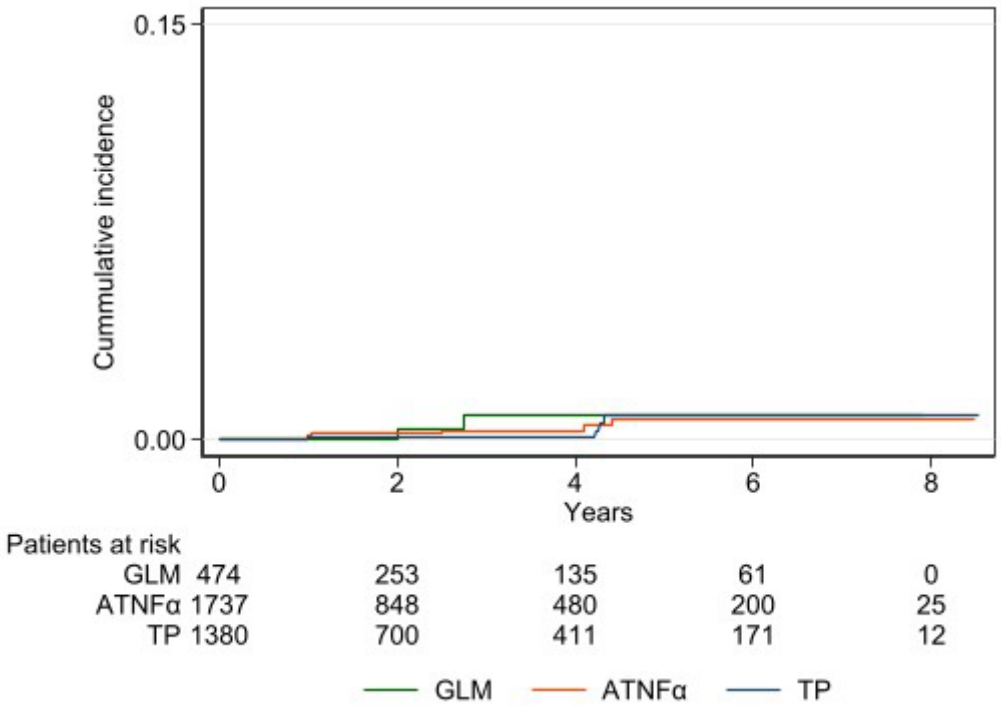
[b] Across all exposure categories, there were 6 unique occurrences of CRC.

Analysis Table 8.2.1 shows the crude IRs of ACN, stratified by potential confounding variables evaluated one at a time. Given the sparsity of outcomes (and consequently

imprecise IRs), it is not possible to draw any inferences about effect modification by the stratification factors evaluated.

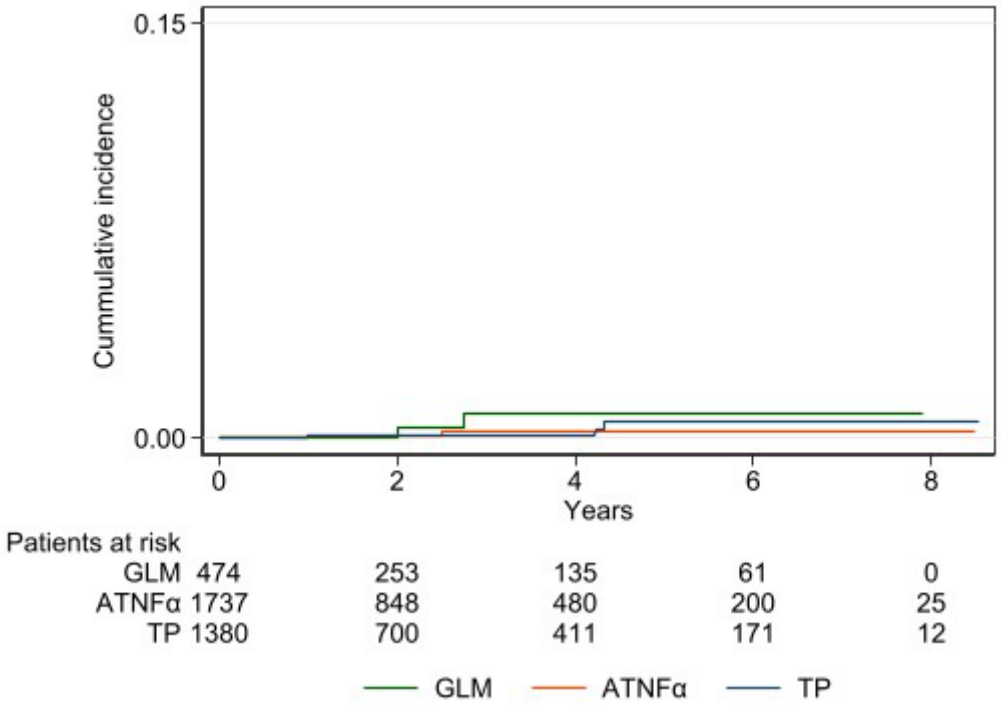
Figure 9 and Figure 10 show the cumulative incidence of ACN and CRC, respectively, among the different exposure groups. See Analysis Figure 1.2 and Analysis Figure 1.3, respectively.

Figure 9: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category



Abbreviations: ATNFα, other anti–tumor necrosis factor alpha agents; GLM, golimumab; TP, thiopurine.

Figure 10: Cumulative Incidence of Colorectal Cancer, by Exposure Category



Abbreviations: ATNFα, other anti–tumor necrosis factor alpha agents; GLM, golimumab; TP, thiopurine.

Table 16 shows the crude HRs for ACN. See Analysis Table 7.2. Among users of GLM, the HRs for ACN were 1.16 (95% CI: 0.23-5.73) and 1.46 (95% CI: 0.27-8.00), respectively, when compared with users of other anti-TNFα agents and TPs.

Table 16: Crude Hazard Ratios for Advanced Colorectal Neoplasia

Comparison	Cox Model Crude HR (95% CI)
GLM vs other anti-TNFα agents	1.16 (0.23-5.73)
GLM vs TP	1.46 (0.27-8.00)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: Statistics are by study exposure and use the applicable risk window of follow-up time specific to the outcome. Results were derived from a single univariable Cox regression model. Only exposure categories present in the data were included in regression models. Exposure categories were not mutually exclusive.

Table 17 shows the crude HRs for CRC. See Analysis Table 7.3. Compared with use of other anti-TNFα agents and use of TPs, GLM use was associated with an increased HR of CRC. However, CIs were wide and included unity, and the comparisons were based on very limited numbers of events (GLM, 2; other anti-TNFα agents, 2; and TP, 3).

Table 17: Crude Hazard Ratios for Colorectal Cancer

Comparison	Cox Model Crude HR (95% CI)
GLM vs other anti-TNFα agents	3.42 (0.48-24.26)
GLM vs TP	1.92 (0.32-11.50)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; TNFα, tumor necrosis factor alpha TP, thiopurine.

Notes: Statistics are by study exposure and use the applicable risk window of follow-up time specific to the outcome. Results were derived from a single univariable Cox regression model. Only exposure categories present in the data were included in regression models. Exposure categories were not mutually exclusive.

Since no cases of HSTCL occurred during the study, the HRs could not be computed.

Table 18 shows the results of univariate Cox models that were conducted to identify candidate variables to include in the adjusted analyses for ACN. See Analysis Table 8.2. The small number of observed events limited the number of covariables that could be used in the models. The following variables were selected based on their association with the outcome and/or its clinical relevance: age group, UC duration, and prior treatment with cyclosporine. Advanced age and UC duration both met the quantitative screening criteria for candidate variables, and both are established risk factors for ACN. Cyclosporine was included because of the magnitude of association with ACN and because it was judged to be a proxy for treatment-resistant disease. Despite its moderate association with ACN, prior screening colonoscopy was not considered because it was judged to be potentially on the causal pathway to diagnosis; the protocol specified that it would be evaluated but not used in any statistical adjustment.

Table 18: Candidate Variable Screening for Inclusion in a Multivariable Model Based on Univariable Association With Advanced Colorectal Neoplasia

Candidate Variable	Cox Model HR (95% CI)
Age group	
35 to <65 years vs 18 to <35 years	1.70 (0.35-8.19)
≥65 years vs 18 to <35 years	5.54 (0.93-33.19)
Sex (male vs female)	1.73 (0.52-5.76)
Calendar year of cohort entry	
2013-2015 vs 2019-2021	0.89 (0.09-8.47)
2016-2018 vs 2019-2021	1.05 (0.11-9.90)
UC duration in years[a]	
≥67th percentile vs <33rd percentile	1.97 (0.36-10.78)
33rd to <67th percentile vs <33rd percentile	2.79 (0.56-13.80)

Table 18: Candidate Variable Screening for Inclusion in a Multivariable Model Based on Univariable Association With Advanced Colorectal Neoplasia

Candidate Variable	Cox Model HR (95% CI)
Maximum extent of disease	
Extensive vs left side only	0.76 (0.22-2.61)
Proctitis vs left side only	NE
Not recorded vs left side only	3.43 (0.67-17.68)
Prior treatment with steroids (yes vs no)	0.46 (0.15-1.45)
Prior treatment with cyclosporine (yes vs no)	5.12 (1.38-18.91)
Hospitalized for UC (yes vs no)	0.82 (0.18-3.76)
Prior diagnosis with PSC (yes vs no)	NE
Prior screening colonoscopy (yes vs no)	3.06 (0.97-9.66)
Number of previous types of anti-TNFα agents	
1 vs 0	NE
2 vs 0	NE

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Each row represents a separate univariable model assessing the association of each candidate variable with the outcome of interest. Hazard ratios and 95% CIs were derived from a Cox regression model.

[a] UC duration was continually updated at any change in a patient's exposure category. At baseline, across the population included in this analysis, the 33rd percentile for UC duration was 1.5 years, and the 67th percentile was 7.5 years.

To provide an additional perspective on the potential confounding effect of prespecified variables, Analysis Table 8.2.2 shows the adjusted IRRs of ACN, stratified by each candidate variable one at a time. The IRRs are Mantel-Haenszel estimates based on a Poisson model that included 3 exposure categories: GLM, other anti-TNFα agents, and TP. In separate comparisons of GLM use with use of other anti-TNFα agents and use of TPs, the crude and adjusted IRRs were generally similar, suggesting no evidence of strong confounding. This finding provides quantitative evidence to support the judgment that the GLM and TP cohorts were sufficiently comparable at baseline for the comparison to proceed. For the 3 variables selected, there were small but potentially notable changes in the IRR point estimates after adjustment, although they were not consistently observed in comparisons of GLM with both comparators (Analysis Table 8.2.2). Adjusting for UC duration, comparing GLM use with use of other anti-TNFα agents, the crude IRR was 1.15 and the adjusted IRR was 1.02. However, the corresponding IRRs in the comparison of GLM with TP were 0.80 and 0.84. Adjusting for prior treatment with cyclosporine, the IRR for the GLM-TP comparison was 0.8 unadjusted and 0.92 adjusted. Corresponding values of IRR comparing GLM with other anti-TNFα agents were 1.15 and 1.19.

Table 19 shows the multivariable analyses adjusting for age group, UC duration, and prior treatment with cyclosporine in a single Cox model that included all exposure categories. See Analysis Table 9.2. GLM use was not associated with an increased risk of

ACN. Based on the longer risk windows for neoplasia outcomes, the adjusted HR for ACN comparing GLM use with other anti-TNFα agents use was 1.09 (95% CI: 0.22-5.44). The adjusted HR for ACN comparing GLM use with TP use was 1.08 (95% CI: 0.19-6.13).

Table 19: Adjusted Hazard Ratios for Advanced Colorectal Neoplasia from Multivariable Cox Regression Model

Variable	Cox Model HR (95% CI)
Comparison	
GLM vs other anti-TNFα agents	1.09 (0.22-5.44)
GLM vs TP	1.08 (0.19-6.13)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Note: Results are from 1 multivariable Cox model including multiple exposure categories. Analysis was adjusted for age group, UC duration, and prior treatment with cyclosporine.

Because there were fewer than 10 individual cases of CRC, consistent with the SAP, no adjusted analyses were attempted for this study outcome.

10.4.2.2 Nested Case-Control Analysis

The nested case-control analysis was performed among those patients with ACN and a random selection of matched control individuals without ACN for whom medical charts could be abstracted. All cases and controls were selected among those that had exposure to GLM, other anti-TNFα agents or TP at the time of the ACN diagnosis or the equivalent date for the controls. The variables "maximum extent of disease," "prior use of steroids," and "prior use of cyclosporine" were categorized as explained in Section 9.8, Data Transformation.

Table 20 summarizes the characteristics of ACN cases and the controls at the time of ACN diagnosis or at an equivalent date for the controls. See Analysis Table 12.2. Overall, 9 patients with ACN and 11 matched UC controls without a diagnosis of ACN were included in the case-control analysis. Both cases and controls were most often exposed to other anti-TNFα agents. Exposure to GLM at the reference date was uncommon for both cases and controls (1 and 2 patients, respectively). As expected, given the epidemiology of ACN in UC, cases were older than controls (mean, 58.2 vs 47.2 years) and had a longer duration of disease (mean, 12.5 vs 10.4 years). Based on very small numbers, patients who were recent switchers after short-term use of another anti-TNFα agent were more common in cases (n=3; 75%) than controls (n=1; 11.1%). The prevalence of potential confounding factors was generally similar between cases and controls (with a somewhat larger proportion of males in the control group), based on very small numbers.

Table 20: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Advanced Colorectal Neoplasia

	Cases N=9	Controls N=11
Exposure to study drug, n (%)		
GLM	1 (11.1)	2 (18.2)
Other anti-TNFα agents	5 (55.6)	6 (54.5)
TP	3 (33.3)	3 (27.3)
Age (years)		
n	9	11
Mean (SD)	58.2 (16.67)	47.2 (19.21)
Median (Q1, Q3)	66.0 (62.0, 67.0)	49.0 (28.0, 65.0)
Min, Max	27.0, 74.0	24.0, 84.0
Age group, n (%)		
18 to <35 years	2 (22.2)	4 (36.4)
35 to <65 years	2 (22.2)	4 (36.4)
≥65 years	5 (55.6)	3 (27.3)
Sex, n (%)		
Male	5 (55.6)	8 (72.7)
Female	4 (44.4)	3 (27.3)
Calendar year of reference date, n (%)		
2013	0 (0)	0 (0)
2014	0 (0)	0 (0)
2015	1 (11.1)	2 (18.2)
2016	0 (0)	0 (0)
2017	1 (11.1)	1 (9.1)
2018	7 (77.8)	8 (72.7)
2019	0 (0)	0 (0)
2020	0 (0)	0 (0)
2021	0 (0)	0 (0)
UC duration in years		
n	8	11
Mean (SD)	12.5 (9.78)	10.4 (6.72)
Median (Q1, Q3)	9.7 (4.4, 20.9)	8.7 (6.5, 12.2)
Min, Max	3.3, 27.1	3.4, 28.0
Maximum extent of disease period 1, n (%)[a]		
Extensive	2 (40.0)	1 (11.1)
Left sided only	1 (20.0)	2 (22.2)
Other	0 (0.0)	2 (22.2)
Proctitis	2 (40.0)	4 (44.4)

Table 20: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Advanced Colorectal Neoplasia

	Cases N=9	Controls N=11
Maximum extent of disease period 2, n (%) [a]		
Extensive	2 (33.3)	5 (45.5)
Left sided only	1 (16.7)	3 (27.3)
Other	0 (0.0)	2 (18.2)
Proctitis	3 (50.0)	1 (9.1)
Treatment with steroids period 1, n (%) [a]		
No	4 (44.4)	4 (36.4)
Yes	5 (55.6)	7 (63.6)
Treatment with steroids period 2, n (%) [a]		
No	4 (44.4)	8 (72.7)
Yes	5 (55.6)	3 (27.3)
Treatment with cyclosporine period 1, n (%) [a]		
No	5 (71.4)	11 (100.0)
Yes	2 (28.6)	0 (0.0)
Treatment with cyclosporine period 2, n (%) [a]		
No	5 (71.4)	11 (100.0)
Yes	2 (28.6)	0 (0.0)
Number of hospitalizations for UC period 1, n (%) [a]		
0	5 (71.4)	7 (70.0)
1 or 2	2 (28.6)	3 (30.0)
Number of hospitalizations for UC period 2, n (%) [a]		
0	5 (71.4)	9 (81.8)
1 or 2	2 (28.6)	2 (18.2)
Prior diagnosis with PSC, n (%)		
No	9 (100)	11 (100)
Yes	0 (0)	0 (0)
Prior screening colonoscopy, n (%)		
No	3 (42.9)	8 (72.7)
Yes	4 (57.1)	3 (27.3)
Number of previous anti-TNFα agents, n (%)		
0	1 (12.5)	2 (18.2)
1-2	5 (62.5)	7 (63.6)
3 or more	2 (25.0)	2 (18.2)

Table 20: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Advanced Colorectal Neoplasia

	Cases N=9	Controls N=11
Recent switcher after use of another anti-TNFα agent, n (%)[b]		
After short-term use (≤3 months)	3 (75.0)	1 (11.1)
After long-term use (>3 months)	0 (0)	1 (11.1)
Did not switch	1 (25.0)	7 (77.8)

Abbreviations: GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Notes: The reference date for a case was the date the patient experienced the outcome, while the reference date for a control was the date that their corresponding case experienced the outcome. For neoplasia outcomes, the exposure period of interest was any time before the reference date. Information on some variables sought in chart review was not always documented in the medical record. In such situations, the sum of patients across all categories of that variable may be less than the sum of case and control patients.

[a] Period 1: the first year after UC diagnosis, or until cohort entry (whichever occurred first). Period 2: the year before the last episode of a study drug commenced, looking backward from the date of study outcome (or an equivalent date among the controls)—this period could extend back only as far as the date of the first UC diagnosis, and thus could be truncated.

[b] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Table 21 shows the crude ORs of ACN for the different exposure categories at the reference date (ie, date of ACN diagnosis or equivalent date among the controls). See Analysis Table 13.2. Compared with exposure to other anti-TNFα agents, exposure to GLM was not associated with increased risk of ACN (crude OR=0.47; 95% CI: 0.04-5.68); however, this estimate was based on only 1 case exposed to GLM. Compared with TP exposure, GLM exposure was also not associated with increased risk of ACN (crude OR=0.42; 95% CI: 0.01-13.27), but this was also based on only 1 case exposed to GLM. Given that fewer than 10 cases of ACN were included in the nested case-control analysis (N=9), no adjusted analyses were conducted.

Table 21: Nested Case-Control Study: Crude Odds Ratios for Advanced Colorectal Neoplasia

Comparison	Crude OR (95% CI)
GLM vs other anti-TNFα agents	0.47 (0.04-5.68)
GLM vs TP	0.42 (0.01-13.27)

Abbreviations: CI, confidence interval; GLM, golimumab; OR, odds ratio; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: Each OR (95% CI) was derived from an univariable conditional logistic regression model, conditional on matching.

10.5 Other Prespecified Subgroup and Sensitivity Analyses

10.5.1 Subgroup Analyses

Several preplanned analyses were performed to examine exposure-outcome associations according to the following subgroups:

- Patients with and without concomitant TP exposure at baseline.
- Patients who at baseline were naive to anti-TNFα agent treatments (ie, had no history of prior use of either GLM or other anti-TNFα agents) and those who were not.
- Patients in the other anti-TNFα agents comparator group who entered that cohort first using infliximab and those who entered the comparator group first using adalimumab.

These subgroup analyses were undertaken to evaluate whether the exposure-outcome associations varied according to factors defining the subgroup. Although subgroup analyses were initially planned for each study outcome; the SAP (Mod5.3.6/ENEIDA - Statistical Analysis Plan) specified that they would be performed only if there were at least 10 events in each subgroup. Because the number of events of ACN and CRC were sparse, the subgroup analyses were performed only for the outcome of colectomy due to intractable disease.

Table 22 shows results of these subgroup analyses using Poisson and Cox regression models. Although multivariable models had been planned, only unadjusted results are presented because several multivariable models failed to converge. Each subgroup analysis was based on a single Poisson and Cox model that included all exposures. To simplify presentation, results here do not display comparisons in the Cox model with "no current exposure to other anti-TNFα agents"; see Analysis Table 10.1.1 through Analysis Table 10.1.6.

Table 22: Colectomy Due to Intractable Disease Subgroup Analyses: Unadjusted Poisson and Cox Regression Models

Subgroup and Exposure Category Comparison	Poisson Model IRR (95% CI)	Cox Model HR (95% CI)
Concomitant TP at baseline		
Without concomitant TP (N=1,724)		
GLM only vs other anti-TNFα agents only	0.11 (0.01-0.80)	0.12 (0.02-0.88)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	2.34 (0.32-17.16)	2.53 (0.34-18.79)
GLM only vs (GLM+other anti-TNFα agents)	0.05 (0.00-0.76)	0.05 (0.00-0.77)

Table 22: Colectomy Due to Intractable Disease Subgroup Analyses: Unadjusted Poisson and Cox Regression Models

Subgroup and Exposure Category Comparison	Poisson Model IRR (95% CI)	Cox Model HR (95% CI)
With concomitant TP (N=1,277)		
GLM only vs other anti-TNFα agents only	1.05 (0.30-3.71)	1.06 (0.30-3.67)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	19.84 (4.54-86.77)	10.64 (2.36-48.00)
GLM only vs (GLM+other anti-TNFα agents)	0.05 (0.01-0.32)	0.10 (0.02-0.61)
Prior anti-TNFα agent therapy		
No history of prior anti-TNFα agent therapy (N=572)		
GLM only vs other anti-TNFα agents only	0.70 (0.13-3.89)	0.90 (0.16-4.97)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	6.02 (0.67-54.18)	3.66 (0.41-33.04)
GLM only vs (GLM+other anti-TNFα agents)	0.12 (0.01-1.29)	0.25 (0.02-2.78)
Experienced users of anti-TNFα agents (N=2,429)		
GLM only vs other anti-TNFα agents only	0.26 (0.06-1.10)	0.23 (0.06-0.96)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	8.07 (1.96-33.31)	6.23 (1.49-26.07)
GLM only vs (GLM+other anti-TNFα agents)	0.03 (0.00-0.23)	0.04 (0.01-0.27)
First anti-TNFα agent used in comparator cohort		
First drug in comparator cohort was infliximab[a] (N=2,355)		
GLM only vs other anti-TNFα agents only	0.26 (0.09-0.74)	0.26 (0.09-0.72)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	4.26 (1.03-17.62)	3.70 (0.88-15.47)
GLM only vs (GLM+other anti-TNFα agents)	0.06 (0.01-0.34)	0.07 (0.01-0.39)

Table 22: Colectomy Due to Intractable Disease Subgroup Analyses: Unadjusted Poisson and Cox Regression Models

Subgroup and Exposure Category Comparison	Poisson Model IRR (95% CI)	Cox Model HR (95% CI)
First drug in comparator cohort was adalimumab[a] (N=1,789)		
GLM only vs other anti-TNFα agents only	0.89 (0.26-3.07)	0.89 (0.26-3.05)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	NE	10.18 (1.24-83.42)
GLM only vs (GLM+other anti-TNFα agents)	0.06 (0.01-0.54)	0.09 (0.01-0.79)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NE, not estimable; TNFα, tumor necrosis factor alpha; TP, thiopurines.

[a] All GLM-only use was included in this comparison with a subgroup of the comparator.

Results from the subgroup analyses were similar to those of the main analyses.

10.5.2 Sensitivity Analyses

10.5.2.1 Varying the Risk Window Start and Stop Dates

Table 23 shows the results of the multivariable analyses using the Poisson and Cox models for colectomy due to intractable disease using an alternative risk window for colectomy that was extended until end of follow-up (ie, "ever exposed, always at risk" approach). See Analysis Table 11.1. Therefore, in this analysis, only the exposure categories of GLM and other anti-TNFα agents were considered, and they are not mutually exclusive. Both the Poisson and Cox models showed similar colectomy risk estimates for GLM compared with other anti-TNFα agents (IRR=0.72 [95% CI: 0.39-1.31] and HR=0.90 [95% CI: 0.81-1.00], respectively). These results point in the same direction as those from the main adjusted analyses (IRR=0.40; HR=0.41; see Table 10), suggesting that risk estimates were not sensitive to alternative specification of the end of the risk window.

Table 23: Adjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Multivariable Poisson and Cox Regression Models; Sensitivity: Risk Window From Exposure Through End of Follow-up

Comparison	Poisson Model IRR (95% CI)	Cox Model HR (95% CI)
GLM vs other anti-TNFα agents	0.72 (0.39-1.31)	0.90 (0.81-1.00)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: The analysis was adjusted for age group, UC duration in years, prior treatment with cyclosporine, and sex. The SAP described other analyses planned to evaluate the potential impact of varying the start and end of the risk window on each neoplasia outcome (ACN, CRC, and HSTCL), repeating the multivariable Cox models used in the main analysis. However, with the shorter, alternative risk windows, the limited number of events became so sparse that there were fewer than 10 events, which was the prespecified minimal threshold for conducting multivariable analyses. Thus, these analyses were not performed.

10.5.2.2 Competing Risk Analysis

To evaluate the potential effect of competing risks on the exposure-outcome associations, a sensitivity analysis was conducted that used a composite endpoint of colectomy due to intractable disease, ACN, and death. Table 24 shows results of a single multivariable Cox regression model for the composite outcome that included all exposure categories. See Analysis Table 11.5.1 and Analysis Table 11.5.2. Exposure to GLM compared with exposure to other anti-TNFα agents was not associated with a modified risk of the composite outcome in a multivariate model (HR=0.72; 95% CI: 0.42-1.26). Exposure to GLM compared with exposure to TPs was also not associated with a significantly modified risk of the composite outcome (HR=1.78; 95% CI: 0.93-3.41).

Table 24: Multivariable Cox Regression Model; Outcome: Colectomy Due to Intractable Disease, Advanced Colorectal Neoplasia, or Death; Sensitivity: Composite Outcome: GLM Versus Other Anti-TNFα Agents and GLM Versus TP

Comparison	Cox Model HR (95% CI)
GLM vs other anti-TNFα agents	0.72 (0.42-1.26)
GLM vs TP	1.78 (0.93-3.41)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Note: The analysis was adjusted for age group, UC duration in years, prior treatment with cyclosporine, and sex.

10.6 Adverse Reactions and Health Outcomes of Interest

During the conduct of the study, ARs and prespecified HOIs were reported for GLM and originator infliximab if encountered during the chart abstraction process for the nested case-control analyses (Table 25), according to the study's Safety Management Plan. Notifications of ARs and HOIs were included in this report if they were received by 31-May-2022.

Table 25: Adverse Reactions and Health Outcomes of Interest Identified in Users of SIMPONI® or REMICADE® [19-Sep-2013 Through 31-May-2022]

Adverse Reaction or HOI	Reporting Reference Number	Event Date (dd/mm/yyyy)	SIMPONI®	REMICADE®
Infusion reaction	ESP171571[a]	18/06/2014		X
Allergic reaction	ESP171711[b]	16/05/2016	X	
Allergic reaction	ESP171711[b]	05/10/2015		X
Pregnancy	ESP171860	10/10/2014	X	
Pregnancy	ESP171861	16/05/2012[c]		X
Infusion reaction	ESP172044	10/06/2014		X
Severe infusion reaction	ESP172117	07/11/2017		X
Pregnancy	ESP180765	Oct 2016[d]		X
Pregnancy	ESP181981	20/02/2015	X	
Infusion reaction	ESP182122	15/03/2015		X
Anaphylaxis	ES20210400098	15/04/2009[c]		X
Prostate cancer	ES20220500036	15/04/2014	X	

Abbreviations: AR, adverse reaction; HOI, health outcome of interest.

Note: Listings include reports of ARs received through 31-May-2022, as well as reports of any health outcomes of interest or other special situations that were specified in the study's Safety Management Plan. Per the protocol, only ARs related to the use of SIMPONI® or REMICADE® should have been reported.

[a] Due to the re-abstraction of patients already abstracted in 2017, this AR was identified and reported a second time.

[b] The reporting reference number provided by the Pharmacovigilance Office of Merck Sharp & Dohme, Corp. (MSD) Spain for both ARs is the same (per confirmed email communication on 13-Sep-2017).

[c] This AR should not have been reported according to the study Safety Management Plan because it occurred before the start of the study period (19-Sep-2013). However, it is included in this table for transparency since it was reported by the study site investigators.

[d] Estimated month of pregnancy based on the delivery date reported as "second half of June 2017."

11 DISCUSSION

11.1 Key Results

This PASS evaluated the risk of various safety outcomes among users of GLM for UC using the ENEIDA registry in Spain. The registry provided quality data on both the exposures and the outcomes of interest in the setting of usual specialty care in Spain and had a very high response rate to the questionnaires for medical chart abstraction. A total of 64 unique events of colectomy due to intractable disease and 10 unique events of ACN were identified among eligible patients during the 8-year study period. No events of HSTCL were identified.

Table 26 summarizes results of comparative analyses for the primary study outcomes, colectomy due to intractable disease and ACN, showing crude and adjusted measures of association.

The crude IR of colectomy due to intractable disease associated with GLM-only use was 4.4 per 1,000 PY, whereas it was 12.4 per 1,000 PY with use of other anti-TNFα agents only, and it was highest during overlapping exposure to both GLM and another anti-TNFα agent (based on only 3 events), 78.6 per 1,000 PY.

Table 26: Summary of Comparative Analyses for Colectomy due to Intractable Disease and Advanced Colonic Neoplasia

Outcome	Exposure Comparison	Number of Events	Cohort Analyses				Nested Case-Control Analysis	
			Poisson Model		Cox Model		Conditional Logistic Model	
			Crude IRR (95% CI)	Adjusted IRR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Colectomy due to intractable disease[a]	GLM only vs other anti-TNFα agents only	Cohort: 4 vs 47 NCC: 3 vs 35	0.35 (0.13-0.98)	0.40 (0.14-1.13)	0.37 (0.13-1.02)	0.41 (0.15-1.15)	0.17 (0.04-0.78)	0.16 (0.02-1.08)
	(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	Cohort: 3 vs 47 NCC: 3 vs 35	6.34 (1.97-20.37)	6.78 (2.08-22.13)	5.33 (1.64-17.34)	4.95 (1.52-16.08)	4.03 (0.40-NE)	8.69 (0.60-124.90)
ACN[b]	GLM vs other anti-TNFα agents	Cohort: 2 vs 6 NCC: 1 vs 5	NP	NP	1.16 (0.23-5.73)	1.09 (0.22-5.44)	0.47 (0.04-5.68)	NP
	GLM vs TP	Cohort: 2 vs 4 NCC: 1 vs 3	NP	NP	1.46 (0.27-8.00)	1.08 (0.19-6.13)	0.42 (0.01-13.27)	NP

Abbreviations: ACN, advanced colonic neoplasia; CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NCC, nested case-control; NE, not estimable; NP, not performed; OR, odds ratio, TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

[a] Poisson and Cox models were adjusted for age group (dichotomized ≥35 years and <35 years), UC duration, prior treatment with cyclosporine, and sex. The conditional logistic model was adjusted for age (dichotomized ≥35 years and <35 years), any hospitalization in period 2, cyclosporine use in period 2, and sex.

[b] Poisson and Cox models were adjusted for age group (3 categories), UC duration, and prior treatment with cyclosporine.

Overall, GLM use was not associated with an increased risk of colectomy due to intractable disease. However, overlapping exposure of both GLM and other anti-TNFα agents was associated with an increased risk of colectomy compared with exposure to other anti-TNFα agents only or to GLM only, but was based on only 3 events. According to the study design, this situation of overlapping exposure could have occurred after patients switched to GLM from another anti-TNFα agent or vice versa, when risk windows attributable to each agent overlapped.

Results from the cohort analyses and the nested case-control analysis were consistent with each other. Moreover, GLM use was not associated with an increased risk of colectomy in (unadjusted) subgroup analyses that stratified on baseline use of TPs, prior use of anti-TNFα agents, or when restricting the other anti-TNFα agents comparator cohort to patients who entered that cohort using infliximab (or adalimumab). Similarly, in a multivariable sensitivity analysis that used a competing risk framework, GLM use was not associated with an increased risk of the composite outcome of colectomy, ACN, or death.

For ACN, the crude IR was 1.5 per 1,000 PY with GLM use, 1.3 per 1,000 PY with use of the other anti-TNFα agents, and 1.0 per 1,000 PY with TP use. Compared with use of other anti-TNFα agents and TPs, GLM use was not associated with an increased risk of ACN in cohort and nested case-control analyses.

Occurrences of CRC were very rare in this study; across all exposure categories, there were 6 unique events. The crude IR was 1.5 per 1,000 PY with GLM use, 0.4 per 1,000 PY with other anti-TNFα agents use, and 0.8 per 1,000 PY with TP use. In comparative analyses of the CRC outcome, the crude point estimates for use of GLM versus use of other anti-TNFα agents was elevated (HR=3.42; 95% CI: 0.48-24.26), as it was when compared with TP use (HR=1.92; 95% CI: 0.32-11.50). However, CIs were wide and based on comparisons of small numbers of events, without any exposure group exceeding 3 events. The sparse number events also precluded conduct of adjusted analyses. In view of these findings, it is not possible to draw a clear inference about the association between study drugs and CRC risk.

Because no occurrences of HSTCL were identified during the study, no estimates of IRs were calculated.

11.2 Limitations

The number of colectomies due to intractable disease was limited, particularly in the exposure categories use of GLM only and overlapping exposure of GLM and other anti-TNFα agents. The number of ACN events was very small, and even fewer CRC events were available. Consequently, CIs, especially for the neoplasia outcome estimates, were wide. These small numbers also precluded the conduct of several planned adjusted analyses and sensitivity analyses.

It is possible that the number of ACN events observed in this study represents an underestimate of the true number. ACN is commonly asymptomatic and detected only during screening colonoscopy. Unlike in a clinical trial setting, in this study, systematic colonoscopies were not performed on the study population according to a pre-established algorithm. It is also not known what proportion of patients in each cohort had received screening according to recommended guidelines for patients with UC. At baseline, a

higher proportion of GLM initiators had undergone at least 1 screening colonoscopy (23.4%) compared with initiators of other anti-TNFα agents (17.0%) and initiators of TPs (13.5%), a pattern that correlates with UC duration in each cohort (median, 6.6 years, 4.1 years, and 2.5 years, respectively). This pattern is expected because one of the main indications for screening colonoscopy is disease duration, but the possibility of ascertainment bias due to differential screening patterns cannot be excluded.

Bias due to confounding is a theoretical possibility in all observational research. As was recognized during the design phase of this study, disease activity could not be measured directly; however, the study used several proxies for disease activity, including disease extent, disease duration, UC hospitalization history, and UC treatment history. Nonetheless, the limited number of outcomes identified constrained the ability to adjust for many potential confounders simultaneously, raising the question of residual confounding. Evidence against this possibility is the observation that adjusting for the limited number of variables most strongly associated with the outcome had minimal effect on the point estimates, which was also true when adjusting for potential confounders one at a time. Subgroup analyses were presented unadjusted since most did not allow inclusion of any adjustment variable. However, given that the main analyses showed little evidence of confounding (ie, crude and adjusted results were very similar), the study team considers it is reasonable to expect that subgroup analyses were also not substantially confounded.

As planned in the study protocol, the cohort analyses adjusted for covariates in a time-dependent fashion at each change in exposure status. This approach adjusts for time-varying confounders but can potentially introduce bias if a covariate is also a collider variable.[20] However, evidence suggests that cohort analyses that conduct adjustment only at baseline or at fixed time intervals may be more biased than those adjusting at each change in exposure status, even if collider stratification bias is introduced.[21]

11.2.1 Validity of the ENEIDA Registry Data

The ENEIDA registry has been used for 32 research studies[22-56] that have been published in peer-reviewed literature since its start of activities in 2006.[16]

Although colectomy due to intractable disease, CRC, and HGD are captured in the ENEIDA registry and are considered mandatory data (Section 9.5.1.1), it is possible that some occurrences of these clinical endpoints were not recorded in the routine ENEIDA data. There was no mechanism to determine the extent to which this occurred. However, since only centers that qualified as research quality contributed data to this study (see Section 9.5.1.1), any center reporting less than 75% of these variables was not included in the analyses, which is expected to limit the extent of exposure and outcome status misclassification. Also, the fact that the IR estimates obtained are in line with those of the published literature (see Section 11.3, Interpretation) supports the validity of the outcome data obtained from the ENEIDA registry.

As part of this PASS, the study team compared the information on a selected list of variables for which information was available in the ENEIDA registry and in the medical charts abstracted for the nested case-control analysis (Annex 2, Agreement of ENEIDA Data With Medical Chart Data). Results from this comparison suggested that although some differences existed between the recording of data in the ENEIDA registry and in the medical charts, as evaluated through the chart abstraction process, data from the 2 sources

were reasonably well aligned for the variables evaluated. The information evaluated on the 2 main pieces of information (ie, diagnosis of the study outcomes and the date of prescription of the drugs of interest) suggests that if ±30 days of discrepancy were allowed for the dates, most dates in the ENEIDA registry would be correct if compared with the corresponding dates in the medical charts. Given the 90-day risk window extension after drug discontinuation in the colectomy analyses and the longer risk window paradigm used in the ACN analyses, the results provided by the cohort study, which are based only on routine ENEIDA data, are considered to be valid.

Indirect evidence of the validity of exposure data in the ENEIDA registry is provided by the profile of new users of anti-TNFα agents in this analysis, which was consistent with clinical expectations. In this analysis, patients in the GLM and other anti-TNFα agents cohorts had a longer duration of UC and more hospitalizations for UC than those in the TP cohort, as expected based on the treatment escalation in patients with UC.

11.3 Interpretation

The number of patients enrolled in each cohort met or exceeded expectations from the protocol, as did the PY of observation.

The patients in the GLM and other anti-TNFα agents cohort appeared to have more severe UC than those in the anti-TNFα agent–naive TP cohort (ie, they had a longer duration of UC and more hospitalizations for UC). As expected, given the treatment escalation in UC, new users of TP in our study had a shorter duration of UC, had less often been hospitalized due to UC, and had less commonly undergone colonoscopies to screen for colon cancer. New users of GLM tended to have switched from another anti-TNFα agent more often than new users of other anti-TNFα agents (ie, adalimumab/infliximab), suggesting that GLM may have been used preferentially after a course of another anti-TNFα agent. This is also supported by the fact that new users of GLM had a longer duration of UC and a higher proportion of prior use of anti-TNFα medications than new users of other anti-TNFα agents.

Duration of follow-up was comparable among the 3 study cohorts. Reasons for censoring for all analyses (ie, colectomy due to intractable disease, ACN, and HSTCL) were similar among the 3 study cohorts except for “lost to follow-up,” which was relatively common and similar in both anti-TNFα cohorts (GLM, 34.6%, and other anti-TNFα agents, 37.3%) but was more common in the TP cohort (50%). The reason for this difference is not clear. Different processes through which patients obtain their medications is one potential explanation. Patients receiving anti-TNFα agents need to visit the hospital pharmacy or day hospital for drug delivery/administration and therefore may be more likely to attend a hospital-based IBD clinic appointment, which will be recorded in the ENEIDA registry. In contrast, patients treated with TPs can fill their prescriptions at community pharmacies and may be less likely to attend clinical visits. The loss to follow-up for approximately 35% of patients in both anti-TNFα agent cohorts was an unexpected finding, for which the explanation is also unclear. Loss to follow-up does not appear to be influenced by changes in healthcare use during the COVID-19 pandemic since the proportion remained relatively stable within each cohort each year over the study period (Analysis Table 4.1.1 through Analysis Table 4.1.9). Censoring due to the initiation of a novel biologic was more common among GLM users and other anti-TNFα agents users than among TP users. This is in line with the expectation that the population treated with an anti-TNFα agent

had more severe UC, which is more likely to be treated with newer drugs if the UC is insufficiently controlled.

Overall, there were 64 colectomies due to intractable disease, with 7 events occurring at any point while exposed to GLM (4 occurred while exposed to GLM only, and 3 with overlapping exposure to both GLM and another anti-TNFα agent). Excluding periods of overlapping exposure, the IR of colectomy due to intractable disease was lower with GLM use only than with use of other anti-TNFα agents only (4.4 [95% CI: 1.2-11.2] per 1,000 PY and 12.4 [95% CI: 9.1-16.5] per 1,000 PY, respectively). Point estimates were less precise for GLM-only use due to the smaller number of colectomy outcomes in this category. Of note, IRs of colectomy for patients exposed to GLM only were consistent with those reported in the literature from other large contemporaneous observational studies of patients with UC in multiple population-based studies: 4.2 per 1,000 PY in the United States in 2016[57]; 4.4 per 1,000 PY in Lothian, Scotland, in 2018[58]; and 4.2 to 1.9 per 1,000 PY among early and late initiators of anti-TNFα agents in Korea in 2010-2016.[59] Patients exposed to only other anti-TNFα agents had higher IRs of colectomy than those reported in the literature. This may be due to the preferential use of infliximab to treat patients with severe flares of UC who may be at an increased risk of colectomy. The subgroup analyses among infliximab initiators that showed a stronger inverse association of GLM exposure with colectomy than that observed among adalimumab initiators supports this hypothesis (see Table 22).

The results from this study may not be directly comparable to the majority of published studies that report on the risk of colectomy specifically among GLM users in real-life care settings. This is because most published studies used an all-cause colectomy case definition, were small, were conducted in patients at high risk for colectomy, and reported only the proportion of colectomy over a mean follow-up period.[60-63] The reported proportion of colectomies ranges from 60 to 110 per 1,000 patients with UC over mean periods of follow-up ranging from 12 to 33 months.

Several factors found to be associated with study outcomes are consistent with other descriptions of UC epidemiology. For the colectomy outcome (see Table 9), risk factors in our study included shorter disease duration, extensive colonic involvement, treatment with cyclosporine, and prior hospitalization for UC (the latter 2 are considered proxies for treatment-resistant disease). For ACN (see Table 18), risk factors of older age, male sex, and longer disease duration found in our study are consistent with the established epidemiology.

The validity of the study methodology is supported by the totality of the evidence reviewed. Specifically, the point estimates from this PASS fall within the ranges published in the literature, and the covariates considered a priori to be potential risk factors behaved as anticipated.

Several factors may explain the difference in IRs associated with GLM use and use of other anti-TNFα agents (excluding overlapping exposure). First, the IR for GLM-only use was based only on 4 events and was therefore prone to random variation. Second, this difference may reflect the way different anti-TNFα agents were prescribed in the UC population. Indeed, evidence suggests that infliximab, 1 of the 2 drugs included in the other anti-TNFα agents cohort, is more effective than GLM in achieving remission among patients with severely active UC, a disease state at high risk for colectomy due to intractable disease.[64] This may have led physicians to preferentially administer infliximab

to patients with more severe UC and who were thus at a greater risk of colectomy. The crude subgroup analysis comparing the risk of colectomy among those exposed to GLM only and those exposed to other anti-TNFα agents only, stratified by the specific comparator agent that qualified a patient for cohort entry, showed different results. It found an inverse association with colectomy for GLM use compared with initiators of infliximab but a similar risk in the comparison with initiators of adalimumab. Preferential prescribing of infliximab to patients with more active disease (who are at a higher risk of colectomy) could potentially explain this difference.

Comparative analyses used 2 alternative analytical approaches for the cohort analysis—Cox and Poisson regression models—and also used a nested case-control approach to address the relationship of GLM with colectomy outcome. Both analytical models for the cohort analysis found very similar results for all the comparisons evaluated, and the nested case-control approach was also in general agreement with the cohort analysis. The consistency of results across methods supports the robustness of the findings.

The adjusted cohort analysis that sought to account for the severity of UC (based on the variables available for adjustment) found results very similar to those of the crude analyses: use of GLM only compared with use of the other anti-TNFα agents only was not associated with an increased risk of colectomy, suggesting there was little confounding by measured covariates in the comparison. Patients with overlapping exposure of both GLM and other anti-TNFα agents were at a greater risk of colectomy than those exposed only to GLM or only to other anti-TNFα agents (based only on 3 colectomy events during 38.2 PYs of overlapping exposure time). Overlapping exposure to both GLM and other anti-TNFα agents occurred during periods when switching from one agent to the other. The elevated risk of colectomy during this period may best be explained by the clinical factors that prompted the switch (rather than drug effects); this interpretation is based on clinical reasoning rather than formal analysis, as the study data set did not include any direct measurements of disease activity. In addition, the limited number of colectomy outcomes constrained the ability to adjust for many potential confounders simultaneously. Residual confounding due to measured factors thus cannot be excluded. However, as anticipated during the study planning, the study team judges that confounding due to disease activity, which was not measured directly, is the biggest potential source of residual confounding in this study.

The nested case-control analysis, based on only 3 cases exposed to GLM only, also found no evidence of an increased risk of colectomy with GLM only compared with other anti-TNFα agents only. It is important to highlight that the nested case-control analysis was not conducted on the same population as the cohort analysis; rather, it was run on a subset of patients from the cohort study population for whom chart abstraction could be conducted (ie, 41 of the 64 colectomy cases included in the cohort analysis and 70 controls that did not undergo colectomy). Of the 30 centers that contributed data to the cohort study, 2 did not participate in the medical chart abstraction due to lack of resources or the need for a separate informed consent form. Patients selected for the nested case-control study were only those who were exposed to a study drug at the time of colectomy (or the equivalent date for the controls), ie, they were informative patients for this analysis. Because only 3 patients exposed to GLM only at the time of the colectomy were included in the analysis, effect estimates are imprecise. However, the fact that this point estimate does not suggest an increased risk of colectomy associated with GLM use—consistent with the result from the cohort analysis—is reassuring. Also, the univariate

models did show the factors associated with colectomy that were expected a priori, ie, extensive disease, treatment with cyclosporine, and hospitalization for UC, the latter 2 of which are proxies for treatment-resistant disease. This finding suggests that the data obtained from the chart abstraction correctly classified the covariate status during follow-up.

Although the precision of some of the sensitivity and subgroup analyses was limited due to small numbers, taken together, they do not suggest that an increased risk of colectomy due to intractable disease existed for users of GLM that were evaluated.

There were only 10 unique ACN events across all cohorts. It is challenging to provide context for the observed IRs of ACN from the published literature. Studies in UC that used the outcome of ACN as defined in this study are uncommon. Several reports that used a similar outcome definition did not study a population comparable to the population in the current study (eg, they were limited to UC patients with low-grade colonic dysplasia).[65-68] To our knowledge, 1 cohort study in an unselected UC population used a similar ACN case definition, but it did not report an IR, only a cumulative incidence based on variable amounts of follow-up time for each study participant.[69] However, some context may be provided from recent studies in UC that reported IRs of CRC.[70,71] The IR estimates of CRC per 1,000 PY in our study (IR=1.5 [95% CI: 0.2-5.4] for GLM; IR=0.4 [95% CI: 0.1-1.6] for other anti-TNFα agents; and IR=0.8 [95% CI: 0.2-2.3] for TP) are compatible with the IR point estimates per 1,000 PY from recent population-based studies of CRC in UC (IR=1.24[70] and IR=1.29[71]).

GLM use was not associated with an increased risk of ACN in cohort and nested case-control analyses.

The small number of CRCs identified during the study precluded the conduct of detailed analyses of this outcome. The elevated point estimates for the association GLM use versus use of anti-TNFα agents (HR=3.42; 95% CI: 0.48-24.26) and use of TPs (HR=1.92; 95% CI: 0.32-11.50) should not be interpreted as causal. Estimates were imprecise and based on comparisons of small numbers of events (2 vs 2 and 2 vs 3, respectively). In addition to random variation, these associations may also be explained by confounding; adjusted analyses could not be conducted because of the sparse number of events.

Analyses were also planned to assess the incidence of HSTCL. To enhance identification of potential HSTCL outcomes, free-text fields were queried, but no cases of HSTCL were identified during the study. This finding was expected given the very low background incidence of HSTCL.

11.4 Generalizability

The ENEIDA registry is currently one of the largest IBD registries in the world. Data for this PASS came from 30 hospitals in Spain judged to have data of research quality.[72] This quality determination is based on the completeness of the information generated by the hospitals on patients with IBD that is uploaded to the registry. During the study period of this PASS, close to 20,000 patients with UC from geographically diverse research-quality centers were available in the registry. The large number of contributing hospitals, which includes several large tertiary care university hospitals and a variety of large and medium-sized hospitals and clinics, makes the data presented in this PASS representative of the

clinical practice among patients with moderate to severe UC in Spain, which, based on the existing clinical guidelines and the umbrella of the EU centralized approval of drugs, is expected to be representative of the clinical care for these patients in the EU.

The study was designed in 2015, and some of the design decisions reflect the treatment landscape of UC at that time. However, the internal validity of the study suggested by the consistency of results across analytical methods and sensitivity analyses implies that results are still valid for users of GLM in the treatment of UC.

12 OTHER INFORMATION

None.

13 CONCLUSION

Results from this PASS do not indicate that there is an increased risk of colectomy due to intractable disease among users of GLM compared with users of other anti-TNFα agents in a prospectively followed population of patients with UC under routine clinical care in Spain. Results were robust to various analytical methods, subgroup analyses, and sensitivity analyses.

This study considered person-time shortly after switching from another anti-TNFα agent to GLM (or vice versa) as a special exposure category when risk windows overlapped. During this period of overlapping exposure, the risk of colectomy due to intractable disease was increased compared with periods of exposure to only GLM or only other anti-TNFα agents, although this estimate was based on only 3 events in the overlap exposure period. The explanation for the elevated risk during the period of overlapping exposure is uncertain, but it may reflect the underlying severity of disease that prompted the change in therapy (ie, confounding by severity of disease). This explanation is consistent with clinical reasoning but cannot be established using study data because direct measurements of disease activity were not available. Adjustment for measured covariates, some of which were proxies of disease activity, only minimally attenuated the elevated risk of colectomy during the period of overlapping exposure.

Results for ACN were based on small numbers but do not suggest an increased risk among users of GLM compared with users of other anti-TNFα agents or users of TP.

No conclusion could be made regarding CRC risk due to the very limited number of CRC events.

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Annex 1: List of Stand-Alone Documents

The documents listed are available upon request.

Number	Document reference number	Date	Title
1	[Number]	31-May-2022	List of investigators
2	[Number]	28-Jun-2018	Medical chart abstraction questionnaire
3	[Number]	26-Jul-2018	Data management plan
4	[Number]	20-Jul-2017	Safety management plan

Annex 2: Agreement of Automated Data With Data From Chart Abstraction

An exploratory analysis was performed to gain perspective on the agreement between selected variables in the ENEIDA register that were used in the main analyses and the corresponding values of these variable obtained through medical chart review. No assumptions were made about which data source represented the gold standard; during the course of the study, the study principal investigators indicated that some study sites use the ENEIDA electronic data as their primary medical record for UC care. This exploratory analysis did not test any hypothesis or have any formal prespecified acceptability thresholds.

Agreement of ENEIDA Data With Medical Chart Data

In Table 27 through Table 30, percentages of agreement are based on the comparison of the information on each selected variable coming from routine ENEIDA data with the corresponding data abstracted from the medical charts of cases and controls in the case-control analysis.

Date of Colectomy

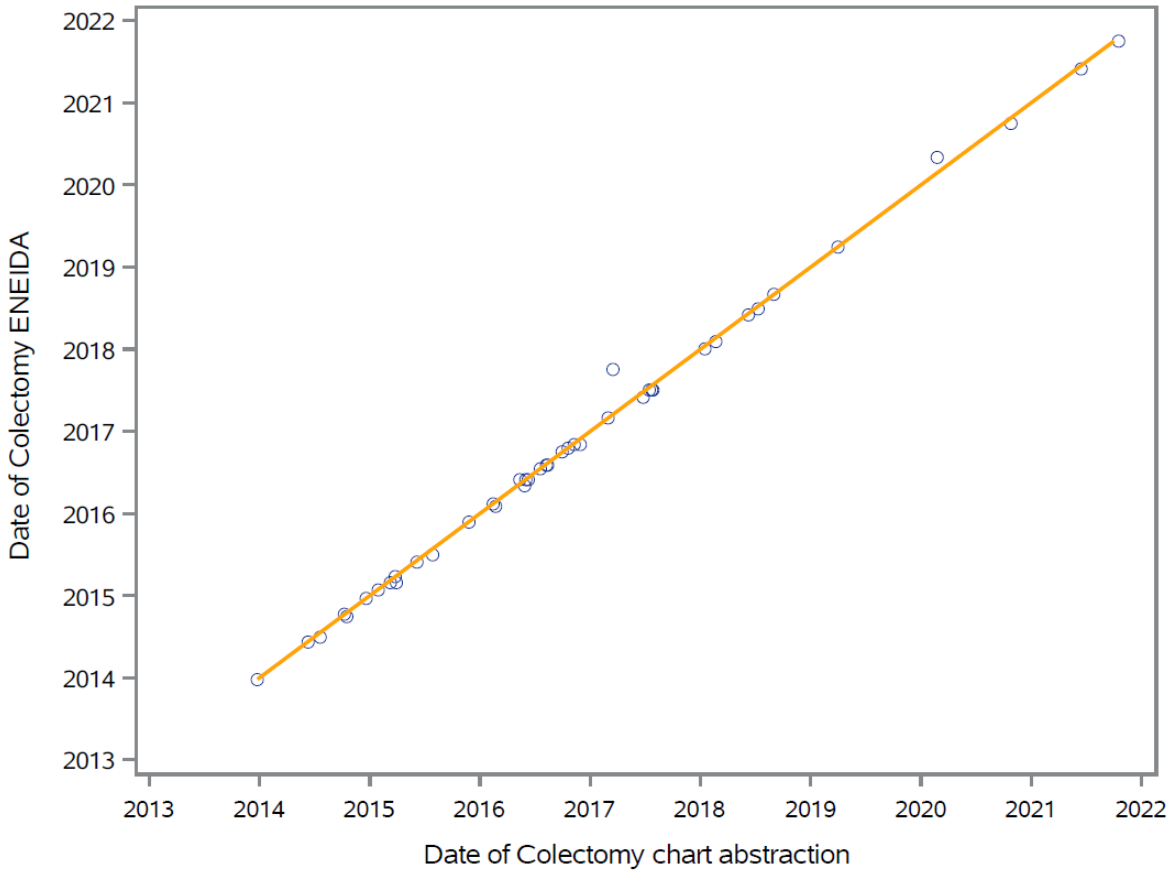
Table 27 summarizes agreement between dates of colectomy available in the ENEIDA registry and dates obtained from 42 abstracted medical charts. Figure 11 suggests that no large systematic differences existed between data sources for the recording of the date of colectomy.

Table 27: Date of Colectomy: Agreement Between Chart Abstraction and ENEIDA Data

Agreement on Date of Colectomy[a]	Percentage, %
Same date	31.0
Same date +/- 1 month	95.2
Disagreement of more than +/- 1 month	4.8

[a] Comparison among 42 patients with nonmissing data in both source documents.

Figure 11: Agreement Between Medical Charts and the ENEIDA Registry for Date of Colectomy



Date of First Recording of Golimumab Use

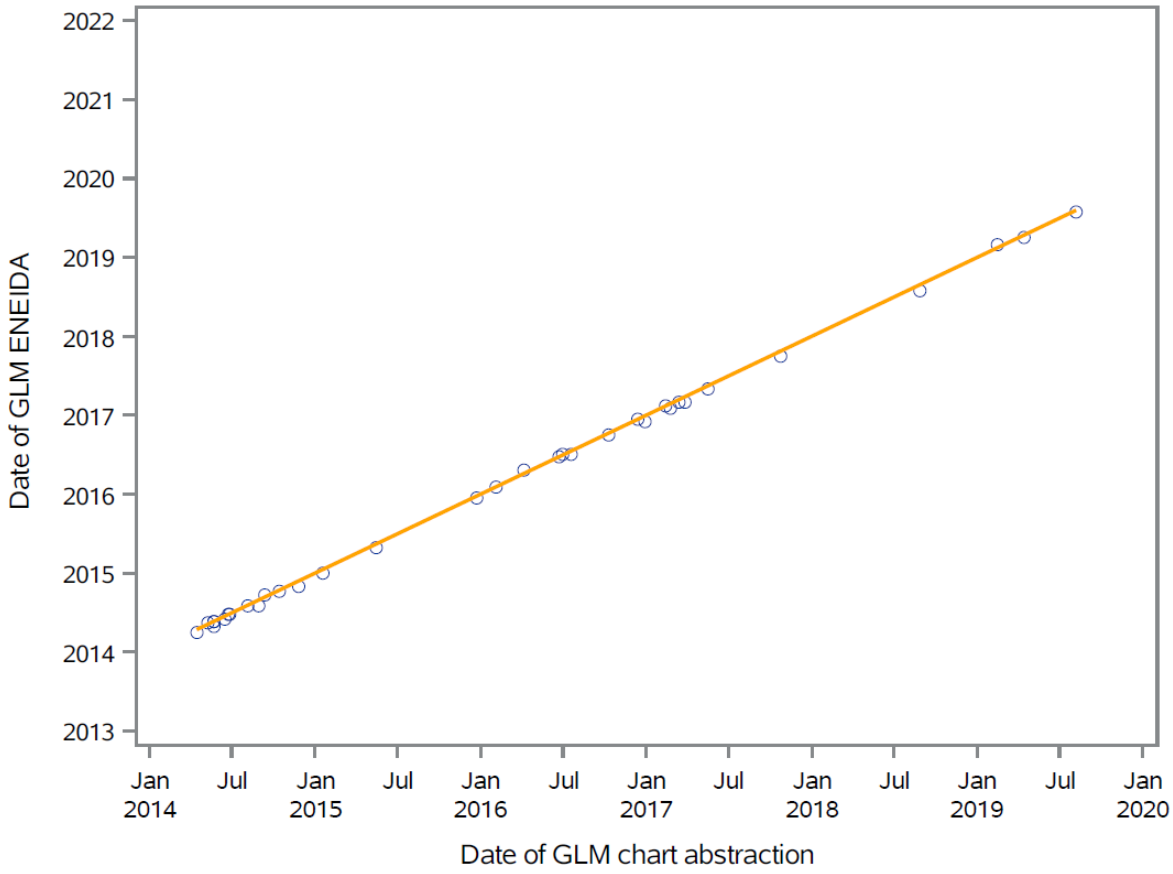
Table 28 describes the agreement between dates of first GLM use available in the ENEIDA registry and dates obtained from 34 abstracted medical charts. Figure 12 suggests that no systematic differences existed between data sources for the recording of the date of first GLM use.

Table 28: Date of First Golimumab Use: Agreement Between Chart Abstraction and ENEIDA Data

Agreement on Date of First Golimumab Use[a]	Percentage, %
Same date	23.5
Same date +/- 1 month	100
Disagreement of more than +/- 1 month	0

[a] Comparison among 34 patients with nonmissing data in both source documents.

Figure 12: Agreement Between Medical Charts and the ENEIDA Registry for Date of First Golimumab Use



Abbreviations: GLM, golimumab.

Number of Prior Anti-TNFα Drugs Used

Table 29 describes the agreement between the recorded number of different types of anti-TNFα agents (ie, GLM, infliximab, adalimumab, and other novel anti-TNFα agents) used by the patient to treat UC since the date of UC diagnosis between the ENEIDA registry and 153 abstracted medical charts.

Table 29: Number of Different Anti-TNFα Agents Used for UC: Agreement Between Chart Abstraction and ENEIDA Data

Difference in Number of Reported Anti-TNFα Agents Used	Percentage, %
Same number	65.4
More in chart	23.5
More in ENEIDA	9.2

Abbreviations: TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Agreement was evaluated for 153 patients for whom information was available in medical charts.

Date of UC Diagnosis

Table 30 describes alignment between dates of UC diagnosis in the ENEIDA registry and dates obtained from abstracted medical charts for 153 patients. Figure 13 suggests that no large systematic differences existed between data sources for the recording of the date of UC diagnosis.

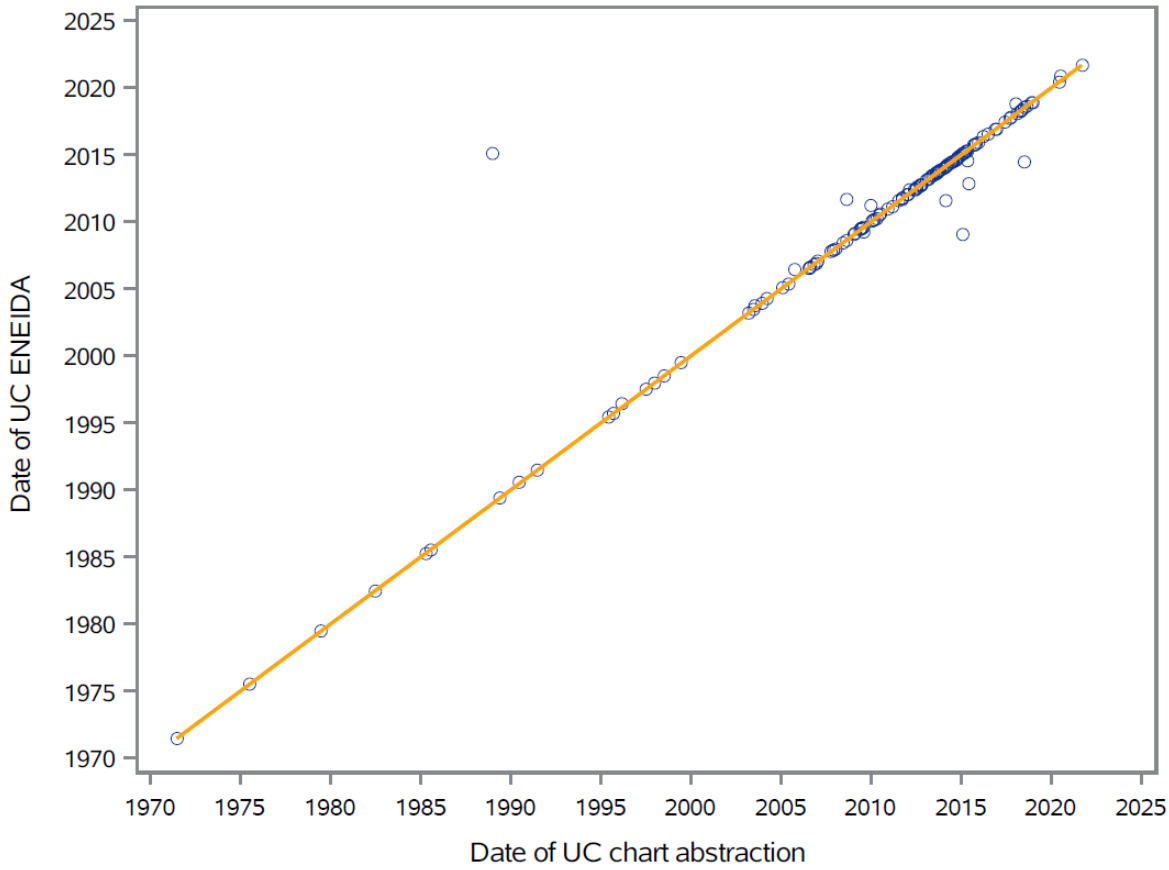
Table 30: Date of UC Diagnosis: Agreement Between Chart Abstraction and ENEIDA Data

Agreement on Date of UC Diagnosis [a]	Percentage, %
Same date	44.7
Same date +/- 1 month	87.9
Disagreement of more than +/- 1 month	12.1

Abbreviations: UC, ulcerative colitis.

[a] Comparison among 153 patients with nonmissing data in both source documents.

Figure 13: Agreement Between Medical Charts and the ENEIDA Registry for Date of UC Diagnosis



Abbreviations: UC, ulcerative colitis.

Annex 3: Analysis Tables

List of Analysis Tables

Analysis Table 1: Assembly of Study Cohorts

Entry Criterion	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
Diagnosis of UC from a qualified site	19,738	19,738	19,738
AND Initiated study drug for first time on or after 19-Sep-2013	546	2021	1,914
AND Age 18 years or older at study drug initiation	540	1,932	1,792
AND Study drug initiated within a credible period (<6 months) after last ENEIDA clinic visit[a]	518	1,864	1,751
AND No previous exposure to any other anti-TNFα before cohort entry[b]			1,396
AND No previous exposure to vedolizumab or other novel biologic agents[c] before cohort entry	488	1,813	1,393
AND No partial or complete colectomy before cohort entry	477	1,744	1,381
AND No ACN before cohort entry	477	1,740	1,380
AND No HSTCL before cohort entry	477	1,740	1,380
AND No double prescription of anti-TNFα, GLM, or vedolizumab or similar novel biologic agents.[d] Final analytical cohort	474	1,737	

Abbreviations: ACN, advanced colonic neoplasia; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Note: Study cohorts are not mutually exclusive. Patients can qualify for more than 1 cohort if they meet all applicable criteria.

[a] Dates of some initial study drug prescriptions did not have corresponding clinic visits (for GLM n=22; for anti-TNFα agent, n=68; for TP n=41).

[b] Criterion to be applied to the thiopurine cohort only; will not affect numbers for GLM or other anti-TNFα agent cohorts.

[c] Agents include the following: vedolizumab, natalizumab, etrolizumab, tocilizumab, ustekinumab, certolizumab, etanercept, or any similar newly marketed therapy.

[d] Overall, 3 patients were excluded for having a prescription for 2 different anti-TNFα agents on the same date. Because coprescription of more than 1 anti-TNFα agent is highly atypical, these patients were excluded out of concern about their data quality.

Analysis Table 2: Patient Characteristics at Cohort Entry

Characteristic	Study Cohort		
	GLM (N=474)	Other Anti-TNFα Agents (N=1,737)	TP (N=1,380)
Age in years			
n	474	1,737	1,380
Mean (SD)	45.1 (14.1)	44.2 (15.3)	43.1 (14.8)
Median (Q1, Q3)	44.0 (36.0,55.0)	44.0 (33.0,55.0)	42.0 (31.0,54.0)
Min, Max	18.0, 87.0	18.0, 98.0	18.0, 92.0
Age group, n (%)			
18-<35	114 (24.1%)	510 (29.4%)	422 (30.6%)
35 to <65 years	319 (67.3%)	1,047 (60.3%)	839 (60.8%)
≥65 years	41 (8.6%)	180 (10.4%)	119 (8.6%)
Sex, n (%)			
Male	236 (49.8%)	910 (52.4%)	740 (53.6%)
Female	238 (50.2%)	827 (47.6%)	640 (46.4%)
Calendar year of cohort entry, n (%)			
2013	2 (0.4%)	64 (3.7%)	59 (4.3%)
2014	77 (16.2%)	203 (11.7%)	233 (16.9%)
2015	67 (14.1%)	238 (13.7%)	247 (17.9%)
2016	71 (15.0%)	232 (13.4%)	214 (15.5%)
2017	75 (15.8%)	232 (13.4%)	169 (12.2%)
2018	63 (13.3%)	196 (11.3%)	135 (9.8%)
2019	58 (12.2%)	202 (11.6%)	133 (9.6%)
2020	35 (7.4%)	188 (10.8%)	101 (7.3%)
2021	26 (5.5%)	182 (10.5%)	89 (6.4%)
UC Duration in years[a]			
n	474	1,737	1,380
Mean (SD)	8.9 (8.1)	7.2 (7.8)	5.4 (6.7)
Median (Q1, Q3)	6.6 (2.2,13.1)	4.1 (1.2,11.0)	2.5 (0.7,8.0)
Min, Max	0.0, 41.0	0.0, 42.6	0.0, 39.4
Maximum extent of disease, n (%)[b]			
Extensive	232 (48.9%)	899 (51.8%)	672 (48.7%)
Left side only	190 (40.1%)	633 (36.4%)	549 (39.8%)
Proctitis	29 (6.1%)	109 (6.3%)	101 (7.3%)
Not recorded	23 (4.9%)	96 (5.5%)	58 (4.2%)

Analysis Table 2: Patient Characteristics at Cohort Entry

Characteristic	Study Cohort		
	GLM (N=474)	Other Anti-TNFα Agents (N=1,737)	TP (N=1,380)
Prior treatment with steroids, n (%)[d]			
No	197 (41.6%)	635 (36.6%)	527 (38.2%)
Yes	277 (58.4%)	1,102 (63.4%)	853 (61.8%)
Prior treatment with cyclosporine, n (%)[d]			
No	449 (94.7%)	1,628 (93.7%)	1,317 (95.4%)
Yes	25 (5.3%)	109 (6.3%)	63 (4.6%)
Hospitalized for UC, n (%)[d]			
No	380 (80.2%)	1,358 (78.2%)	1,178 (85.4%)
Yes	94 (19.8%)	379 (21.8%)	202 (14.6%)
Prior diagnosis with PSC, n (%)[e]			
No	177 (37.3%)	469 (27.0%)	261 (18.9%)
Yes	5 (1.1%)	19 (1.1%)	20 (1.4%)
Unknown/missing	292 (61.6%)	1,249 (71.9%)	1,099 (79.6%)
Prior screening colonoscopy, n (%)[d]			
No	363 (76.6%)	1,442 (83.0%)	1,194 (86.5%)
Yes	111 (23.4%)	295 (17.0%)	186 (13.5%)
Number of previous other anti-TNFα agents, n (%)[d]			
0	307 (64.8%)	1,503 (86.5%)	1,380 (100%)
1	113 (23.8%)	227 (13.1%)	0 (0%)
2	54 (11.4%)	7 (0.4%)	0 (0%)
Recent switcher after use of another anti-TNFα agent, n (%)[c]			
After short-term use (≤3 months)	109 (23.0%)	165 (9.5%)	0 (0%)
After long-term use (>3 months)	50 (10.5%)	49 (2.8%)	0 (0%)
Did not switch	315 (66.5%)	1,523 (87.7%)	0 (0%)

Abbreviations: GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] UC duration was the time between the date of UC diagnosis and cohort entry date.

[b] Maximum extent of disease reflects the value for this patient ascertained on 30-Mar-2022, when data extraction occurred. This value may not reflect the actual maximal disease extent at the time of cohort entry. In ENEIDA data, there is only 1 value of this variable per patient; this variable is not date stamped and is subject to continual updating to reflect the maximum extent of disease reached.

Analysis Table 2: Patient Characteristics at Cohort Entry

Characteristic	Study Cohort		
	GLM (N=474)	Other Anti-TNFα Agents (N=1,737)	TP (N=1,380)

[c] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

[d] During the period from UC diagnosis to cohort entry date.

[e] Ever before cohort entry date.

Analysis Table 2.1: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome Colectomy, and ACN

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=164)	Other Reasons (N=310)	Lost to Follow-up (N=647)	Other Reasons (N=1,090)	Lost to Follow-up (N=690)	Other Reasons (N=690)
Age in years						
n	164	310	647	1,090	690	690
Mean (SD)	44.8 (13.6)	45.3 (14.3)	43.0 (14.1)	45.0 (15.9)	42.7 (14.6)	43.5 (15.1)
Median (Q1, Q3)	43.5 (35.0,54.0)	44.5 (36.0,55.0)	43.0 (32.0,53.0)	45.0 (33.0,56.0)	43.0 (31.0,53.0)	42.0 (31.0,54.0)
Min, Max	18.0, 87.0	18.0, 84.0	18.0, 87.0	18.0, 98.0	18.0, 87.0	18.0, 92.0
Age group, n (%)						
18-<35	40 (24.4%)	74 (23.9%)	193 (29.8%)	317 (29.1%)	215 (31.2%)	207 (30.0%)
35 to <65 years	112 (68.3%)	207 (66.8%)	405 (62.6%)	642 (58.9%)	421 (61.0%)	418 (60.6%)
≥65 years	12 (7.3%)	29 (9.4%)	49 (7.6%)	131 (12.0%)	54 (7.8%)	65 (9.4%)
Sex, n (%)						
Male	85 (51.8%)	151 (48.7%)	348 (53.8%)	562 (51.6%)	387 (56.1%)	353 (51.2%)
Female	79 (48.2%)	159 (51.3%)	299 (46.2%)	528 (48.4%)	303 (43.9%)	337 (48.8%)
Calendar year of cohort entry, n (%)						
2013	1 (0.6%)	1 (0.3%)	25 (3.9%)	39 (3.6%)	30 (4.3%)	29 (4.2%)
2014	31 (18.9%)	46 (14.8%)	94 (14.5%)	109 (10.0%)	134 (19.4%)	99 (14.3%)
2015	20 (12.2%)	47 (15.2%)	91 (14.1%)	147 (13.5%)	125 (18.1%)	122 (17.7%)

Analysis Table 2.1: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome Colectomy, and ACN

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=164)	Other Reasons (N=310)	Lost to Follow-up (N=647)	Other Reasons (N=1,090)	Lost to Follow-up (N=690)	Other Reasons (N=690)
2016	23 (14.0%)	48 (15.5%)	82 (12.7%)	150 (13.8%)	100 (14.5%)	114 (16.5%)
2017	19 (11.6%)	56 (18.1%)	87 (13.4%)	145 (13.3%)	90 (13.0%)	79 (11.4%)
2018	30 (18.3%)	33 (10.6%)	84 (13.0%)	112 (10.3%)	71 (10.3%)	64 (9.3%)
2019	18 (11.0%)	40 (12.9%)	76 (11.7%)	126 (11.6%)	65 (9.4%)	68 (9.9%)
2020	12 (7.3%)	23 (7.4%)	69 (10.7%)	119 (10.9%)	53 (7.7%)	48 (7.0%)
2021	10 (6.1%)	16 (5.2%)	39 (6.0%)	143 (13.1%)	22 (3.2%)	67 (9.7%)
UC duration in years[a]						
n	164	310	647	1,090	690	690
Mean (SD)	8.1 (8.4)	9.3 (7.9)	7.0 (7.6)	7.2 (7.8)	5.6 (6.9)	5.2 (6.5)
Median (Q1, Q3)	5.2 (1.6,12.0)	7.5 (2.6,13.3)	4.0 (1.1,10.4)	4.1 (1.2,11.4)	2.9 (0.6,8.0)	2.2 (0.7,7.8)
Min, Max	0.0, 36.3	0.0, 41.0	0.0, 42.6	0.0, 40.4	0.0, 34.8	0.0, 39.4
Maximum extent of disease, n (%)[b]						
Extensive	75 (45.7%)	157 (50.6%)	340 (52.6%)	559 (51.3%)	326 (47.2%)	346 (50.1%)
Left side only	63 (38.4%)	127 (41.0%)	216 (33.4%)	417 (38.3%)	273 (39.6%)	276 (40.0%)
Proctitis	13 (7.9%)	16 (5.2%)	46 (7.1%)	63 (5.8%)	57 (8.3%)	44 (6.4%)
Not recorded	13 (7.9%)	10 (3.2%)	45 (7.0%)	51 (4.7%)	34 (4.9%)	24 (3.5%)

Analysis Table 2.1: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome Colectomy, and ACN

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=164)	Other Reasons (N=310)	Lost to Follow-up (N=647)	Other Reasons (N=1,090)	Lost to Follow-up (N=690)	Other Reasons (N=690)
Prior treatment with steroids, n (%)						
No	78 (47.6%)	119 (38.4%)	272 (42.0%)	363 (33.3%)	287 (41.6%)	240 (34.8%)
Yes	86 (52.4%)	191 (61.6%)	375 (58.0%)	727 (66.7%)	403 (58.4%)	450 (65.2%)
Prior treatment with cyclosporine, n (%)						
No	157 (95.7%)	292 (94.2%)	626 (96.8%)	1,002 (91.9%)	670 (97.1%)	647 (93.8%)
Yes	7 (4.3%)	18 (5.8%)	21 (3.2%)	88 (8.1%)	20 (2.9%)	43 (6.2%)
Hospitalized for UC, n (%)						
No	132 (80.5%)	248 (80.0%)	515 (79.6%)	843 (77.3%)	597 (86.5%)	581 (84.2%)
Yes	32 (19.5%)	62 (20.0%)	132 (20.4%)	247 (22.7%)	93 (13.5%)	109 (15.8%)
Prior diagnosis with PSC, n (%)						
No	61 (37.2%)	116 (37.4%)	180 (27.8%)	289 (26.5%)	131 (19.0%)	130 (18.8%)
Yes	0 (0%)	5 (1.6%)	4 (0.6%)	15 (1.4%)	10 (1.4%)	10 (1.4%)
Unknown/missing	103 (62.8%)	189 (61.0%)	463 (71.6%)	786 (72.1%)	549 (79.6%)	550 (79.7%)
Prior screening colonoscopy, n (%)						
No	130 (79.3%)	233 (75.2%)	540 (83.5%)	902 (82.8%)	604 (87.5%)	590 (85.5%)
Yes	34 (20.7%)	77 (24.8%)	107 (16.5%)	188 (17.2%)	86 (12.5%)	100 (14.5%)

Analysis Table 2.1: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome Colectomy, and ACN

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=164)	Other Reasons (N=310)	Lost to Follow-up (N=647)	Other Reasons (N=1,090)	Lost to Follow-up (N=690)	Other Reasons (N=690)
Number of previous other anti-TNFα agents, n(%)						
0	107 (65.2%)	200 (64.5%)	578 (89.3%)	925 (84.9%)	690 (100%)	690 (100%)
1	39 (23.8%)	74 (23.9%)	67 (10.4%)	160 (14.7%)	0 (0%)	0 (0%)
2	18 (11.0%)	36 (11.6%)	2 (0.3%)	5 (0.5%)	0 (0%)	0 (0%)
Recent switcher after use of another anti-TNFα agent, n (%)[c]						
After short-term use (≤3 months)	38 (23.2%)	71 (22.9%)	44 (6.8%)	121 (11.1%)	0 (0%)	0 (0%)
After long-term use (>3 months)	16 (9.8%)	34 (11.0%)	22 (3.4%)	27 (2.5%)	0 (0%)	0 (0%)
Did not switch	110 (67.1%)	205 (66.1%)	581 (89.8%)	942 (86.4%)	0 (0%)	0 (0%)

Abbreviations: GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] UC duration was the time between the date of UC diagnosis and cohort entry date.

[b] Maximum extent of disease reflects the value for this patient ascertained on 30-Mar-2022, when data extraction occurred. This value may not reflect the actual maximal disease extent at the time of cohort entry. In ENEIDA data, there is only 1 value of this variable per patient; this variable is not date stamped and is subject to continual updating to reflect the maximum extent of disease reached.

[c] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Analysis Table 2.2: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome HSTCL

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=165)	Other Reasons (N=309)	Lost to Follow-up (N=676)	Other Reasons (N=1,061)	Lost to Follow-up (N=698)	Other Reasons (N=682)
Age in years						
n	165	309	676	1,061	698	682
Mean (SD)	44.9 (13.7)	45.3 (14.3)	43.2 (14.3)	44.9 (15.8)	43.0 (14.7)	43.3 (14.9)
Median (Q1, Q3)	44.0 (35.0,55.0)	44.0 (36.0,55.0)	43.0 (32.0,54.0)	45.0 (33.0,56.0)	43.0 (31.0,54.0)	42.0 (31.0,53.0)
Min, Max	18.0, 87.0	18.0, 84.0	18.0, 87.0	18.0, 98.0	18.0, 87.0	18.0, 92.0
Age group, n (%)						
18-<35	40 (24.2%)	74 (23.9%)	201 (29.7%)	309 (29.1%)	216 (30.9%)	206 (30.2%)
35 to <65 years	112 (67.9%)	207 (67.0%)	421 (62.3%)	626 (59.0%)	425 (60.9%)	414 (60.7%)
≥65 years	13 (7.9%)	28 (9.1%)	54 (8.0%)	126 (11.9%)	57 (8.2%)	62 (9.1%)
Sex, n (%)						
Male	86 (52.1%)	150 (48.5%)	365 (54.0%)	545 (51.4%)	391 (56.0%)	349 (51.2%)
Female	79 (47.9%)	159 (51.5%)	311 (46.0%)	516 (48.6%)	307 (44.0%)	333 (48.8%)
Calendar year of cohort entry, n (%)						
2013	1 (0.6%)	1 (0.3%)	30 (4.4%)	34 (3.2%)	31 (4.4%)	28 (4.1%)
2014	31 (18.8%)	46 (14.9%)	101 (14.9%)	102 (9.6%)	135 (19.3%)	98 (14.4%)
2015	20 (12.1%)	47 (15.2%)	93 (13.8%)	145 (13.7%)	127 (18.2%)	120 (17.6%)
2016	23 (13.9%)	48 (15.5%)	87 (12.9%)	145 (13.7%)	103 (14.8%)	111 (16.3%)
2017	20 (12.1%)	55 (17.8%)	89 (13.2%)	143 (13.5%)	90 (12.9%)	79 (11.6%)

Analysis Table 2.2: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome HSTCL

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=165)	Other Reasons (N=309)	Lost to Follow-up (N=676)	Other Reasons (N=1,061)	Lost to Follow-up (N=698)	Other Reasons (N=682)
2018	30 (18.2%)	33 (10.7%)	86 (12.7%)	110 (10.4%)	71 (10.2%)	64 (9.4%)
2019	18 (10.9%)	40 (12.9%)	79 (11.7%)	123 (11.6%)	65 (9.3%)	68 (10.0%)
2020	12 (7.3%)	23 (7.4%)	71 (10.5%)	117 (11.0%)	54 (7.7%)	47 (6.9%)
2021	10 (6.1%)	16 (5.2%)	40 (5.9%)	142 (13.4%)	22 (3.2%)	67 (9.8%)
UC duration in years[a]						
n	165	309	676	1,061	698	682
Mean (SD)	8.2 (8.5)	9.3 (7.9)	6.9 (7.6)	7.3 (7.9)	5.6 (6.8)	5.2 (6.5)
Median (Q1, Q3)	5.3 (1.6,12.1)	7.5 (2.6,13.2)	3.8 (1.1,10.3)	4.2 (1.2,11.6)	2.9 (0.6,8.0)	2.3 (0.7,7.8)
Min, Max	0.0, 36.3	0.0, 41.0	0.0, 42.6	0.0, 40.4	0.0, 34.8	0.0, 39.4
Maximum extent of disease, n (%)[b]						
Extensive	75 (45.5%)	157 (50.8%)	360 (53.3%)	539 (50.8%)	331 (47.4%)	341 (50.0%)
Left side only	64 (38.8%)	126 (40.8%)	221 (32.7%)	412 (38.8%)	275 (39.4%)	274 (40.2%)
Proctitis	13 (7.9%)	16 (5.2%)	47 (7.0%)	62 (5.8%)	57 (8.2%)	44 (6.5%)
Not recorded	13 (7.9%)	10 (3.2%)	48 (7.1%)	48 (4.5%)	35 (5.0%)	23 (3.4%)
Prior treatment with steroids, n (%)						
No	78 (47.3%)	119 (38.5%)	281 (41.6%)	354 (33.4%)	289 (41.4%)	238 (34.9%)
Yes	87 (52.7%)	190 (61.5%)	395 (58.4%)	707 (66.6%)	409 (58.6%)	444 (65.1%)

Analysis Table 2.2: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome HSTCL

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=165)	Other Reasons (N=309)	Lost to Follow-up (N=676)	Other Reasons (N=1,061)	Lost to Follow-up (N=698)	Other Reasons (N=682)
Prior treatment with cyclosporine, n (%)						
No	157 (95.2%)	292 (94.5%)	649 (96.0%)	979 (92.3%)	675 (96.7%)	642 (94.1%)
Yes	8 (4.8%)	17 (5.5%)	27 (4.0%)	82 (7.7%)	23 (3.3%)	40 (5.9%)
Hospitalized for UC, n (%)						
No	133 (80.6%)	247 (79.9%)	534 (79.0%)	824 (77.7%)	603 (86.4%)	575 (84.3%)
Yes	32 (19.4%)	62 (20.1%)	142 (21.0%)	237 (22.3%)	95 (13.6%)	107 (15.7%)
Prior diagnosis with PSC, n (%)						
No	61 (37.0%)	116 (37.5%)	186 (27.5%)	283 (26.7%)	131 (18.8%)	130 (19.1%)
Yes	0 (0%)	5 (1.6%)	4 (0.6%)	15 (1.4%)	11 (1.6%)	9 (1.3%)
Unknown/missing	104 (63.0%)	188 (60.8%)	486 (71.9%)	763 (71.9%)	556 (79.7%)	543 (79.6%)
Prior screening colonoscopy, n (%)						
No	131 (79.4%)	232 (75.1%)	568 (84.0%)	874 (82.4%)	612 (87.7%)	582 (85.3%)
Yes	34 (20.6%)	77 (24.9%)	108 (16.0%)	187 (17.6%)	86 (12.3%)	100 (14.7%)
Number of previous other anti-TNFα agents, n(%)						
0	108 (65.5%)	199 (64.4%)	602 (89.1%)	901 (84.9%)	698 (100%)	682 (100%)
1	39 (23.6%)	74 (23.9%)	72 (10.7%)	155 (14.6%)	0 (0%)	0 (0%)
2	18 (10.9%)	36 (11.7%)	2 (0.3%)	5 (0.5%)	0 (0%)	0 (0%)

Analysis Table 2.2: Patient Characteristics at Cohort Entry Depending on Reason for End of Follow-up, Outcome HSTCL

Characteristic	Study Cohort					
	GLM (N=474)		Other Anti-TNFα Agents (N=1,737)		TP (N=1,380)	
	Lost to Follow-up (N=165)	Other Reasons (N=309)	Lost to Follow-up (N=676)	Other Reasons (N=1,061)	Lost to Follow-up (N=698)	Other Reasons (N=682)
Recent switcher after use of another anti-TNFα agent, n (%)[c]						
After short-term use (≤3 months)	38 (23.0%)	71 (23.0%)	47 (7.0%)	118 (11.1%)	0 (0%)	0 (0%)
After long-term use (>3 months)	16 (9.7%)	34 (11.0%)	24 (3.6%)	25 (2.4%)	0 (0%)	0 (0%)
Did not switch	111 (67.3%)	204 (66.0%)	605 (89.5%)	918 (86.5%)	0 (0%)	0 (0%)

Abbreviations: ENEIDA, National Study on Inflammatory Bowel Disease Genetic and Environmental Determinants (Spain); GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] UC duration was the time between the date of UC diagnosis and cohort entry date.

[b] Maximum extent of disease reflects the value for this patient ascertained on 30-Mar-2022, when data extraction occurred. This value may not reflect the actual maximal disease extent at the time of cohort entry. In ENEIDA data, there is only 1 value of this variable per patient; this variable is not date stamped and is subject to continual updating to reflect the maximum extent of disease.

[c] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Analysis Table 3.1: Duration of Follow-up by Cohort and Year of Cohort Entry, ACN Outcome

Characteristic	Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Months of follow-up[a]			
n	474	1,737	1,380
Mean (SD)	34 (26.1)	32 (26.3)	34 (26.6)
Median (Q1, Q3)	27 (12.0, 51.7)	23 (9.9, 51.3)	25 (9.9, 54.1)
Min, Max	0.8, 95.0	0.1, 101.9	0.6, 102.3
Cohort entry 2013 (months of follow-up[a])			
n	2	64	59
Mean (SD)	22 (5.2)	59 (31.1)	53 (34.2)
Median (Q1, Q3)	22 (18.1, 25.4)	56 (30.0, 89.9)	50 (21.0, 86.0)
Min, Max	18.1, 25.4	0.1, 101.9	5.9, 102.3
Cohort entry 2014 (months of follow-up[a])			
n	77	203	233
Mean (SD)	53 (34.9)	55 (33.1)	48 (32.1)
Median (Q1, Q3)	65 (17.1, 87.8)	61 (21.6, 88.3)	51 (15.9, 78.9)
Min, Max	1.3, 95.0	0.6, 98.9	2.3, 97.0
Cohort entry 2015 (months of follow-up[a])			
n	67	238	247
Mean (SD)	42 (29.7)	45 (28.5)	42 (28.9)
Median (Q1, Q3)	33 (13.4, 74.2)	49 (14.8, 75.5)	41 (11.8, 71.7)
Min, Max	1.5, 86.9	0.1, 85.9	1.2, 86.4
Cohort entry 2016 (months of follow-up[a])			
n	71	232	214
Mean (SD)	40 (26.9)	37 (24.9)	37 (25.0)
Median (Q1, Q3)	40 (13.7, 67.9)	32 (12.6, 62.0)	33 (11.9, 63.9)
Min, Max	0.8, 74.9	0.3, 74.9	1.0, 74.4
Cohort entry 2017 (months of follow-up[a])			
n	75	232	169
Mean (SD)	31 (19.7)	35 (20.5)	31 (20.0)
Median (Q1, Q3)	28 (11.0, 52.4)	38 (13.6, 54.5)	28 (11.0, 52.9)
Min, Max	2.0, 62.9	0.9, 62.9	2.5, 62.9

Analysis Table 3.1: Duration of Follow-up by Cohort and Year of Cohort Entry, ACN Outcome

Characteristic	Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Cohort entry 2018 (months of follow-up[a])			
n	63	196	135
Mean (SD)	30 (15.8)	24 (16.3)	28 (15.8)
Median (Q1, Q3)	33 (14.9, 44.9)	21 (8.9, 40.5)	30 (10.0, 42.5)
Min, Max	0.9, 50.9	0.4, 50.9	3.5, 50.9
Cohort entry 2019 (months of follow-up[a])			
n	58	202	133
Mean (SD)	25 (11.3)	21 (11.0)	21 (11.0)
Median (Q1, Q3)	30 (14.2, 33.7)	24 (10.9, 30.9)	22 (8.9, 30.9)
Min, Max	4.0, 38.9	1.0, 38.9	0.6, 38.1
Cohort entry 2020 (months of follow-up[a])			
n	35	188	101
Mean (SD)	16 (6.9)	15 (6.9)	14 (6.1)
Median (Q1, Q3)	17 (8.6, 21.0)	16 (7.9, 20.8)	15 (8.9, 18.5)
Min, Max	5.4, 26.9	1.0, 26.9	2.0, 26.9
Cohort entry 2021 (months of follow-up[a])			
n	26	182	89
Mean (SD)	9 (3.3)	8 (3.4)	8 (3.5)
Median (Q1, Q3)	9 (7.9, 12.6)	7 (5.8, 10.7)	7 (5.9, 10.9)
Min, Max	3.0, 14.9	0.5, 14.9	2.8, 14.9

Abbreviations: GLM, golimumab; ACN, advanced colonic neoplasia; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine.

[a] Follow-up for the ACN used an "ever exposed, always at risk" approach.

Analysis Table 3.2: Duration of Follow-up by Cohort and Year of Cohort Entry, Colectomy Outcome

Characteristic	Cohort	
	GLM[a]	Other Anti-TNFα Agents[a]
	N=471	N=1,734
Months of follow-up[b]		
n	471	1,734
Mean (SD)	23 (23.5)	26 (24.0)
Median (Q1, Q3)	13 (5.9, 32.9)	17 (7.6, 38.4)
Min, Max	0.0, 94.1	0.0, 101.8
Cohort entry 2013 (months of follow-up[b])		
n	2	64
Mean (SD)	22 (5.2)	44 (34.2)
Median (Q1, Q3)	22 (18.0, 25.4)	36 (13.4, 79.3)
Min, Max	18.0, 25.4	0.1, 101.8
Cohort entry 2014 (months of follow-up[b])		
n	77	202
Mean (SD)	33 (34.1)	41 (32.9)
Median (Q1, Q3)	16 (4.0, 69.1)	29 (10.2, 74.0)
Min, Max	0.3, 94.1	0.0, 98.9
Cohort entry 2015 (months of follow-up[b])		
n	66	237
Mean (SD)	25 (27.4)	36 (27.6)
Median (Q1, Q3)	11 (6.0, 41.9)	29 (10.8, 61.6)
Min, Max	0.0, 86.5	0.0, 85.8
Cohort entry 2016 (months of follow-up[b])		
n	70	232
Mean (SD)	28 (26.8)	31 (24.2)
Median (Q1, Q3)	14 (4.9, 60.1)	23 (8.1, 54.2)
Min, Max	0.4, 73.8	0.3, 74.9
Cohort entry 2017 (months of follow-up[b])		
n	75	232
Mean (SD)	19 (18.2)	29 (21.1)
Median (Q1, Q3)	11 (5.9, 30.0)	27 (8.9, 51.9)
Min, Max	1.0, 59.9	0.0, 62.9

Analysis Table 3.2: Duration of Follow-up by Cohort and Year of Cohort Entry, Colectomy Outcome

Characteristic	Cohort	
	GLM[a]	Other Anti-TNFα Agents[a]
	N=471	N=1,734
Cohort entry 2018 (months of follow-up[b])		
n	63	195
Mean (SD)	23 (16.3)	21 (15.9)
Median (Q1, Q3)	20 (8.0, 38.6)	16 (7.0, 35.9)
Min, Max	0.9, 50.9	1.4, 50.9
Cohort entry 2019 (months of follow-up[b])		
n	58	202
Mean (SD)	21 (12.4)	20 (11.1)
Median (Q1, Q3)	26 (7.1, 31.9)	19 (9.6, 29.9)
Min, Max	1.0, 36.9	1.0, 38.9
Cohort entry 2020 (months of follow-up[b])		
n	34	188
Mean (SD)	11 (7.0)	13 (7.0)
Median (Q1, Q3)	9 (5.9, 18.9)	14 (6.8, 18.9)
Min, Max	1.0, 24.1	1.0, 26.9
Cohort entry 2021 (months of follow-up[b])		
n	26	182
Mean (SD)	8 (3.9)	8 (3.3)
Median (Q1, Q3)	8 (4.9, 11.9)	7 (4.9, 10.2)
Min, Max	0.9, 14.9	0.4, 14.9

Abbreviations: GLM, golimumab; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha.

[a] This table includes only those patients who contributed person-time only to the GLM cohort or to the other anti-TNFα agent cohort after cohort entry. This table does not include the follow-up time of 6 patients who during all follow-up time were exposed exclusively to GLM in combination with other anti-TNFα agents (3 patients in the GLM cohort and 3 patients in the other anti-TNFα agent cohort), although that person-time is included in the comparative analyses in the overlapping (ie, combined) exposure group.

[b] Follow-up for the colectomy analyses includes a 90-day extension period of the risk window after discontinuation (ie, stop date) of the evaluated treatments.

Analysis Table 3.3: Duration of Follow-up by Cohort and Year of Cohort Entry, HSTCL Outcome

Characteristic	Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Months of follow-up [a]			
n	474	1,737	1,380
Mean (SD)	35 (26.5)	33 (26.5)	34 (26.7)
Median (Q1, Q3)	28 (13.0, 52.9)	25 (10.7, 52.7)	25 (9.9, 54.7)
Min, Max	0.8, 95.0	0.4, 101.9	0.6, 102.3
Cohort entry 2013 (months of follow-up [a])			
n	2	64	59
Mean (SD)	22 (5.2)	65 (29.0)	53 (34.5)
Median (Q1, Q3)	22 (18.1, 25.4)	70 (36.0, 91.6)	50 (21.0, 88.0)
Min, Max	18.1, 25.4	9.8, 101.9	5.9, 102.3
Cohort entry 2014 (months of follow-up [a])			
n	77	203	233
Mean (SD)	59 (33.0)	58 (31.7)	48 (32.2)
Median (Q1, Q3)	78 (20.0, 88.9)	66 (26.3, 89.0)	51 (15.9, 79.8)
Min, Max	2.5, 95.0	3.0, 98.9	2.3, 97.0
Cohort entry 2015 (months of follow-up [a])			
n	67	238	247
Mean (SD)	42 (29.6)	47 (28.1)	42 (28.9)
Median (Q1, Q3)	33 (13.4, 74.2)	52 (15.7, 75.7)	42 (11.8, 72.0)
Min, Max	1.5, 86.9	2.0, 85.9	2.3, 86.4
Cohort entry 2016 (months of follow-up [a])			
n	71	232	214
Mean (SD)	40 (26.8)	38 (24.4)	37 (24.9)
Median (Q1, Q3)	40 (13.7, 67.9)	38 (14.5, 62.2)	33 (11.9, 63.9)
Min, Max	0.8, 74.9	1.6, 74.9	2.6, 74.4
Cohort entry 2017 (months of follow-up [a])			
n	75	232	169
Mean (SD)	31 (19.6)	35 (20.2)	31 (20.0)
Median (Q1, Q3)	28 (11.9, 52.4)	39 (14.0, 54.5)	28 (11.0, 52.9)
Min, Max	2.0, 62.9	0.9, 62.9	2.5, 62.9

Analysis Table 3.3: Duration of Follow-up by Cohort and Year of Cohort Entry, HSTCL Outcome

Characteristic	Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Cohort entry 2018 (months of follow-up[a])			
n	63	196	135
Mean (SD)	30 (16.0)	24 (16.2)	28 (15.8)
Median (Q1, Q3)	33 (14.9, 45.1)	21 (8.9, 40.5)	30 (10.0, 42.5)
Min, Max	0.9, 50.9	0.4, 50.9	3.5, 50.9
Cohort entry 2019 (months of follow-up[a])			
n	58	202	133
Mean (SD)	25 (11.3)	22 (10.8)	21 (10.9)
Median (Q1, Q3)	30 (14.2, 33.7)	24 (10.9, 30.9)	22 (8.9, 30.9)
Min, Max	4.0, 38.9	3.9, 38.9	0.6, 38.1
Cohort entry 2020 (months of follow-up[a])			
n	35	188	101
Mean (SD)	16 (6.9)	15 (6.8)	15 (6.1)
Median (Q1, Q3)	17 (8.6, 21.0)	16 (8.9, 20.9)	15 (8.9, 18.9)
Min, Max	5.4, 26.9	1.5, 26.9	4.4, 26.9
Cohort entry 2021 (months of follow-up[a])			
n	26	182	89
Mean (SD)	10 (3.1)	8 (3.3)	8 (3.5)
Median (Q1, Q3)	9 (7.9, 13.0)	7 (5.9, 10.9)	7 (5.9, 10.9)
Min, Max	3.9, 14.9	0.5, 14.9	2.8, 14.9

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine.

[a] Follow-up for the HSTCL used an “ever exposed, always at risk” approach.

Analysis Table 4.1.1: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2013[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=2	N=64	N=59
Withdrawal from registry	0 (0.0)	4 (6.3)	3 (5.1)
Death	0 (0.0)	1 (1.6)	4 (6.8)
End of study period	0 (0.0)	7 (10.9)	12 (20.3)
Total or partial colectomy for any cause	0 (0.0)	5 (7.8)	2 (3.4)
ACN or CRC diagnosis	0 (0.0)	2 (3.1)	1 (1.7)
Lost to follow-up[b]	1 (50.0)	25 (39.1)	30 (50.8)
Initiation of vedolizumab or other novel biologic agents	1 (50.0)	20 (31.3)	7 (11.9)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.2: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2014[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=77	N=203	N=233
Withdrawal from registry	6 (7.8)	12 (5.9)	22 (9.4)
Death	0 (0.0)	2 (1.0)	2 (0.9)
End of study period	13 (16.9)	35 (17.2)	34 (14.6)
Total or partial colectomy for any cause	6 (7.8)	13 (6.4)	2 (0.9)
ACN or CRC diagnosis	0 (0.0)	1 (0.5)	2 (0.9)
Lost to follow-up[b]	31 (40.3)	94 (46.3)	134 (57.5)
Initiation of vedolizumab or other novel biologic agents	21 (27.3)	46 (22.7)	37 (15.9)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.3: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2015[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=67	N=238	N=247
Withdrawal from registry	1 (1.5)	15 (6.3)	11 (4.5)
Death	1 (1.5)	2 (0.8)	1 (0.4)
End of study period	13 (19.4)	37 (15.5)	50 (20.2)
Total or partial colectomy for any cause	1 (1.5)	7 (2.9)	6 (2.4)
ACN or CRC diagnosis	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up[b]	20 (29.9)	91 (38.2)	125 (50.6)
Initiation of vedolizumab or other novel biologic agents	31 (46.3)	86 (36.1)	54 (21.9)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.4: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2016[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=71	N=232	N=214
Withdrawal from registry	1 (1.4)	5 (2.2)	5 (2.3)
Death	0 (0.0)	0 (0.0)	3 (1.4)
End of study period	19 (26.8)	40 (17.2)	54 (25.2)
Total or partial colectomy for any cause	1 (1.4)	11 (4.7)	5 (2.3)
ACN or CRC diagnosis	1 (1.4)	1 (0.4)	1 (0.5)
Lost to follow-up[b]	23 (32.4)	82 (35.3)	100 (46.7)
Initiation of vedolizumab or other novel biologic agents	26 (36.6)	93 (40.1)	46 (21.5)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.5: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2017[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=75	N=232	N=169
Withdrawal from registry	2 (2.7)	4 (1.7)	2 (1.2)
Death	0 (0.0)	2 (0.9)	3 (1.8)
End of study period	15 (20.0)	55 (23.7)	38 (22.5)
Total or partial colectomy for any cause	2 (2.7)	7 (3.0)	0 (0.0)
ACN or CRC diagnosis	0 (0.0)	1 (0.4)	0 (0.0)
Lost to follow-up[b]	19 (25.3)	87 (37.5)	90 (53.3)
Initiation of vedolizumab or other novel biologic agents	37 (49.3)	76 (32.8)	35 (20.7)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	1 (0.6)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed "lost to follow-up" and censored 6 months after the last follow-up visit.

Analysis Table 4.1.6: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2018[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=63	N=196	N=135
Withdrawal from registry	1 (1.6)	1 (0.5)	4 (3.0)
Death	0 (0.0)	1 (0.5)	1 (0.7)
End of study period	15 (23.8)	38 (19.4)	38 (28.1)
Total or partial colectomy for any cause	0 (0.0)	3 (1.5)	0 (0.0)
ACN or CRC diagnosis	1 (1.6)	0 (0.0)	0 (0.0)
Lost to follow-up[b]	30 (47.6)	84 (42.9)	71 (52.6)
Initiation of vedolizumab or other novel biologic agents	16 (25.4)	69 (35.2)	21 (15.6)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.7: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2019[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=58	N=202	N=133
Withdrawal from registry	1 (1.7)	3 (1.5)	2 (1.5)
Death	1 (1.7)	0 (0.0)	0 (0.0)
End of study period	28 (48.3)	59 (29.2)	39 (29.3)
Total or partial colectomy for any cause	0 (0.0)	7 (3.5)	1 (0.8)
ACN or CRC diagnosis	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up[b]	18 (31.0)	76 (37.6)	65 (48.9)
Initiation of vedolizumab or other novel biologic agents	10 (17.2)	57 (28.2)	26 (19.5)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.8: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2020[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=35	N=188	N=101
Withdrawal from registry	0 (0.0)	2 (1.1)	0 (0.0)
Death	0 (0.0)	1 (0.5)	0 (0.0)
End of study period	13 (37.1)	64 (34.0)	38 (37.6)
Total or partial colectomy for any cause	0 (0.0)	4 (2.1)	2 (2.0)
ACN or CRC diagnosis	0 (0.0)	1 (0.5)	0 (0.0)
Lost to follow-up[b]	12 (34.3)	69 (36.7)	53 (52.5)
Initiation of vedolizumab or other novel biologic agents	10 (28.6)	47 (25.0)	8 (7.9)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.9: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2021[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=26	N=182	N=89
Withdrawal from registry	0 (0.0)	1 (0.5)	1 (1.1)
Death	0 (0.0)	2 (1.1)	0 (0.0)
End of study period	13 (50.0)	124 (68.1)	65 (73.0)
Total or partial colectomy for any cause	1 (3.8)	3 (1.6)	0 (0.0)
ACN or CRC diagnosis	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up[b]	10 (38.5)	39 (21.4)	22 (24.7)
Initiation of vedolizumab or other novel biologic agents	2 (7.7)	13 (7.1)	1 (1.1)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.1.10: Reasons for End of Follow-up for All Outcomes Except HTSCL: Cohort Entry, 2013-2021[a]

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Withdrawal from registry	12 (2.5)	47 (2.7)	50 (3.6)
Death	2 (0.4)	11 (0.6)	14 (1.0)
End of study period	129 (27.2)	459 (26.4)	368 (26.7)
Total or partial colectomy for any cause	11 (2.3)	60 (3.5)	18 (1.3)
ACN or CRC diagnosis	2 (0.4)	6 (0.3)	4 (0.3)
Lost to follow-up[b]	164 (34.6)	647 (37.2)	690 (50.0)
Initiation of vedolizumab or other novel biologic agents	154 (32.5)	507 (29.2)	235 (17.0)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	1 (0.1)

Abbreviations: ACN, advanced colonic neoplasia; CRC, colorectal cancer; GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts are not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] The outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.1: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2013

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=2	N=64	N=59
Withdrawal from registry	0 (0.0)	5 (7.8)	4 (6.8)
Death	0 (0.0)	1 (1.6)	4 (6.8)
End of study period	0 (0.0)	8 (12.5)	13 (22.0)
Lost to follow-up[a]	1 (50.0)	30 (46.9)	31 (52.5)
Initiation of vedolizumab or other novel biologic agents	1 (50.0)	20 (31.3)	7 (11.9)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.2: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2014

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=77	N=203	N=233
Withdrawal from registry	7 (9.1)	14 (6.9)	22 (9.4)
Death	0 (0.0)	2 (1.0)	2 (0.9)
End of study period	18 (23.4)	36 (17.7)	37 (15.9)
Lost to follow-up[a]	31 (40.3)	101 (49.8)	135 (57.9)
Initiation of vedolizumab or other novel biologic agents	21 (27.3)	50 (24.6)	37 (15.9)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.3: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2015

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=67	N=238	N=247
Withdrawal from registry	1 (1.5)	15 (6.3)	11 (4.5)
Death	1 (1.5)	2 (0.8)	1 (0.4)
End of study period	13 (19.4)	40 (16.8)	51 (20.6)
Lost to follow-up[a]	20 (29.9)	93 (39.1)	127 (51.4)
Initiation of vedolizumab or other novel biologic agents	32 (47.8)	88 (37.0)	57 (23.1)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.4: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2016

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=71	N=232	N=214
Withdrawal from registry	1 (1.4)	7 (3.0)	6 (2.8)
Death	0 (0.0)	2 (0.9)	3 (1.4)
End of study period	19 (26.8)	41 (17.7)	55 (25.7)
Lost to follow-up[a]	23 (32.4)	87 (37.5)	103 (48.1)
Initiation of vedolizumab or other novel biologic agents	28 (39.4)	95 (40.9)	47 (22.0)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.5: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2017

	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
Reason, n (%)	**N=75**	**N=232**	**N=169**
Withdrawal from registry	3 (4.0)	5 (2.2)	2 (1.2)
Death	0 (0.0)	2 (0.9)	3 (1.8)
End of study period	15 (20.0)	55 (23.7)	38 (22.5)
Lost to follow-up[a]	20 (26.7)	89 (38.4)	90 (53.3)
Initiation of vedolizumab or other novel biologic agents	37 (49.3)	81 (34.9)	35 (20.7)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	1 (0.6)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.6: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2018

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=63	N=196	N=135
Withdrawal from registry	1 (1.6)	2 (1.0)	4 (3.0)
Death	0 (0.0)	1 (0.5)	1 (0.7)
End of study period	16 (25.4)	38 (19.4)	38 (28.1)
Lost to follow-up[a]	30 (47.6)	86 (43.9)	71 (52.6)
Initiation of vedolizumab or other novel biologic agents	16 (25.4)	69 (35.2)	21 (15.6)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.7: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2019

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=58	N=202	N=133
Withdrawal from registry	1 (1.7)	3 (1.5)	2 (1.5)
Death	1 (1.7)	0 (0.0)	0 (0.0)
End of study period	28 (48.3)	59 (29.2)	39 (29.3)
Lost to follow-up[a]	18 (31.0)	79 (39.1)	65 (48.9)
Initiation of vedolizumab or other novel biologic agents	10 (17.2)	61 (30.2)	27 (20.3)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.8: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2020

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=35	N=188	N=101
Withdrawal from registry	0 (0.0)	2 (1.1)	0 (0.0)
Death	0 (0.0)	1 (0.5)	0 (0.0)
End of study period	13 (37.1)	66 (35.1)	39 (38.6)
Lost to follow-up[a]	12 (34.3)	71 (37.8)	54 (53.5)
Initiation of vedolizumab or other novel biologic agents	10 (28.6)	48 (25.5)	8 (7.9)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.9: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2021

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=26	N=182	N=89
Withdrawal from registry	0 (0.0)	1 (0.5)	1 (1.1)
Death	0 (0.0)	2 (1.1)	0 (0.0)
End of study period	14 (53.8)	126 (69.2)	65 (73.0)
Lost to follow-up[a]	10 (38.5)	40 (22.0)	22 (24.7)
Initiation of vedolizumab or other novel biologic agents	2 (7.7)	13 (7.1)	1 (1.1)
Prescription of 2 anti-TNFα on at the same date	0 (0.00)	0 (0.00)	0 (0.0)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 4.2.10: Reasons for End of Follow-up for HSTCL Outcome: Cohort Entry, 2013-2021

Reason, n (%)	Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=474	N=1,737	N=1,380
Withdrawal from registry	14 (3.0)	54 (3.1)	52 (3.8)
Death	2 (0.4)	13 (0.7)	14 (1.0)
End of study period	136 (28.7)	469 (27.0)	375 (27.2)
Lost to follow-up[a]	165 (34.8)	676 (38.9)	698 (50.6)
Initiation of vedolizumab or other novel biologic agents	157 (33.1)	525 (30.2)	240 (17.4)
Prescription of 2 anti-TNFα agents on the same date	0 (0.00)	0 (0.00)	1 (0.1)

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Study cohorts were not mutually exclusive. Patients could qualify for more than 1 cohort if they met all applicable criteria.

[a] Patients who had no recorded follow-up visit for at least 13 months after the last clinical contact (ie, missed 2 follow-up visits) were deemed “lost to follow-up” and censored 6 months after the last follow-up visit.

Analysis Table 5.1: Patterns of Persistence and Changing of Study Medications Over Time After Cohort Entry for All Outcomes Except HSTCL[a]

Characteristic	First Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=275 [b]	N=1,141 [b]	N=1,380 [b]
Months on GLM			
n	275	70	131
Mean (SD)	24.7 (25.9)	20.7 (21.7)	18.7 (19.7)
Median (Q1, Q3)	13.9 (4.1, 33.9)	11.5 (5.9, 31.1)	9.9 (4.0, 29.9)
Min, Max	0.0, 92.6	0.9, 90.9	0.0, 94.1
Months on any other anti-TNFα agent			
n	71	1,141	537
Mean (SD)	21.5 (22.6)	25.7 (24.9)	23.6 (23.0)
Median (Q1, Q3)	12.0 (5.0, 30.2)	15.9 (6.4, 37.0)	14.0 (5.5, 37.0)
Min, Max	0.0, 79.9	0.0, 101.8	0.0, 100.2
Months on TP[c]			
n	53	338	1,380
Mean (SD)	18.4 (21.1)	25.2 (25.6)	30.7 (27.3)
Median (Q1, Q3)	8.3 (3.0, 29.0)	13.9 (4.0, 45.9)	22.0 (6.8, 52.0)
Min, Max	0.0, 80.2	0.0, 100.0	0.0, 102.3
Months to first change[d]			
n	275	1,141	1,380
Mean (SD)	24.3 (26.0)	22.5 (23.4)	29.0 (26.8)
Median (Q1, Q3)	13.2 (4.0, 33.9)	13.0 (5.2, 31.9)	19.9 (6.0, 48.3)
Min, Max	0.0, 92.6	0.0, 100.8	0.0, 102.1
Months to second change[e]			
n	101	439	643
Mean (SD)	29.5 (25.7)	31.4 (25.9)	32.5 (25.9)
Median (Q1, Q3)	22.0 (8.3, 45.6)	24.0 (9.9, 49.2)	25.0 (10.0, 51.0)
Min, Max	1.0, 95.0	0.0, 101.0	0.0, 101.2

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha, TP, thiopurine.

Note: This table categorizes the study population into the 3 groups based on the exposure that first qualified the patient for study entry (ie, by their first study cohort). The results presented reflects drug utilization as documented in the ENEIDA record and does not necessarily reflect person-time attributable to exposure categories used in analyses of study outcomes. Utilization was assessed from the time of first cohort entry until the first censoring event for the outcomes of colectomy due to intractable disease or ACN.

Note: All patients contributed at least 1 day on each therapy. Minimum values of 0.0 reflect a rounding issue: 1 day represents 0.03 of a month, which rounds to 0.0 months.

[a] These outcomes include colectomy due to intractable disease, ACN and CRC.

[b] Number of patients who entered the study based on use of this study exposure.

[c] Time on TP reflects periods during primary therapy (ie, without anti-TNFα therapies) or when TP was received as concomitant therapy to anti-TNFα therapies.

[d] Months to first addition or subtraction of a drug that could have qualified for study entry. For patients who joined the study in the GLM or other anti-TNFα agent cohorts, the first change may have involved adding TP to the baseline biologic therapy (or stopping the TP if it was concomitant therapy at baseline). However, switching from adalimumab to infliximab (or vice versa) in the other anti-TNFα agent cohort was not counted as a change. Switching from GLM to one of the other anti-TNFα agents (or vice versa), on the other hand, would count.

[e] Months to second addition or subtraction of a study cohort drug. Same considerations for addition and subtraction described in footnote d apply here as well.

Analysis Table 5.2: Patterns of Persistence and Changing of Study Medications Over Time After Cohort Entry for HSTCL Outcome

Characteristic	First Study Cohort		
	GLM	Other Anti-TNFα Agents	TP
	N=275 [a]	N=1,141 [a]	N=1,380 [a]
Months on GLM			
n	275	71	131
Mean (SD)	24.7 (25.9)	20.6 (21.6)	18.7 (19.7)
Median (Q1, Q3)	13.9 (4.1, 33.9)	12.0 (5.9, 31.1)	9.9 (4.0, 29.9)
Min, Max	0.0, 92.6	0.9, 90.9	0.0, 94.1
Months on any other anti-TNFα agent			
n	71	1,141	538
Mean (SD)	21.6 (22.6)	25.8 (25.0)	23.7 (23.0)
Median (Q1, Q3)	12.0 (5.0, 30.2)	16.0 (6.4, 37.0)	14.1 (5.9, 37.0)
Min, Max	0.0, 79.9	0.0, 101.8	0.0, 100.2
Months on TP[b]			
n	53	340	1,380
Mean (SD)	18.4 (21.1)	25.4 (25.9)	30.9 (27.4)
Median (Q1, Q3)	8.3 (3.0, 29.0)	13.9 (4.0, 46.7)	22.1 (6.9, 52.0)
Min, Max	0.0, 80.2	0.0, 100.0	0.0, 102.3
Months to first change[c]			
n	275	1,141	1,380
Mean (SD)	24.3 (26.0)	22.6 (23.5)	29.1 (26.8)
Median (Q1, Q3)	13.2 (4.0, 33.9)	13.0 (5.0, 31.9)	20.0 (6.0, 48.6)
Min, Max	0.0, 92.6	0.0, 100.8	0.0, 102.1
Months to second change[d]			
n	101	442	644
Mean (SD)	29.6 (25.7)	31.8 (26.1)	32.7 (26.0)
Median (Q1, Q3)	22.0 (8.3, 45.6)	24.0 (9.9, 49.9)	25.0 (10.1, 51.0)
Min, Max	1.0, 95.0	0.0, 101.0	0.0, 101.2

Abbreviations: GLM, golimumab; HSTCL, hepatosplenic T-cell lymphoma; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha, TP, thiopurine.

Note: This table categorizes the study population into the 3 groups based on the exposure that first qualified the patient for study entry (ie, by their first study cohort). The results presented reflects drug utilization as documented in the ENEIDA record and does not necessarily reflect person-time attributable to exposure categories used in analyses of study outcomes. Utilization was assessed from the time of first cohort entry until the first censoring event for the outcome of HSTCL.

Note: All patients contributed at least 1 day on each therapy. Minimum values of 0.0 reflect a rounding issue: 1 day represents 0.03 of a month, which rounds to 0.0 months.

[a] Number of patients who entered study based on use of this study medication.

[b] Time on TP reflects periods during primary therapy (ie, without anti-TNFα therapies) or when TP was received as concomitant therapy to anti-TNFα therapies.

[c] Months to first addition or subtraction of a drug that could have qualified for study entry. For patients who joined the study in the GLM or other anti-TNFα gent cohorts, the first change may have involved adding TP to the baseline biologic therapy (or stopping the TP if it was concomitant therapy at baseline). However, switching from adalimumab to infliximab (or vice versa) in the other anti-TNFα agent cohort was not counted as a change. Switching from GLM to one of the other anti-TNFα agents (or vice versa), on the other hand, would count.

[d] Months to second addition or subtraction of a study cohort drug. Same considerations for addition and subtraction described in footnote c apply here as well.

Analysis Table 6.1.1: Crude Incidence Rates for Colectomy Due to Intractable Disease by Mutually Exclusive Exposure Category

Statistic	Exposure Category			
	GLM Only	Other Anti-TNFα Agents Only	GLM+Other Anti-TNFα Agents	No Anti-TNFα Agent Exposure[a]
Colectomy due to intractable disease				
n	4	47	3	10
Person-years	912.3	3,791.9	38.2	770.2
IR per 1,000 PY	4.4	12.4	78.6	13.0
95% CI	1.2, 11.2	9.1, 16.5	16.2, 229.7	6.2, 23.9

Abbreviations: CI, confidence interval; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha.

Notes: PY were calculated based on the risk window described in Section 9.3.1.1. Because patients may have changed therapy during the study, patients may have contributed to more than 1 exposure category during follow-up.

[a] Refers to person-time when there was no exposure to GLM or other anti-TNFα agents between episodes of GLM or other anti-TNFα agent use.

Analysis Table 6.1.2: Crude Incidence Rates for Neoplasia Outcomes by Exposure Category

Outcome	Exposure Category		
	GLM	Other Anti-TNFα Agents	TP
Advanced colorectal neoplasia[a]			
n	2	6	4
Person-years	1,347.8	4,637.2	3,871.8
IR per 1,000 PY	1.5	1.3	1.0
95% CI	0.2, 5.4	0.5, 2.8	0.3, 2.6
Colorectal cancer[b]			
n	2	2	3
Person-years	1,347.8	4,637.2	3,871.8
IR per 1,000 PY	1.5	0.4	0.8
95% CI	0.2, 5.4	0.1, 1.6	0.2, 2.3
Hepatosplenic T-cell lymphoma			
n	0	0	0
Person-years	1,393.2	4,798.9	3,892.0
IR per 1,000 PY	0.0	0.0	0.0
95% CI	0.0, 2.6	0.0, 0.8	0.0, 0.9

Abbreviations: ACN, advanced colorectal neoplasia; CI, confidence interval; CRC, colorectal cancer; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: PY at risk were specific to each outcome and based on the applicable risk window for each outcome. Patients could have been exposed to more than 1 study drug during the course of follow-up; because risk windows could overlap, a single outcome could be attributed to more than 1 exposure category.

[a] Across all exposure categories, there were 10 unique occurrences of ACN.

[b] Across all exposure categories, there were 6 unique occurrences of CRC.

Analysis Table 6.2.1.1: Crude Incidence Rates for Colectomy Due to Intractable Disease for Patients Exposed to Other Anti-TNFα Agents; Initiator of Infliximab or Biosimilars: Yes

Statistic	Exposure Category			
	GLM Only	Other Anti-TNFα Agents Only	GLM+Other Anti-TNFα Agents	No Anti-TNFα Agent Exposure[a]
Colectomy due to intractable disease				
n	2	41	2	5
Person-years	144.9	2,455.9	28.1	490.5
IR per 1,000 PY	13.8	16.7	71.1	10.2
95% CI	1.7, 49.9	12.0, 22.6	8.6, 256.8	3.3, 23.8

Abbreviations: CI, confidence interval; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha.

Notes: PY were calculated based on the risk window described in Section 9.3.1.1. Because patients may have changed therapy during the study, patients may have contributed to more than 1 exposure category during follow-up.

[a] Refers to person-time when there was no exposure to GLM or other anti-TNFα agents between episodes of GLM or other anti-TNFα agent use.

Analysis Table 6.2.1.2: Crude Incidence Rates for Neoplasia Outcomes for Patients Exposed to Other Anti-TNFα Agents; Initiator of Infliximab or Biosimilars: Yes

Outcome	Exposure Category		
	GLM	Other Anti-TNFα Agents	TP
Advanced colorectal neoplasia			
n	1	5	1
Person-years	401.4	2,998.3	969.2
IR per 1,000 PY	2.5	1.7	1.0
95% CI	0.1, 13.9	0.5, 3.9	0.0, 5.7
Colorectal cancer			
n	1	1	0
Person-years	401.4	2,998.3	969.2
IR per 1,000 PY	2.5	0.3	0.0
95% CI	0.1, 13.9	0.0, 1.9	0.0, 3.8
Hepatosplenic T-cell lymphoma			
n	0	0	0
Person-years	430.4	3,126.2	982.5
IR per 1,000 PY	0.0	0.0	0.0
95% CI	0.0, 8.6	0.0, 1.2	0.0, 3.8

Abbreviations: CI, confidence interval; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: PY at risk were specific to each outcome and based on the applicable risk window for each outcome. Patients could have been exposed to more than 1 study drug during the course of follow-up; because risk windows could overlap, a single outcome could be attributed to more than 1 exposure category.

Analysis Table 6.2.2.1: Crude Incidence Rates for Colectomy Due to Intractable Disease for Patients Exposed to Other Anti-TNFα Agents; Initiator of Adalimumab or Biosimilars: Yes

Statistic	Exposure Category			
	GLM Only	Other Anti-TNFα Agents Only	GLM+Other Anti-TNFα Agents	No Anti-TNFα Agent Exposure [a]
Colectomy due to intractable disease				
n	0	7	1	3
Person-years	86.8	1,424.7	13.8	215.7
IR per 1,000 PY	0.0	4.9	72.3	13.9
95% CI	0.0, 42.5	2.0, 10.1	1.8, 403.0	2.9, 40.6

Abbreviations: CI, confidence interval; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha.

Notes: PY were calculated based on the risk window described in Section 9.3.1.1. Because patients may have changed therapy during the study, patients may have contributed to more than 1 exposure category during follow-up.

[a] Refers to person-time when there was no exposure to GLM or other anti-TNFα agents between episodes of GLM or other anti-TNFα agent use.

Analysis Table 6.2.2.2: Crude Incidence Rates for Neoplasia Outcomes for Patients Exposed to Other Anti-TNFα Agents; Initiator of Adalimumab or Biosimilars: Yes

Outcome	Exposure Category		
	GLM	Other Anti-TNFα Agents	TP
Advanced colorectal neoplasia			
n	0	1	0
Person-years	151.7	1,641.1	358.0
IR per 1,000 PY	0.0	0.6	0.0
95% CI	0.0, 24.3	0.0, 3.4	0.0, 10.3
Colorectal cancer			
n	0	1	0
Person-years	151.7	1,641.1	358.0
IR per 1,000 PY	0.0	0.6	0.0
95% CI	0.0, 24.3	0.0, 3.4	0.0, 10.3
Hepatosplenic T-cell lymphoma			
n	0	0	0
Person-years	152.0	1,674.8	358.1
IR per 1,000 PY	0.0	0.0	0.0
95% CI	0.0, 24.3	0.0, 2.2	0.0, 10.3

Abbreviations: CI, confidence interval; GLM, golimumab; IR, incidence rate; PY, person-years; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: PY at risk were specific to each outcome and based on the applicable risk window for each outcome. Patients could have been exposed to more than 1 study drug during the course of follow-up; because risk windows could overlap, a single outcome could be attributed to more than 1 exposure category.

Analysis Table 7.1: Crude Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease

Comparison	Poisson Model	Cox Model
	Crude IRR (95% CI)	Crude HR (95% CI)
GLM only vs other anti-TNFα agents only	0.35 (0.13, 0.98)	0.37 (0.13, 1.02)
GLM only vs (GLM+other anti-TNFα agents)	0.06 (0.01, 0.25)	0.07 (0.02, 0.31)
GLM only vs no anti-TNFα agent exposure	NA	0.09 (0.03, 0.31)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	6.34 (1.97, 20.37)	5.33 (1.64, 17.34)
(GLM+other anti-TNFα agents) vs no anti-TNFα agents exposure	NA	1.33 (0.35, 5.06)
Other anti-TNFα agents only vs no anti-TNFα agent exposure	NA	0.25 (0.12, 0.53)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NA, not applicable; TNFα, tumor necrosis factor alpha.

Notes: Statistics are by study exposure and use the applicable risk window of follow-up time specific to the outcome. Incidence rate ratios and 95% CIs were derived from a single univariable Poisson regression with log-time offset considering only time exposed to at least 1 study drug. Hazard ratios and 95% CIs were derived from a single univariable Cox regression model. Only exposure categories present in the data were included in regression models.

Analysis Table 7.2: Crude Hazard Ratios for Advanced Colorectal Neoplasia

Comparison	Cox Model
	Crude HR (95% CI)
GLM vs other anti-TNFα agents	1.16 (0.23, 5.73)
GLM only vs TP	1.46 (0.27, 8.00)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: Statistics are by study exposure and use the applicable risk window of follow-up time specific to the outcome. Results were derived from a single univariable Cox regression model. Only exposure categories present in the data will be included in regression models.

Analysis Table 7.3: Crude Hazard Ratios for Colorectal Cancer

Comparison	Cox Model
	Crude HR (95% CI)
GLM vs other anti-TNFα agents	3.42 (0.48, 24.26)
GLM only vs TP	1.92 (0.32, 11.50)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Notes: Statistics are by study exposure and use the applicable risk window of follow-up time specific to the outcome. Results were derived from a single univariable Cox regression model. Only exposure categories present in the data will be included in regression models.

Analysis Table 8.1: Candidate Variable Screening for Inclusion in a Multivariable Model Based on Univariable Association With Colectomy Due to Intractable Disease

Candidate Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Age group		
35 to <65 years vs 18 to <35 years	1.10 (0.57, 2.11)	0.94 (0.52, 1.67)
≥65 years vs 18 to <35 years	2.32 (0.97, 5.54)	2.12 (1.01, 4.45)
Sex (male vs female)	1.56 (0.89, 2.73)	1.37 (0.83, 2.26)
Calendar year of cohort entry		
2013-2015 vs 2019-2021	0.65 (0.32, 1.34)	1.59 (0.82, 3.05)
2016-2018 vs 2019-2021	0.72 (0.35, 1.48)	1.16 (0.60, 2.27)
UC duration in years[a]		
≥67th percentile vs <33rd percentile	0.50 (0.26, 0.95)	0.55 (0.31, 0.99)
33rd to <67th percentile vs <33rd percentile	0.48 (0.24, 0.93)	0.45 (0.24, 0.84)
Maximum extent of disease		
Extensive vs left side only	1.41 (0.78, 2.57)	1.61 (0.92, 2.81)
Proctitis vs left side only	0.39 (0.05, 2.95)	0.70 (0.16, 3.00)
Not recorded vs left side only	1.86 (0.61, 5.63)	1.60 (0.54, 4.72)
Prior treatment with steroids (yes vs no)	1.38 (0.77, 2.47)	1.56 (0.90, 2.69)
Prior treatment with cyclosporine (yes vs no)	3.46 (1.72, 6.98)	3.66 (1.99, 6.73)
Hospitalized for UC (yes vs no)	1.44 (0.79, 2.63)	1.27 (0.73, 2.21)
Prior diagnosis with PSC (yes vs no)	0.50 (0.21, 1.19)	NE
Prior screening colonoscopy (yes vs no)	NE	0.62 (0.30, 1.31)
Number of previous anti-TNFα agents		
1 vs 0	NE	2.14 (1.16, 3.96)
≥2 vs 0	NE	NE
Recent switcher after use of another anti-TNFα agent[b]		
After short-term use (≤3 months) vs did not switch	NE	3.74 (0.51, 27.51)
After long-term use (>3 months) vs did not switch	6.04 (1.47, 24.86)	6.71 (1.60, 28.26)

Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; NE, not estimable; PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Each row represents a separate univariable model assessing the association of each candidate variable with the outcome of interest. Incidence rate ratios and 95% confidence intervals were derived from Poisson regression models with log-time offset. Hazard ratios and 95% confidence intervals were derived from a Cox regression model.

[a] UC duration was continually updated, as described in the report. At the start of the treatment (ie, at baseline), the 33rd percentile for UC duration was 2.0 years, and the 67th percentile was 8.6 years.

[b] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Analysis Table 8.1.1: Incidence Rates of Colectomy Due to Intractable Disease Stratified by Potential Confounding Variables One at a Time

Candidate Variables	Exposure								
	GLM Only			Other Anti-TNFα Agents Only			GLM+Other Anti-TNFα Agents		
	n	PY	IR (95% CI)	n	PY	IR (95% CI)	n	PY	IR (95% CI)
Age group									
18 to <35 years	0	207	0.0 (0.0-17.8)	10	1,120	8.9 (4.3-16.4)	3	11	271.6 (56.0-793.8)
35 to <65 years	4	634	6.3 (1.7-16.2)	28	2,348	11.9 (7.9-17.2)	0	23	0.0 (0.0-162.1)
≥65 years	0	72	0.0 (0.0-51.4)	9	324	27.8 (12.7-52.8)	0	4	0.0 (0.0-843.5)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
Sex									
Male	3	431	7.0 (1.4-20.3)	28	2,026	13.8 (9.2-20.0)	3	19	155.5 (32.1-454.4)
Female	1	481	2.1 (0.1-11.6)	19	1,766	10.8 (6.5-16.8)	0	19	0.0 (0.0-195.4)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
Calendar year of cohort entry									
2013-2015	1	135	7.4 (0.2-41.3)	11	637	17.3 (8.6-30.9)	0	5	0.0 (0.0-711.9)
2016-2018	3	395	7.6 (1.6-22.2)	15	1,667	9.0 (5.0-14.8)	3	17	178.0 (36.7-520.1)
2019-2021	0	383	0.0 (0.0-9.6)	21	1,488	14.1 (8.7-21.6)	0	16	0.0 (0.0-228.6)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
UC duration in years									
<33rd percentile	1	186	5.4 (0.1-30.0)	22	1,202	18.3 (11.5-27.7)	2	13	156.1 (18.9-563.8)
33rd to <67th percentile	2	338	5.9 (0.7-21.4)	12	1,341	9.0 (4.6-15.6)	1	13	79.5 (2.0-443.0)
≥67th percentile	1	389	2.6 (0.1-14.3)	13	1,249	10.4 (5.5-17.8)	0	13	0.0 (0.0-288.5)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)

Analysis Table 8.1.1: Incidence Rates of Colectomy Due to Intractable Disease Stratified by Potential Confounding Variables One at a Time

Candidate Variables	Exposure								
	GLM Only			Other Anti-TNFα Agents Only			GLM+Other Anti-TNFα Agents		
	n	PY	IR (95% CI)	n	PY	IR (95% CI)	n	PY	IR (95% CI)
Maximum extent of disease									
Extensive	1	464	2.2 (0.1-12.0)	29	1,939	15.0 (10.0-21.5)	2	18	108.3 (13.1-391.3)
Left side only	3	350	8.6 (1.8-25.1)	13	1,449	9.0 (4.8-15.3)	1	15	64.8 (1.6-361.2)
Proctitis	0	54	0.0 (0.0-67.7)	1	218	4.6 (0.1-25.5)	0	3	0.0 (0.0-1281.7)
Not recorded	0	44	0.0 (0.0-84.7)	4	185	21.6 (5.9-55.4)	0	1	0.0 (0.0-2621.8)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
Prior treatment with steroids (yes vs no)									
No	3	408	7.4 (1.5-21.5)	13	1,417	9.2 (4.9-15.7)	1	14	71.2 (1.8-396.5)
Yes	1	505	2.0 (0.1-11.0)	34	2,375	14.3 (9.9-20.0)	2	24	82.9 (10.0-299.5)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
Prior treatment with cyclosporine (yes vs no)									
No	3	846	3.6 (0.7-10.4)	38	3,533	10.8 (7.6-14.8)	2	37	54.3 (6.6-196.3)
Yes	1	66	15.1 (0.4-84.1)	9	259	34.8 (15.9-66.0)	1	1	728.7 (18.4-4059.8)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
Hospitalized for UC									
No	3	718	4.2 (0.9-12.2)	32	2,925	10.9 (7.5-15.4)	3	29	105.1 (21.7-307.2)
Yes	1	194	5.2 (0.1-28.7)	15	867	17.3 (9.7-28.6)	0	10	0.0 (0.0-382.8)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)

Analysis Table 8.1.1: Incidence Rates of Colectomy Due to Intractable Disease Stratified by Potential Confounding Variables One at a Time

Candidate Variables	Exposure								
	GLM Only			Other Anti-TNFα Agents Only			GLM+Other Anti-TNFα Agents		
	n	PY	IR (95% CI)	n	PY	IR (95% CI)	n	PY	IR (95% CI)
Prior diagnosis with PSC									
No	2	357	5.6 (0.7-20.2)	12	1,137	10.6 (5.5-18.4)	0	13	0.0 (0.0-291.5)
Yes	0	5	0.0 (0.0-697.0)	0	35	0.0 (0.0-104.9)	0	1	0.0 (0.0-2611.1)
Unknown/missing	2	550	3.6 (0.4-13.1)	35	2,620	13.4 (9.3-18.6)	3	24	124.4 (25.7-363.6)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
Prior screening colonoscopy									
No	4	695	5.8 (1.6-14.7)	41	3,075	13.3 (9.6-18.1)	3	29	104.6 (21.6-305.7)
Yes	0	217	0.0 (0.0-17.0)	6	717	8.4 (3.1-18.2)	0	9	0.0 (0.0-388.5)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)
Number of previous anti-TNFα agents									
0	2	582	3.4 (0.4-12.4)	40	3,135	12.8 (9.1-17.4)			
1	1	127	7.9 (0.2-43.7)	6	456	13.2 (4.8-28.7)	3	32	94.1 (19.4-275.0)
2+	1	203	4.9 (0.1-27.5)	1	201	5.0 (0.1-27.7)	0	6	0.0 (0.0-586.5)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)

Analysis Table 8.1.1: Incidence Rates of Colectomy Due to Intractable Disease Stratified by Potential Confounding Variables One at a Time

Candidate Variables	Exposure								
	GLM Only			Other Anti-TNFα Agents Only			GLM+Other Anti-TNFα Agents		
	n	PY	IR (95% CI)	n	PY	IR (95% CI)	n	PY	IR (95% CI)
Recent switcher after use of another anti-TNFα agent									
After short-term use (≤3 months)	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)			
After long-term use (>3 months)							1	8	131.1 (3.3-730.4)
Did not switch							2	31	65.5 (7.9-236.5)
Overall	4	912	4.4 (1.2-11.2)	47	3,792	12.4 (9.1-16.5)	3	38	78.6 (16.2-229.7)

Abbreviations: GLM, golimumab; CI, confidence interval; IR, incident rate; n, number of events; PSC, primary sclerosing cholangitis; PY, person-years; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Empty cells signify that there are no persons in this exposure category.

Analysis Table 8.1.2: Incidence Rate Ratios for Colectomy Due to Intractable Disease: Univariable Poisson Analyses (Overall and Stratum-Specific Mantel-Haenszel Adjusted Estimates)

Candidate Variables	GLM Only IRR (95% CI)	Other Anti-TNFα Agents Only IRR (95% CI)	GLM+Other Anti-TNFα Agents IRR (95% CI)
Age group			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.34 (0.1-1.0)	1 (Ref.)	6.11 (1.9-19.6)
% difference	-2.60%		-3.66%
Sex			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.36 (0.1-1.0)	1 (Ref.)	6.39 (2.0-20.5)
% difference	2.59%		0.77%
Calendar year of cohort entry			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.36 (0.1-1.0)	1 (Ref.)	6.40 (2.0-20.6)
% difference	1.09%		0.90%
UC duration in years			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.38 (0.1-1.1)	1 (Ref.)	6.25 (1.9-20.1)
% difference	8.00%		-1.44%
Maximum extent of disease			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.35 (0.1-1.0)	1 (Ref.)	6.55 (2.0-21.1)
% difference	0.21%		3.29%
Prior treatment with steroids (yes vs no)			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.36 (0.1-1.0)	1 (Ref.)	6.33 (2.0-20.3)
% difference	0.62%		-0.23%
Prior treatment with cyclosporine (yes vs no)			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.35 (0.1-1.0)	1 (Ref.)	6.77 (2.1-21.7)
% difference	-0.91%		6.80%
Hospitalized for UC			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.36 (0.1-1.0)	1 (Ref.)	6.27 (2.0-20.1)
% difference	0.72%		-1.17%

Analysis Table 8.1.2: Incidence Rate Ratios for Colectomy Due to Intractable Disease: Univariable Poisson Analyses (Overall and Stratum-Specific Mantel-Haenszel Adjusted Estimates)

Candidate Variables	GLM Only IRR (95% CI)	Other Anti-TNFα Agents Only IRR (95% CI)	GLM+Other Anti-TNFα Agents IRR (95% CI)
Prior diagnosis with PSC			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.36 (0.1-1.0)	1 (Ref.)	6.59 (2.1-21.1)
% difference	0.39%		3.91%
Prior screening colonoscopy			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.36 (0.1-1.0)	1 (Ref.)	6.50 (2.0-20.8)
% difference	2.99%		2.52%
Number of previous anti-TNFα agents			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.37 (0.1-1.1)	1 (Ref.)	6.63 (1.7-26.1)
% difference	3.83%		4.61%
Recent switcher after use of another anti-TNFα agent			
Overall	0.35 (0.1-1.0)	1 (Ref.)	6.34 (2.0-20.4)
Mantel-Haenszel	0.35 (0.1-1.0)	1 (Ref.)	NE
% difference	0.00%		NE

Abbreviations: GLM, golimumab; IRR, incidence rate ratio; NE, not estimable; PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Analysis Table 8.2: Candidate Variable Screening for Inclusion in a Multivariable Model Based on Univariable Association With Advanced Colorectal Neoplasia

Candidate Variable	Cox Model
	HR (95% CI)
Age group	
35 to <65 years vs 18 to <35 years	1.70 (0.35, 8.19)
≥65 years vs 18 to <35 years	5.54 (0.93, 33.19)
Sex (male vs female)	1.73 (0.52, 5.76)
Calendar year of cohort entry	
2013-2015 vs 2019-2021	0.89 (0.09, 8.47)
2016-2018 vs 2019-2021	1.05 (0.11, 9.90)
UC duration in years[a]	
≥67th percentile vs <33rd percentile	1.97 (0.36, 10.78)
33rd to <67th percentile vs <33rd percentile	2.79 (0.56, 13.80)
Maximum extent of disease	
Extensive vs left side only	0.76 (0.22, 2.61)
Proctitis vs left side only	NE
Not recorded vs left side only	3.43 (0.67, 17.68)
Prior treatment with steroids (yes vs no)	0.46 (0.15, 1.45)
Prior treatment with cyclosporine (yes vs no)	5.12 (1.38, 18.91)
Hospitalized for UC (yes vs no)	0.82 (0.18, 3.76)
Prior diagnosis with PSC (yes vs no)	NE
Prior screening colonoscopy (yes vs no)	3.06 (0.97, 9.66)
Number of previous anti-TNFα agents	
1 vs 0	NE
2 vs 0	NE

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Each row represents a separate univariable model assessing the association of each candidate variable with the outcome of interest. Hazard ratios and 95% confidence intervals were derived from a Cox regression model.

[a] UC duration was continually updated at any change in a patient's exposure category. At baseline, across the population included in this analysis, the 33rd percentile for UC duration was 1.5 years, and the 67th percentile was 7.5 years.

Analysis Table 8.2.1: Incidence Rates of Advanced Colorectal Neoplasia Stratified by Potential Confounding Variables One at a Time

Candidate Variables	Exposure								
	GLM			Other Anti-TNFα Agents			TP		
	n	PY	IR (95% CI)	n	PY	IR (95% CI)	n	PY	IR (95% CI)
Age group									
18 to <35 years	0	347	0.0 (0.0-10.6)	2	1,337	1.5 (0.2-5.4)	0	1,256	0.0 (0.0-2.9)
35 to <65 years	2	892	2.2 (0.3-8.1)	2	2,904	0.7 (0.1-2.5)	3	2,306	1.3 (0.3-3.8)
≥65 years	0	109	0.0 (0.0-33.7)	2	396	5.1 (0.6-18.2)	1	310	3.2 (0.1-18.0)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
Sex									
Male	2	663	3.0 (0.4-10.9)	4	2,455	1.6 (0.4-4.2)	2	2,112	1.0 (0.1-3.4)
Female	0	685	0.0 (0.0-5.4)	2	2,182	0.9 (0.1-3.3)	2	1,760	1.1 (0.1-4.1)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
Calendar year of cohort entry									
2013-2015	0	130	0.0 (0.0-28.4)	1	576	1.7 (0.0-9.7)	0	416	0.0 (0.0-8.9)
2016-2018	0	675	0.0 (0.0-5.5)	3	2,413	1.2 (0.3-3.6)	3	2,048	1.5 (0.3-4.3)
2019-2021	2	543	3.7 (0.4-13.3)	2	1,647	1.2 (0.1-4.4)	1	1,408	0.7 (0.0-4.0)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
UC duration in years									
<33rd percentile	0	255	0.0 (0.0-14.4)	1	1,394	0.7 (0.0-4.0)	1	1,513	0.7 (0.0-3.7)
33rd to <67th percentile	0	443	0.0 (0.0-8.3)	2	1,499	1.3 (0.2-4.8)	2	1,322	1.5 (0.2-5.5)
≥67th percentile	2	649	3.1 (0.4-11.1)	3	1,744	1.7 (0.4-5.0)	1	1,037	1.0 (0.0-5.4)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)

Analysis Table 8.2.1: Incidence Rates of Advanced Colorectal Neoplasia Stratified by Potential Confounding Variables One at a Time

Candidate Variables	Exposure								
	GLM			Other Anti-TNFα Agents			TP		
	n	PY	IR (95% CI)	n	PY	IR (95% CI)	n	PY	IR (95% CI)
Maximum extent of disease									
Extensive	1	684	1.5 (0.0-8.2)	3	2,383	1.3 (0.3-3.7)	1	1,928	0.5 (0.0-2.9)
Left side only	1	533	1.9 (0.0-10.5)	2	1,760	1.1 (0.1-4.1)	2	1,535	1.3 (0.2-4.7)
Proctitis	0	75	0.0 (0.0-49.2)	0	261	0.0 (0.0-14.1)	0	246	0.0 (0.0-15.0)
Not recorded	0	56	0.0 (0.0-65.3)	1	233	4.3 (0.1-23.9)	1	162	6.2 (0.2-34.4)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
Prior treatment with steroids (yes vs no)									
No	2	590	3.4 (0.4-12.3)	4	1,729	2.3 (0.6-5.9)	1	1,467	0.7 (0.0-3.8)
Yes	0	758	0.0 (0.0-4.9)	2	2,908	0.7 (0.1-2.5)	3	2,405	1.3 (0.3-3.6)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
Prior treatment with cyclosporine (yes vs no)									
No	2	1,263	1.6 (0.2-5.7)	4	4,283	0.9 (0.3-2.4)	3	3,707	0.8 (0.2-2.4)
Yes	0	85	0.0 (0.0-43.5)	2	354	5.6 (0.7-20.4)	1	165	6.1 (0.2-33.8)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
Hospitalized for UC									
No	2	1,071	1.9 (0.2-6.7)	4	3,553	1.1 (0.3-2.9)	4	3,283	1.2 (0.3-3.1)
Yes	0	277	0.0 (0.0-13.3)	2	1,084	1.8 (0.2-6.7)	0	589	0.0 (0.0-6.3)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)

Analysis Table 8.2.1: Incidence Rates of Advanced Colorectal Neoplasia Stratified by Potential Confounding Variables One at a Time

Candidate Variables	Exposure								
	GLM			Other Anti-TNFα Agents			TP		
	n	PY	IR (95% CI)	n	PY	IR (95% CI)	n	PY	IR (95% CI)
Prior diagnosis with PSC									
No	2	561	3.6 (0.4-12.9)	3	1,399	2.1 (0.4-6.3)	0	877	0.0 (0.0-4.2)
Yes	0	10	0.0 (0.0-360.0)	0	44	0.0 (0.0-83.3)	0	42	0.0 (0.0-88.5)
Unknown/missing	0	776	0.0 (0.0-4.8)	3	3,194	0.9 (0.2-2.7)	4	2,953	1.4 (0.4-3.5)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
Prior screening colonoscopy									
No	1	1,019	1.0 (0.0-5.5)	4	3,743	1.1 (0.3-2.7)	2	3,271	0.6 (0.1-2.2)
Yes	1	329	3.0 (0.1-16.9)	2	894	2.2 (0.3-8.1)	2	600	3.3 (0.4-12.0)
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)
Number of previous anti-TNFα agents									
0	1	888	1.1 (0.0-6.3)	4	3,964	1.0 (0.3-2.6)	4	3,872	1.0 (0.3-2.6)
1	1	332	3.0 (0.1-16.8)	1	655	1.5 (0.0-8.5)			
2+	0	128	0.0 (0.0-28.9)	1	18	56.0 (1.4-311.9)			
Overall	2	1,348	1.5 (0.2-5.4)	6	4,637	1.3 (0.5-2.8)	4	3,872	1.0 (0.3-2.6)

Abbreviations: GLM, golimumab; CI, confidence interval; IR, incident rate; n, number of events; PSC, primary sclerosing cholangitis; PY, person-years; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Note: Empty cells signify that there are no persons in this exposure category.

Analysis Table 8.2.2: Incidence Rate Ratios for Advanced Colorectal Neoplasia: Univariable Poisson Analyses (Overall and Stratum-Specific Mantel-Haenszel Adjusted Estimates)

Candidate Variables	GLM IR (95% CI)	Other Anti-TNFα Agents IR (95% CI)	TP IR (95% CI)
Age group			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.16 (0.2-5.9)	1 (Ref.)	0.82 (0.2-2.8)
% difference	1.48%		2.36%
Sex			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.19 (0.2-5.8)	1 (Ref.)	0.80 (0.2-2.8)
% difference	3.36%		-0.35%
Calendar year of cohort entry			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.13 (0.2-5.8)	1 (Ref.)	0.82 (0.2-2.9)
% difference	-1.79%		-0.37%
UC duration in years			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.02 (0.2-5.3)	1 (Ref.)	0.84 (0.2-3.1)
% difference	-10.81%		5.48%
Maximum extent of disease			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.16 (0.2-5.8)	1 (Ref.)	0.82 (0.2-2.9)
% difference	1.38%		3.19%
Prior treatment with steroids (yes vs no)			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.04 (0.2-5.3)	1 (Ref.)	0.80 (0.2-2.8)
% difference	-9.11%		-0.26%
Prior treatment with cyclosporine (yes vs no)			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.19 (0.2-6.0)	1 (Ref.)	0.92 (0.3-3.3)
% difference	3.84%		15.17%
Hospitalized for UC			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.15 (0.2-5.8)	1 (Ref.)	0.79 (0.2-2.9)
% difference	0.51%		-0.80%

Analysis Table 8.2.2: Incidence Rate Ratios for Advanced Colorectal Neoplasia: Univariable Poisson Analyses (Overall and Stratum-Specific Mantel-Haenszel Adjusted Estimates)

Candidate Variables	GLM IR (95% CI)	Other Anti-TNFα Agents IR (95% CI)	TP IR (95% CI)
Prior diagnosis with PSC			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	0.99 (0.2-5.2)	1 (Ref.)	0.80 (0.2-3.0)
% difference	-13.89%		0.22%
Prior screening colonoscopy			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	1.09 (0.2-5.5)	1 (Ref.)	0.85 (0.2-3.0)
% difference	-5.10%		6.23%
Number of previous anti-TNFα agents			
Overall	1.15 (0.3-4.6)	1 (Ref.)	0.80 (0.3-2.5)
Mantel-Haenszel	0.76 (0.2-2.8)	1 (Ref.)	1.02 (0.3-4.1)
% difference	-33.65%		-28.24%

Abbreviations: GLM, golimumab; PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; TP, thiopurines; UC, ulcerative colitis.

Analysis Table 8.3: Contingency Table of Recent Switcher After Use of Another Anti-TNFα Agent and Exposure to GLM+Other Anti-TNFα Agents

Exposure to GLM+Other Anti-TNFα Agents	Recent Switcher After Use of Another Anti-TNFα Agent [a]	
	No	Yes
No	2,928	0
Yes	0	185

Abbreviations: GLM, golimumab; TNFα, tumor necrosis factor alpha.

[a] The variable "recent switcher after use of another anti-TNFα agent" refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent. It collapses both categories shown in Table 3 (ie, "after short-term use" and "after long-term use").

Analysis Table 9.1: Adjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Multivariable Poisson and Cox Regression Models

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM only	0.40 (0.14, 1.13)	0.41 (0.15, 1.15)
GLM+other anti-TNFα agents	6.78 (2.08, 22.13)	4.95 (1.52, 16.08)
No anti-TNFα agent exposure	NA	3.15 (1.45, 6.82)
Other anti-TNFα agents only	Ref.	Ref.
Other exposure category		
GLM only vs (GLM+other anti-TNFα agents)	0.06 (0.01, 0.26)	0.08 (0.02, 0.38)
GLM only vs No anti-TNFα agent exposure	NA	0.13 (0.04, 0.45)
(GLM+other anti-TNFα agents) vs No anti-TNFα agent exposure	NA	1.57 (0.41, 6.04)
Age group		
18 to <35 years	Ref.	Ref.
35 or more	1.51 (0.79, 2.88)	1.28 (0.72, 2.28)
UC duration in years		
<33rd percentile	Ref.	Ref.
33rd to <67th percentile	0.50 (0.26, 0.98)	0.62 (0.34, 1.11)
≥67th percentile	0.46 (0.23, 0.91)	0.48 (0.25, 0.91)
Prior treatment with cyclosporine		
Yes	3.62 (1.76, 7.42)	3.21 (1.72, 5.97)
No	Ref.	Ref.
Sex		
Female	0.66 (0.37, 1.18)	0.75 (0.46, 1.24)
Male	Ref.	Ref.

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NA, not applicable; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Results are from 1 multivariable Poisson model and 1 multivariable Cox model, both of which included multiple exposure categories.

Analysis Table 9.2: Adjusted Hazard Ratios for Advanced Colorectal Neoplasia From Multivariable Cox Regression Model

Variable	Cox Model
	HR (95% CI)
Exposure category	
GLM vs other anti-TNFα agents	1.09 (0.22, 5.44)
GLM vs TP	1.08 (0.19, 6.13)
Age group	
18 to <35 years	Ref.
≥35 years and <65 years	1.27 (0.25, 6.48)
≥65 years	4.36 (0.70, 27.23)
UC duration in years	
<33rd percentile	Ref.
33rd to <67th percentile	1.93 (0.35, 10.82)
≥67th percentile	2.64 (0.49, 14.22)
Prior treatment with cyclosporine	
Yes	5.47 (1.44, 20.80)
No	Ref.

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; NA, not applicable; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Note: Results are from 1 multivariable Cox model included multiple exposure categories.

Analysis Table 10.1.1: Unadjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Univariate Poisson and Cox Regression Models; Subgroup: Patients Without Concomitant TP Exposure at Baseline

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM only	0.11 (0.01, 0.80)	0.12 (0.02, 0.88)
GLM+other anti-TNFα agents	2.34 (0.32, 17.16)	2.53 (0.34, 18.79)
No anti-TNFα agent exposure	NA	3.56 (1.40, 9.06)
Other anti-TNFα agents only	Ref.	Ref.
Other exposure category		
GLM only vs (GLM+other anti-TNFα agents)	0.05 (0.00, 0.76)	0.05 (0.00, 0.77)
GLM only vs no anti-TNFα agent exposure	NA	0.03 (0.00, 0.29)
(GLM+other anti-TNFα agents) vs no anti-TNFα agent exposure	NA	0.71 (0.08, 6.00)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NA, not applicable; TNFα, tumor necrosis factor alpha; TP, thiopurines.

Note: Due to convergency issues, model was not adjusted by any covariate.

Analysis Table 10.1.2: Unadjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Univariate Poisson and Cox Regression Models; Subgroup: Patients With Concomitant TP Exposure at Baseline

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM only	1.05 (0.30, 3.71)	1.06 (0.30, 3.67)
GLM+other anti-TNFα agents	19.84 (4.54, 86.77)	10.64 (2.36, 48.00)
No anti-TNFα agent exposure	NA	4.55 (1.19, 17.35)
Other anti-TNFα agents only	Ref.	Ref.
Other exposure category		
GLM only vs (GLM+other anti-TNFα agents)	0.05 (0.01, 0.32)	0.10 (0.02, 0.61)
GLM only vs no anti-TNFα agent exposure	NA	0.23 (0.04, 1.24)
(GLM+other anti-TNFα agents) vs no anti-TNFα agent exposure	NA	2.34 (0.35, 15.73)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NA, not applicable; TNFα, tumor necrosis factor alpha; TP, thiopurines.

Note: Due to convergency issues, model was not adjusted by any covariate.

Analysis Table 10.1.3: Unadjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Univariate Poisson and Cox Regression Models; Subgroup: Patients Without Priory History of Anti-TNFα Agent Use

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM only	0.70 (0.13, 3.89)	0.90 (0.16, 4.97)
GLM+other anti-TNFα agents	6.02 (0.67, 54.18)	3.66 (0.41, 33.04)
No anti-TNFα agent exposure	NA	7.08 (1.69, 29.70)
Other anti-TNFα agents only	Ref.	Ref.
Other exposure category		
GLM only vs (GLM+other anti-TNFα agents)	0.12 (0.01, 1.29)	0.25 (0.02, 2.78)
GLM only vs no anti-TNFα agent exposure	NA	0.13 (0.02, 0.71)
(GLM+other anti-TNFα agents) vs no anti-TNFα agent exposure	NA	0.52 (0.05, 4.87)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NA, not applicable; TNFα, tumor necrosis factor alpha.

Note: Due to convergency issues, model was not adjusted by any covariate.

Analysis Table 10.1.4: Unadjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Univariate Poisson and Cox Regression Models; Subgroup: Patients With Priory History of Anti-TNFα Agent Use

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM only	0.26 (0.06, 1.10)	0.23 (0.06, 0.96)
GLM+other anti-TNFα agents	8.07 (1.96, 33.31)	6.23 (1.49, 26.07)
No anti-TNFα agent exposure	NA	3.11 (1.20, 8.09)
Other anti-TNFα agents only	Ref.	Ref.
Other exposure category		
GLM only vs (GLM+other anti-TNFα agents)	0.03 (0.00, 0.23)	0.04 (0.01, 0.27)
GLM only vs no anti-TNFα agent exposure	NA	0.07 (0.01, 0.40)
(GLM+other anti-TNFα agents) vs no anti-TNFα agent exposure	NA	2.00 (0.37, 10.72)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NA, not applicable; TNFα, tumor necrosis factor alpha.

Note: Due to convergency issues, model was not adjusted by any covariate.

Analysis Table 10.1.5: Unadjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Univariate Poisson and Cox Regression Models; Subgroup: Using Only Patients Exposed to An Other Anti-TNFα Agent Whose Entry Into the Cohort Was Qualified by the Initiation of Infliximab

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM only	0.26 (0.09, 0.74)	0.26 (0.09, 0.72)
GLM+other anti-TNFα agents	4.26 (1.03, 17.62)	3.70 (0.88, 15.47)
No anti-TNFα agent exposure	NA	1.56 (0.77, 3.13)
Other anti-TNFα agents only	Ref.	Ref.
Other exposure category		
GLM only vs (GLM+other anti-TNFα agents)	0.06 (0.01, 0.34)	0.07 (0.01, 0.39)
GLM only vs no anti-TNFα agent exposure	NA	0.17 (0.05, 0.53)
(GLM+other anti-TNFα agents) vs no anti-TNFα agent exposure	NA	2.38 (0.51, 11.07)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NA, not applicable; TNFα, tumor necrosis factor alpha.

Note: Due to convergency issues, model was not adjusted by any covariate.

Analysis Table 10.1.6: Unadjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Univariate Poisson and Cox Regression Models; Subgroup: Using Only Patients Exposed to An Other Anti-TNFα Agent Whose Entry Into the Cohort Was Qualified by the Initiation of Adalimumab

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM only	0.89 (0.26, 3.07)	0.89 (0.26, 3.05)
GLM+other anti-TNFα agents	NE	10.18 (1.24, 83.42)
No anti-TNFα agent exposure	NA	3.44 (1.30, 9.10)
Other anti-TNFα agents only	Ref.	Ref.
Other exposure category		
GLM only vs (GLMs+ other anti-TNFα agents)	0.06 (0.01, 0.54)	0.09 (0.01, 0.79)
GLM only vs no anti-TNFα agent exposure	NA	0.26 (0.08, 0.83)
(GLM+other anti-TNFα agents) vs None	NA	2.946 (0.37, 23.45)

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; NE, not estimable; NA, not applicable; TNFα, tumor necrosis factor alpha.

Note: Due to convergency issues, model was not adjusted by any covariate.

Analysis Table 11.1: Adjusted Incidence Rate Ratios and Hazard Ratios for Colectomy Due to Intractable Disease From Multivariable Poisson and Cox Regression Models; Sensitivity: Risk Window From Exposure Through End of Follow-up

Variable	Poisson Model	Cox Model
	IRR (95% CI)	HR (95% CI)
Exposure category		
GLM	0.72 (0.39, 1.31)	0.90 (0.81, 1.00)
Other anti-TNFα agents	Ref.	Ref.
Age group		
18 to <35 years	Ref.	Ref.
35 or more	1.17 (0.64, 2.14)	1.03 (0.93, 1.13)
UC duration in years		
<33rd percentile	Ref.	Ref.
33rd to <67th percentile	0.67 (0.36, 1.25)	0.89 (0.80, 0.99)
≥67th percentile	0.49 (0.25, 0.95)	0.92 (0.82, 1.02)
Prior treatment with cyclosporine		
Yes	3.12 (1.54, 6.34)	0.71 (0.59, 0.86)
No	Ref.	Ref.
Sex		
Female	0.62 (0.36, 1.07)	1.05 (0.96, 1.14)
Male	Ref.	Ref.

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Analysis Table 11.5.1: Multivariable Cox Regression Model; Outcome: Colectomy Due to Intractable Disease, Advanced Colorectal Neoplasia, or Death; Sensitivity: Composite Outcome: GLM Versus Other Anti-TNFα Agents

Variable	Cox Model
	HR (95% CI)
Exposure category	
GLM	0.72 (0.42, 1.26)
Other anti-TNFα agents	Ref.
Age group	
18 to <35 years	Ref.
35 or more	1.67 (1.05, 2.65)
UC duration in years	
<33rd percentile	Ref.
33rd to <67th percentile	1.07 (0.69, 1.67)
≥67th percentile	0.75 (0.47, 1.21)
Prior treatment with cyclosporine	
Yes	3.26 (2.01, 5.30)
No	Ref.
Sex	
Female	0.67 (0.46, 0.97)
Male	Ref.

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Analysis Table 11.5.2: Multivariable Cox Regression Model; Outcome: Colectomy Due to Intractable Disease, Advanced Colorectal Neoplasia, or Death; Sensitivity: Composite Outcome: GLM Versus Thiopurine

Variable	Cox Model
	HR (95% CI)
Exposure category	
GLM	1.78 (0.93, 3.41)
TP	Ref.
Age group	
18 to <35 years	Ref.
35 or more	1.67 (1.05, 2.65)
UC duration in years	
<33rd percentile	Ref.
33rd to <67th percentile	1.07 (0.69, 1.67)
≥67th percentile	0.75 (0.47, 1.21)
Prior treatment with cyclosporine	
Yes	3.26 (2.01, 5.30)
No	Ref.
Sex	
Female	0.67 (0.46, 0.97)
Male	Ref.

Abbreviations: CI, confidence interval; GLM, golimumab; HR, hazard ratio; IRR, incidence rate ratio; TP, thiopurine; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Analysis Table 12.1: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Colectomy Due to Intractable Disease

	Cases N=41	Controls N=70
Exposure category, n (%)		
GLM+other anti-TNFα agents	3 (7.3)	2 (2.9)
None	0 (0.0)	0 (0.0)
GLM only	3 (7.3)	19 (27.1)
Other anti-TNFα agents only	35 (85.4)	49 (70.0)
Age (years)		
n	41	70
Mean (SD)	49.7 (18.2)	46.3 (17.1)
Median (Q1, Q3)	52.0 (35.0,64.0)	47.0 (33.0,57.0)
Min, Max	19.0,82.0	19.0,84.0
Age group, n (%)		
18 to <35	10 (24.4)	22 (31.4)
35 to <65	21 (51.2)	37 (52.9)
≥18	10 (24.4)	11 (15.7)
Sex, n (%)		
Male	28 (68.3)	39 (55.7)
Female	13 (31.7)	31 (44.3)
Calendar year of reference date, n (%)		
2013	2 (4.9)	3 (4.3)
2014	6 (14.6)	11 (15.7)
2015	8 (19.5)	14 (20.0)
2016	12 (29.3)	22 (31.4)
2017	8 (19.5)	12 (17.1)
2018	3 (7.3)	5 (7.1)
2019	2 (4.9)	3 (4.3)
2020	0 (0.0)	0 (0.0)
2021	0 (0.0)	0 (0.0)
UC duration in years		
n	41	69
Mean (SD)	7.9 (9.3)	7.2 (8.8)
Median (Q1, Q3)	4.6 (1.0,10.6)	4.4 (1.1,9.3)
Min, Max	0.0,38.9	0.1,43.0

Analysis Table 12.1: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Colectomy Due to Intractable Disease

	Cases N=41	Controls N=70
Maximum extent of disease period 1, n (%)[a]		
Extensive	14 (43.8)	26 (47.3)
Left side only	12 (37.5)	18 (32.7)
Other	0 (0.0)	3 (5.5)
Proctitis	6 (18.8)	8 (14.5)
Maximum extent of disease period 2, n (%)[a]		
Extensive	22 (56.4)	23 (41.8)
Left side only	9 (23.1)	22 (40.0)
Other	2 (5.1)	2 (3.6)
Proctitis	6 (15.4)	8 (14.5)
Treatment with steroids period 1, n (%)[a]		
No	12 (29.3)	21 (30.0)
Yes	29 (70.7)	49 (70.0)
Treatment with steroids period 2, n (%)[a]		
No	8 (19.5)	19 (27.1)
Yes	33 (80.5)	51 (72.9)
Treatment with cyclosporine period 1, n (%)[a]		
No	35 (87.5)	68 (100.0)
Yes	5 (12.5)	0 (0.0)
Treatment with cyclosporine period 2, n (%)[a]		
No	32 (78.0)	65 (97.0)
Yes	9 (22.0)	2 (3.0)
Number of hospitalizations for UC period 1, n (%)[a]		
0	17 (48.6)	43 (67.2)
1 or 2	16 (45.7)	17 (26.6)
3 or more	2 (5.7)	4 (6.3)
Number of hospitalizations for UC period 2, n (%)[a]		
0	12 (30.0)	40 (58.8)
1 or 2	27 (67.5)	25 (36.8)
3 or more	1 (2.5)	3 (4.4)
Prior diagnosis with PSC, n (%)		
No	41 (100.0)	68 (97.1)
Yes	0 (0.0)	2 (2.9)

Analysis Table 12.1: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Colectomy Due to Intractable Disease

	Cases N=41	Controls N=70
Prior screening colonoscopy period 2, n (%)[a]		
No	28 (71.8)	44 (67.7)
Yes	11 (28.2)	21 (32.3)
Number of previous anti-TNFα agents, n (%)		
0	0 (0.0)	4 (5.9)
1	24 (58.5)	40 (58.8)
2	15 (36.6)	19 (27.9)
3 or more	2 (4.9)	5 (7.4)
Recent switcher after use of another anti-TNFα agent, n(%)[b]		
After short-term use (≤3 months)	6 (14.6)	12 (17.1)
After long-term use (>3 months)	3 (7.3)	4 (5.7)
Did not switch	32 (78.0)	54 (77.1)

Abbreviations: GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurines; UC, ulcerative colitis.

Notes: The reference date for a case was the date that the patient experienced the outcome, while the reference date for a control was the date that their corresponding case experienced the outcome. For the colectomy, due to intractable disease outcome, TP was considered an exposure per the protocol. For the colectomy outcome, the exposure period of interest is anytime within 90 days before the reference date. Information on some variables sought in chart review was not always documented in the medical record. In such situations, the sum of patients across all categories of that variable may be less than the sum of case and control patients.

[a] Period 1: the first year after UC diagnosis, or until cohort entry (whichever occurred first). Period 2: the year before the last episode of a study drug commenced, looking backward from the date of study outcome (or an equivalent date among the controls)—this period could extend back only as far as the date of the first UC diagnosis, and thus could be truncated.

[b] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Analysis Table 12.2: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Advanced Colorectal Neoplasia

	Cases N=9	Controls N=11
Exposure category, n (%)		
GLM	1 (11.1)	2 (18.2)
Other anti-TNFα agents	5 (55.6)	6 (54.5)
TP	3 (33.3)	3 (27.3)
Age (years)		
n	9	11
Mean (SD)	58.2 (16.7)	47.2 (19.2)
Median (Q1, Q3)	66.0 (62.0,67.0)	49.0 (28.0,65.0)
Min, Max	27.0,74.0	24.0,84.0
Age group, n (%)		
18 to <35	2 (22.2)	4 (36.4)
35 to <65	2 (22.2)	4 (36.4)
≥65	5 (55.6)	3 (27.3)
Sex, n (%)		
Male	5 (55.6)	8 (72.7)
Female	4 (44.4)	3 (27.3)
Calendar year of reference date, n (%)		
2013	0 (0.0)	0 (0.0)
2014	0 (0.0)	0 (0.0)
2015	1 (11.1)	2 (18.2)
2016	0 (0.0)	0 (0.0)
2017	1 (11.1)	1 (9.1)
2018	7 (77.8)	8 (72.7)
2019	0 (0.0)	0 (0.0)
2020	0 (0.0)	0 (0.0)
2021	0 (0.0)	0 (0.0)
UC duration in years		
n	8	11
Mean (SD)	12.5 (9.8)	10.4 (6.7)
Median (Q1, Q3)	9.7 (4.4,20.9)	8.7 (6.5,12.2)
Min, Max	3.3,27.1	3.4,28.0

Analysis Table 12.2: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Advanced Colorectal Neoplasia

	Cases N=9	Controls N=11
Maximum extent of disease period 1, n (%)[a]		
Extensive	2 (40.0)	1 (11.1)
Left side only	1 (20.0)	2 (22.2)
Other	0 (0.0)	2 (22.2)
Proctitis	2 (40.0)	4 (44.4)
Maximum extent of disease period 2, n (%)[a]		
Extensive	2 (33.3)	5 (45.5)
Left side only	1 (16.7)	3 (27.3)
Other	0 (0.0)	2 (18.2)
Proctitis	3 (50.0)	1 (9.1)
Treatment with steroids period 1, n (%)[a]		
No	4 (44.4)	4 (36.4)
Yes	5 (55.6)	7 (63.6)
Treatment with steroids period 2, n (%)[a]		
No	4 (44.4)	8 (72.7)
Yes	5 (55.6)	3 (27.3)
Treatment with cyclosporine period 1, n (%)[a]		
No	5 (71.4)	11 (100.0)
Yes	2 (28.6)	0 (0.0)
Treatment with cyclosporine period 2, n (%)[a]		
No	5 (71.4)	11 (100.0)
Yes	2 (28.6)	0 (0.0)
Number of hospitalizations for UC period 1, n (%)[a]		
0	5 (71.4)	7 (70.0)
1 or 2	2 (28.6)	3 (30.0)
Number of hospitalizations for UC period 2, n (%)[a]		
0	5 (71.4)	9 (81.8)
1 or 2	2 (28.6)	2 (18.2)
Prior diagnosis with PSC, n (%)		
No	9 (100.0)	11 (100.0)
Yes	0 (0.0)	0 (0.0)

Analysis Table 12.2: Nested Case-Control Study: Description of Cases and Controls at the Reference Date; Outcome: Advanced Colorectal Neoplasia

	Cases N=9	Controls N=11
Prior screening colonoscopy,[a] n (%)		
No	3 (42.9)	8 (72.7)
Yes	4 (57.1)	3 (27.3)
Number of previous anti-TNFα agents, n (%)		
0	1 (12.5)	2 (18.2)
1	4 (50.0)	6 (54.5)
2	1 (12.5)	1 (9.1)
3 or more	2 (25.0)	2 (18.2)
Recent switcher after use of another anti-TNFα agent, n(%)[b]		
Within 3 months	3 (75.0)	1 (11.1)
More than 3 months	0 (0.0)	1 (11.1)
Did not switch	1 (25.0)	7 (77.8)

Abbreviations: GLM, golimumab; PSC, primary sclerosing cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNFα, tumor necrosis factor alpha; TP, thiopurine; UC, ulcerative colitis.

Notes: The reference date for a case was the date that the patient experienced the outcome, while the reference date for a control was the date that their corresponding case experienced the outcome. For neoplasia outcomes, the exposure period of interest was any time before the reference date. Information on some variables sought in chart review was not always documented in the medical record. In such situations, the sum of patients across all categories of that variable may be les than the sum of case and control patients.

[a] Period 1: the first year after UC diagnosis, or until cohort entry (whichever occurred first). Period 2: the year before the last episode of a study drug commenced, looking backward from the date of study outcome (or an equivalent date among the controls)—this period could extend back only as far as the date of the first UC diagnosis, and thus could be truncated.

[b] Recent switcher refers to a patient who started a new anti-TNFα agent within 90 days of discontinuing another anti-TNFα agent.

Analysis Table 13.1: Nested Case-Control Study: Crude Odds Ratios for Colectomy Due to Intractable Disease

Comparison	Crude OR (95% CI)
GLM only vs other anti-TNFα agents only	0.17 (0.04, 0.78)
GLM only vs (GLM+other anti-TNFα agents)	0.04 (0.00, NE)
(GLM+other anti-TNFα agents) vs other anti-TNFα agents only	4.03 (0.40, NE)

Abbreviations: CI, confidence interval; GLM, golimumab; NE, not estimable; OR, odds ratio; TNFα, tumor necrosis factor alpha.

Note: Each odds ratio (95% CI) was derived from an univariable conditional logistic regression model, conditional on matching.

Analysis Table 13.2: Nested Case-Control Study: Crude Odds Ratios for Advanced Colorectal Neoplasia

Comparison	Crude OR (95% CI)
GLM vs other anti-TNFα agents	0.47 (0.04, 5.68)
GLM vs TP	0.42 (0.01, 13.27)

Abbreviations: CI, confidence interval; GLM, golimumab; OR, odds ratio; TNFα, tumor necrosis factor alpha; TP, thiopurine.

Note: Each odds ratio (95% CI) was derived from an univariable conditional logistic regression model, conditional on matching.

Analysis Table 14.1: Candidate Variable Screening for Inclusion in Multivariable Model in Nested Case-Control Based on Univariable Association with Colectomy Due to Intractable Disease

Candidate Variable	OR (95% CI)
Age group	
≥35 years and <65 years vs 18 to <35 years	1.28 (0.50, 3.32)
≥65 years vs 18 to <35 years	2.10 (0.61, 7.24)
Sex (male vs female)	1.54 (0.67, 3.54)
UC duration in years[a]	
≥67th percentile vs <33rd percentile	NE
33rd to <67th percentile vs <33rd percentile	NE
Maximum extent of disease period 1[b]	
Proctitis vs extensive	1.57 (0.39, 6.36)
Left side only vs extensive	1.23 (0.38, 3.95)
Not recorded vs extensive	NE
Maximum extent of disease period 2[b]	
Proctitis vs extensive	0.72 (0.20, 2.55)
Left side only vs extensive	0.39 (0.13, 1.13)
Not recorded vs extensive	1.08 (0.15, 7.75)
Prior treatment with steroids period 1[b] (yes vs no)	1.09 (0.40, 2.97)
Prior treatment with steroids period 2[b] (yes vs no)	0.67 (0.26, 1.72)
Prior treatment with cyclosporine period[b] 1 (yes vs no)	NE
Prior treatment with cyclosporine period 2[b] (yes vs no)	0.14 (0.03, 0.65)
Number of hospitalizations for UC period 1[b]	
1 or 2 vs 0	2.30 (0.86, 6.16)
≥3 vs 0	1.35 (0.19, 9.45)
Number of hospitalizations for UC period 2[b]	
1 or 2 vs 0	3.88 (1.52, 9.92)
≥3 vs 0	1.63 (0.15, 17.63)
Prior diagnosis with PSC (yes vs no)	NE
Prior screening colonoscopy (yes vs no)	0.66 (0.23, 1.89)
Number of previous anti-TNFα agents	
1 vs 0	NE
2 vs 0	NE
3 or more vs 0	NE

Analysis Table 14.1: Candidate Variable Screening for Inclusion in Multivariable Model in Nested Case-Control Based on Univariable Association with Colectomy Due to Intractable Disease

Candidate Variable	OR (95% CI)
Recent switcher after use of another anti-TNFα agent[c]	
After short-term use (≤3 months) vs did not switch	0.88 (0.30, 2.63)
After long-term use (>3 months) vs did not switch	1.18 (0.25, 5.53)

Abbreviations: CI, confidence interval; NE, not estimable; OR, odds ratio PSC, primary sclerosing cholangitis; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Note: Each row represents a separate univariable regression model assessing the association of each candidate variable with the outcome. Odds ratios and 95% CI were derived from conditional logistic regression models.

[a] Ulcerative colitis duration was ascertained on the date of the event or the corresponding reference date for control patients. The 33rd percentile was 2.6 years, and the 67th percentile was 8.3 years.

[b] Period 1: the first year after UC diagnosis, or until cohort entry, (whichever occurred first). Period 2: the year before the last episode of a study drug commenced, looking backward from the date of study outcome (or an equivalent date among the controls)—this period could extend back only as far as the date of the first UC diagnosis, and thus could be truncated.

[c] Recent switcher refers to a patient who started a new anti-TNα agent within 90 days of discontinuing another anti-TNFα agent.

Analysis Table 15.1: Nested Case-Control Study: Multivariable Adjusted Conditional Logistic Regression Model; Outcome: Colectomy Due to Intractable Disease

Comparison	OR (95% CI)
Study therapy exposure	
Other anti-TNFα agents only	Ref.
GLM only	0.16 (0.02, 1.08)
(GLM+other anti-TNFα agents)	8.69 (0.60, 124.90)
GLM only vs (GLM+other anti-TNFα agents)	0.02 (0.00, 0.50)
Prior treatment with cyclosporine period 2 (yes vs no)	7.00 (0.65, 75.67)
Number of hospitalizations for UC period 2 (yes vs no)	2.97 (0.90, 9.80)
Age group	
Age (35 or more vs 18 to 35 years)	2.15 (0.58, 7.92)
Female vs male	0.92 (0.30, 2.81)

Abbreviations: CI, confidence interval; GLM, golimumab; OR, odds ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Annex 4: Analysis Figures

List of Analysis Figures

Analysis Figure 1.5.7.3: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: >1

Analysis Figure 1.5.8.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Patients Exposed to an Other Anti-TNFα Agent for Which Entry Into the Cohort Was Qualified by the Initiation of Infliximab: Yes

Analysis Figure 1.5.8.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Patients Exposed to an Other Anti-TNFα Agent for Which Entry Into the Cohort Was Qualified by the Initiation of Adalimumab: Yes

Analysis Figure 1.6.1.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Sex: Male

Analysis Figure 1.6.1.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Sex: Female

Analysis Figure 1.6.2.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Time Since Initial UC Diagnosis: <10 years

Analysis Figure 1.6.2.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Time Since Initial UC Diagnosis: 10 to <20 Years

Analysis Figure 1.6.2.3: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Time Since Initial UC Diagnosis: ≥20 Years

Analysis Figure 1.6.3.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Disease Extent: Extensive

Analysis Figure 1.6.3.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Disease Extent: Other

Analysis Figure 1.6.4.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; History of UC Hospitalization or Cyclosporine Use: Yes

Analysis Figure 1.6.4.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; History of UC Hospitalization or Cyclosporine Use: No

Analysis Figure 1.6.5.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Previous Use of Systemic Steroids: Yes

Analysis Figure 1.6.5.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Previous Use of Systemic Steroids: No

Analysis Figure 1.6.6.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Overlapping Use of Thiopurines: Yes

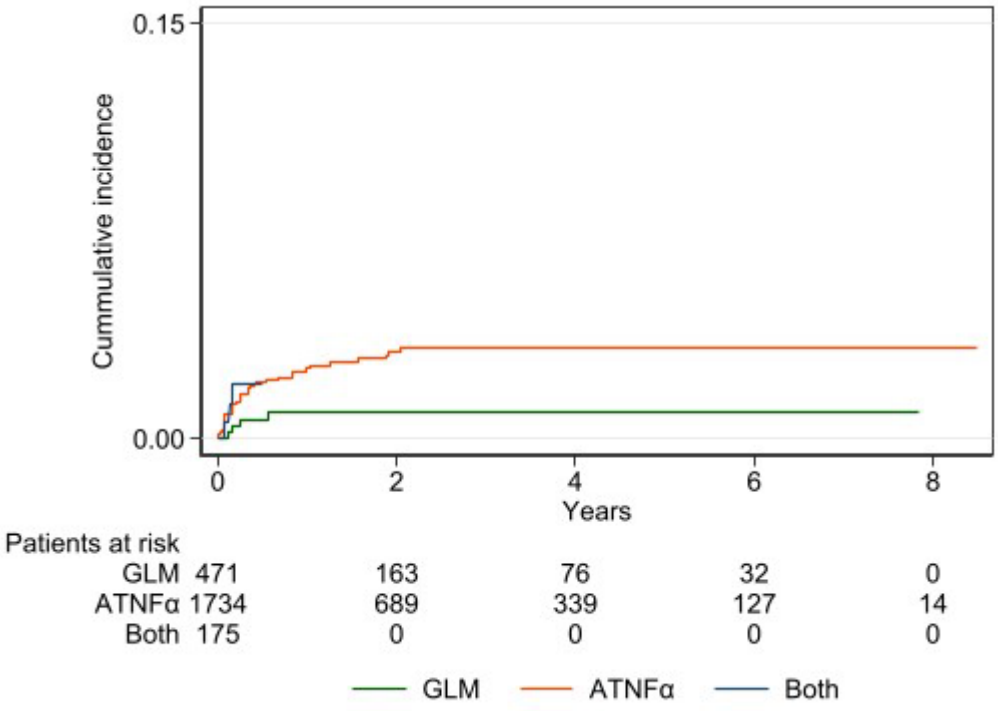
Analysis Figure 1.6.6.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Overlapping Use of Thiopurines: No

Analysis Figure 1.6.7.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: 0

Analysis Figure 1.6.7.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: 1

Analysis Figure 1.6.7.3: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: >1

Analysis Figure 1.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category

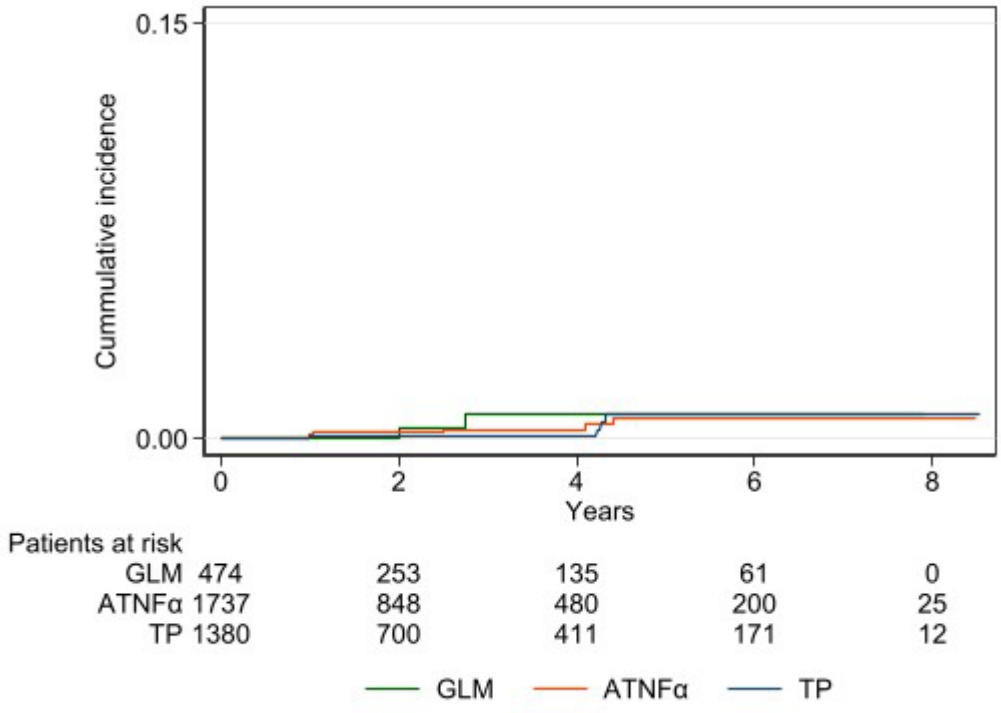


ATNFα, other anti–tumor necrosis factor alpha agents; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

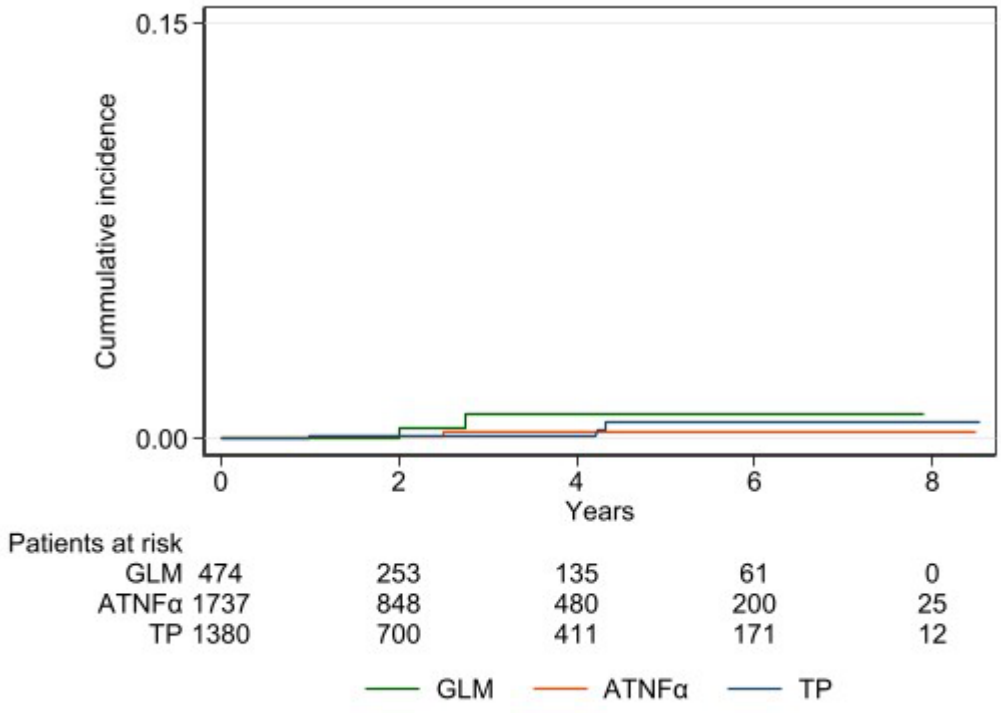
Note: Colectomies due to intractable disease were identified during the period up to 90 days after each drug discontinuation.

Analysis Figure 1.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category



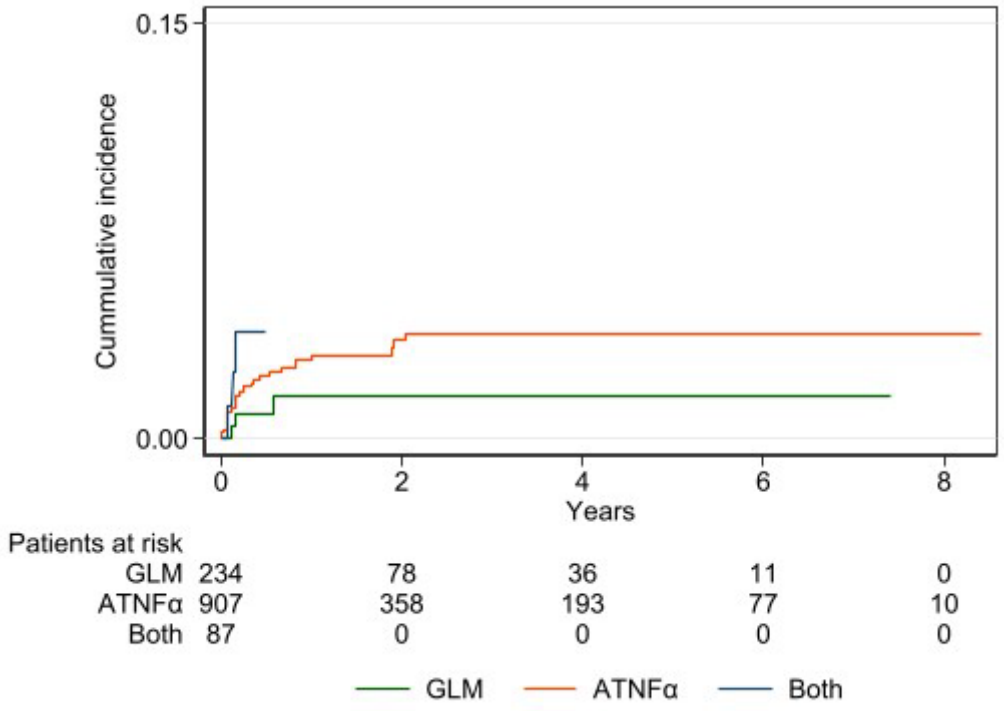
ATNFα, other anti–tumor necrosis factor alpha agents; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.3: Cumulative Incidence of Colorectal Cancer, by Exposure Category



ATNFα, other anti–tumor necrosis factor alpha agents; GLM, golimumab; TP, thiopurine.

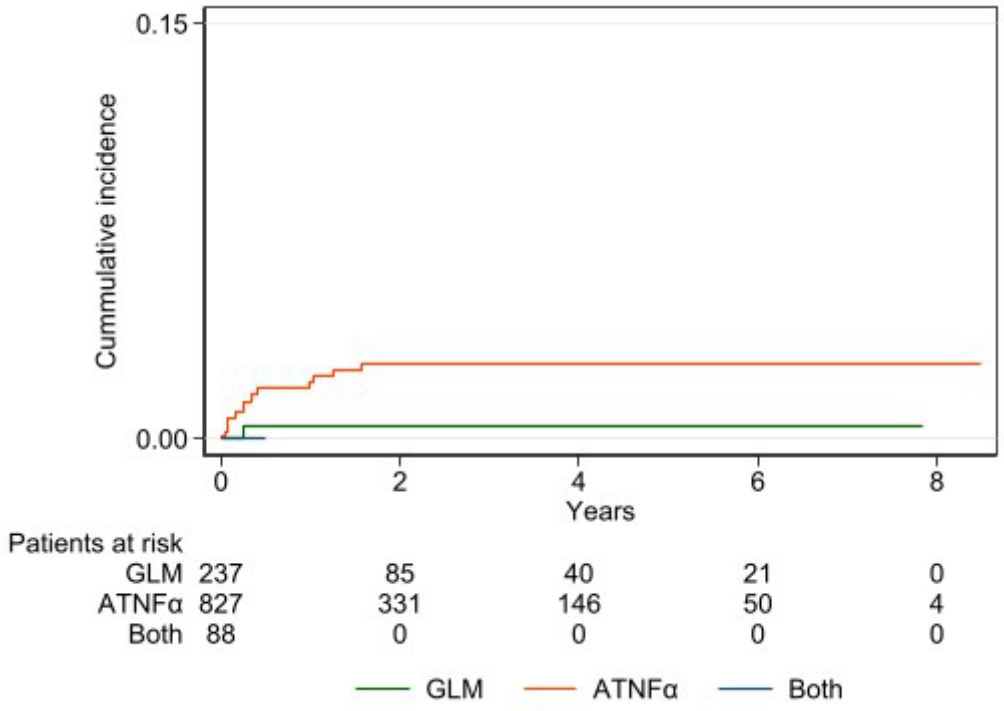
Analysis Figure 1.5.1.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Sex: Male



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

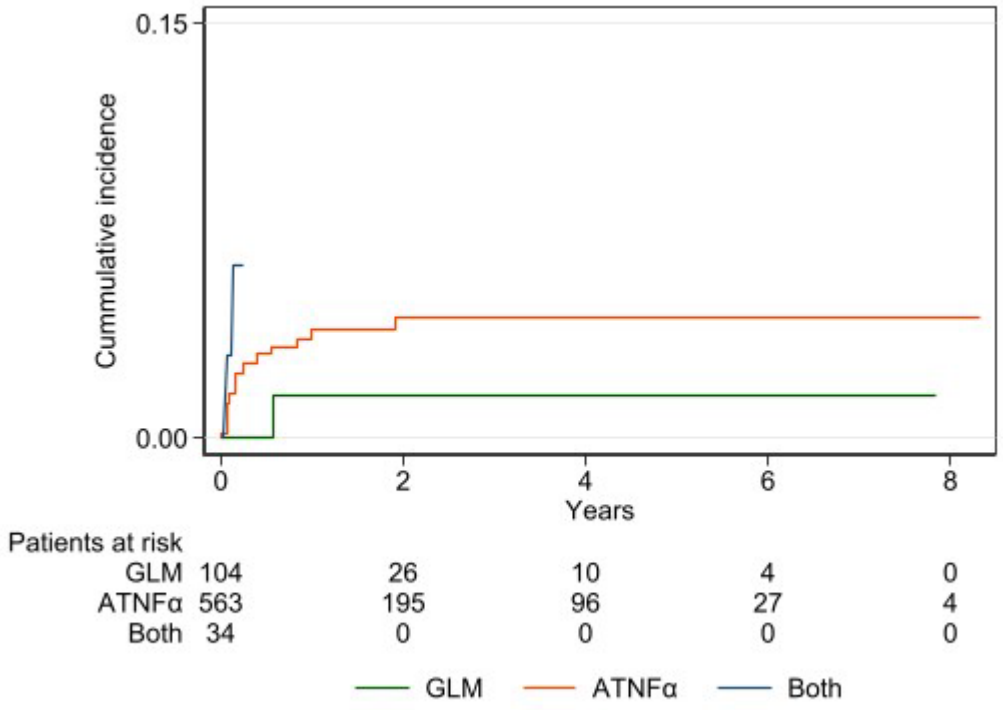
Analysis Figure 1.5.1.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Sex: Female



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

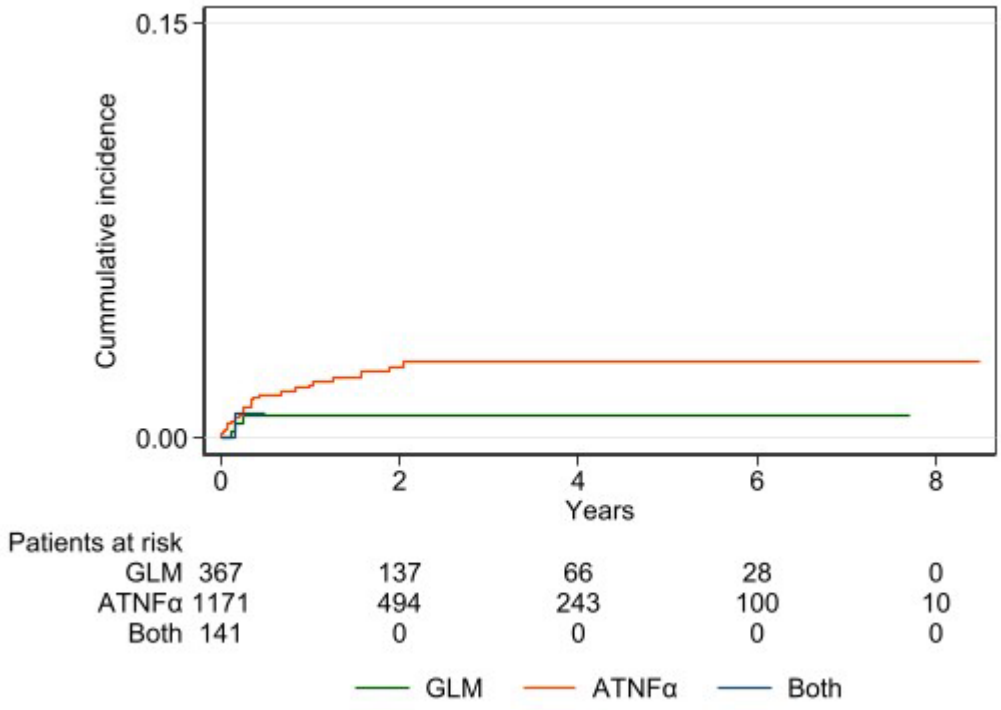
Analysis Figure 1.5.2.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Time Since Initial UC Diagnosis: <2 Years



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; UC, ulcerative colitis.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

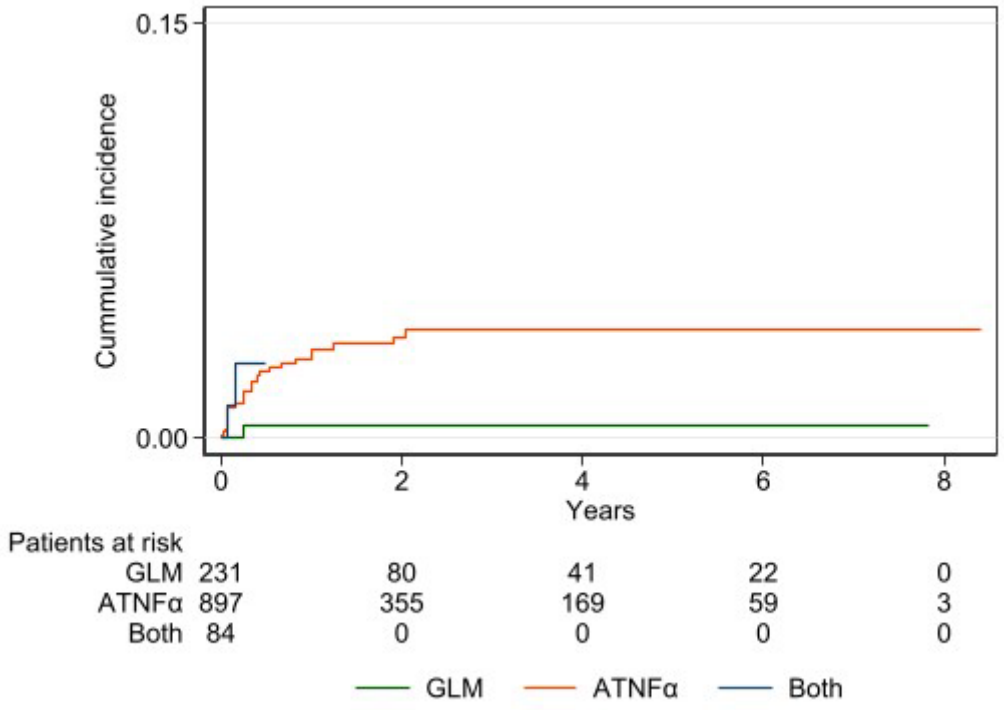
Analysis Figure 1.5.2.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Time Since Initial UC Diagnosis: ≥2 Years



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; UC, ulcerative colitis.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

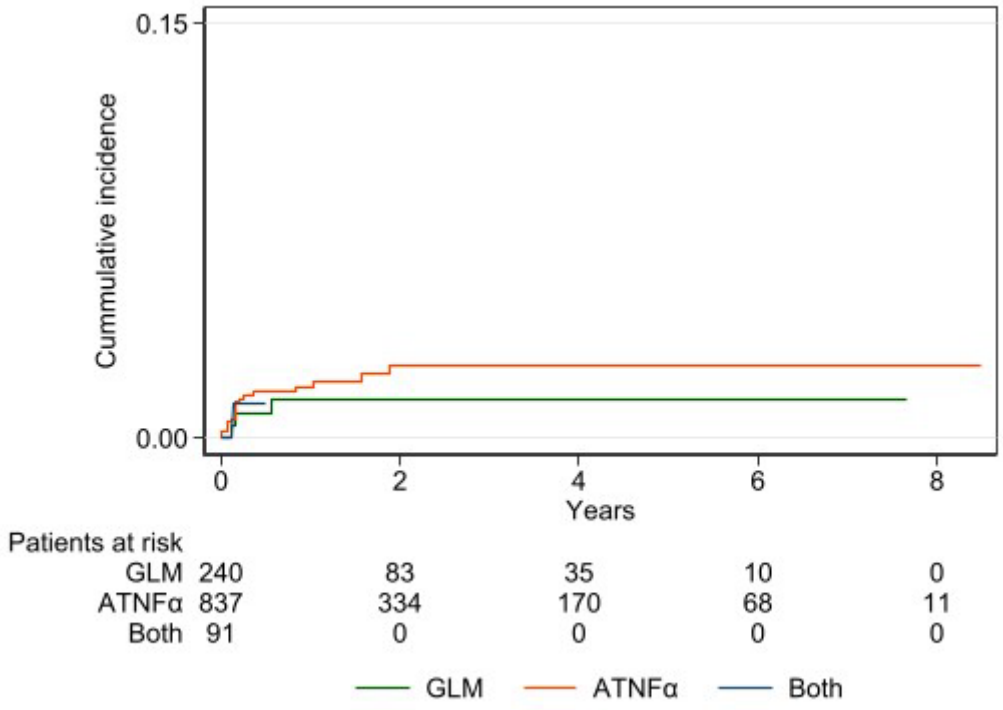
Analysis Figure 1.5.3.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Disease Extent: Extensive



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

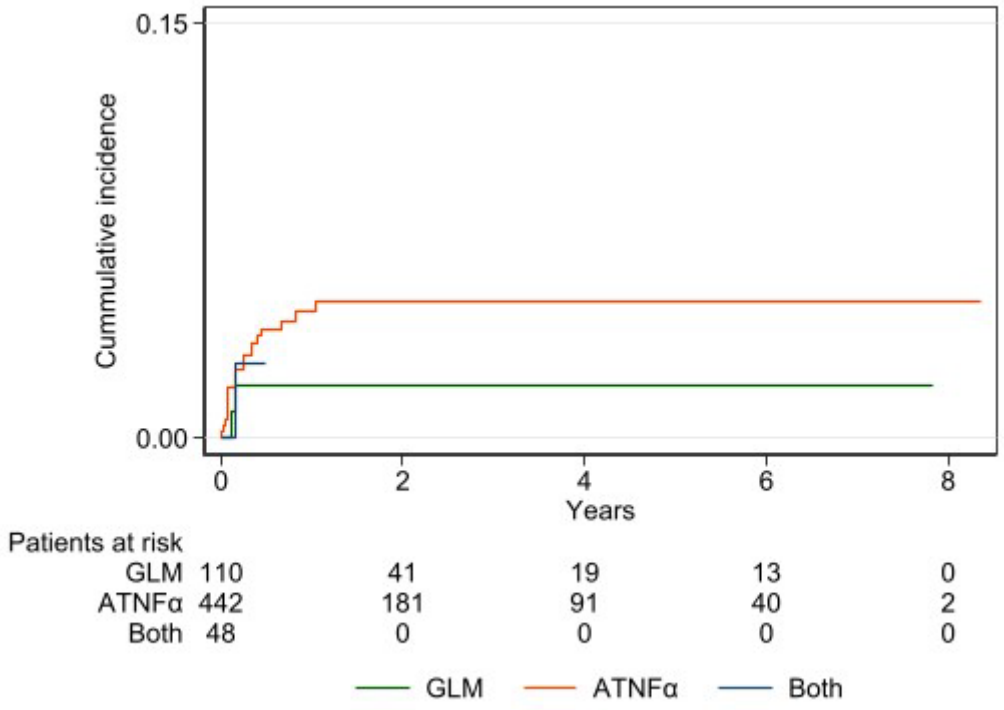
Analysis Figure 1.5.3.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Disease Extent: Other



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

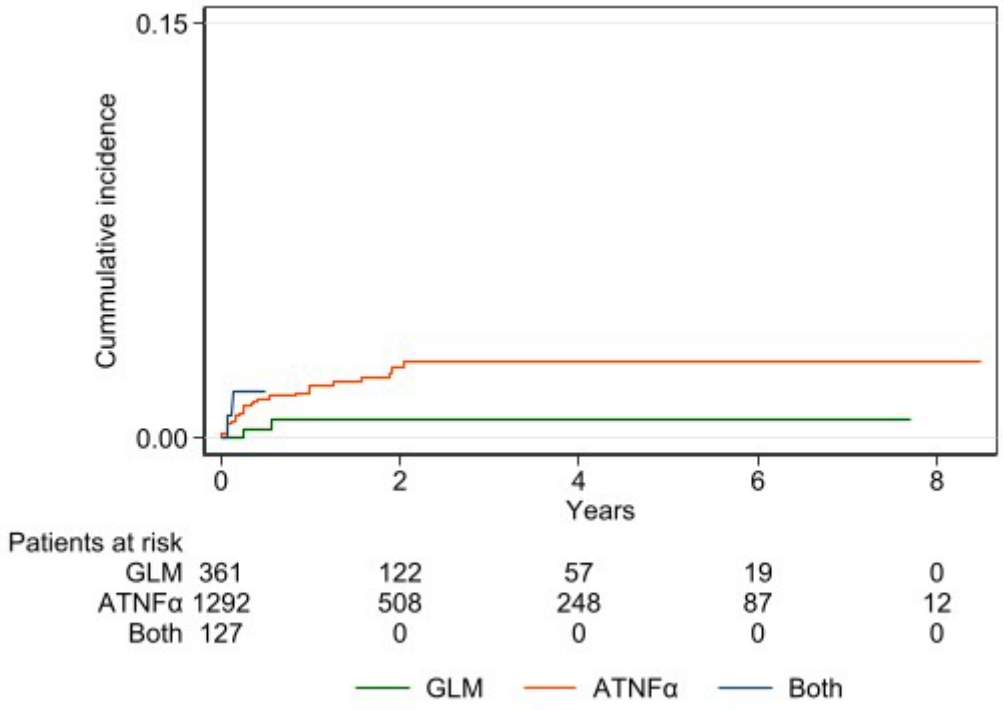
Analysis Figure 1.5.4.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: History of UC Hospitalization or Cyclosporine Use: Yes



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; UC, ulcerative colitis.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

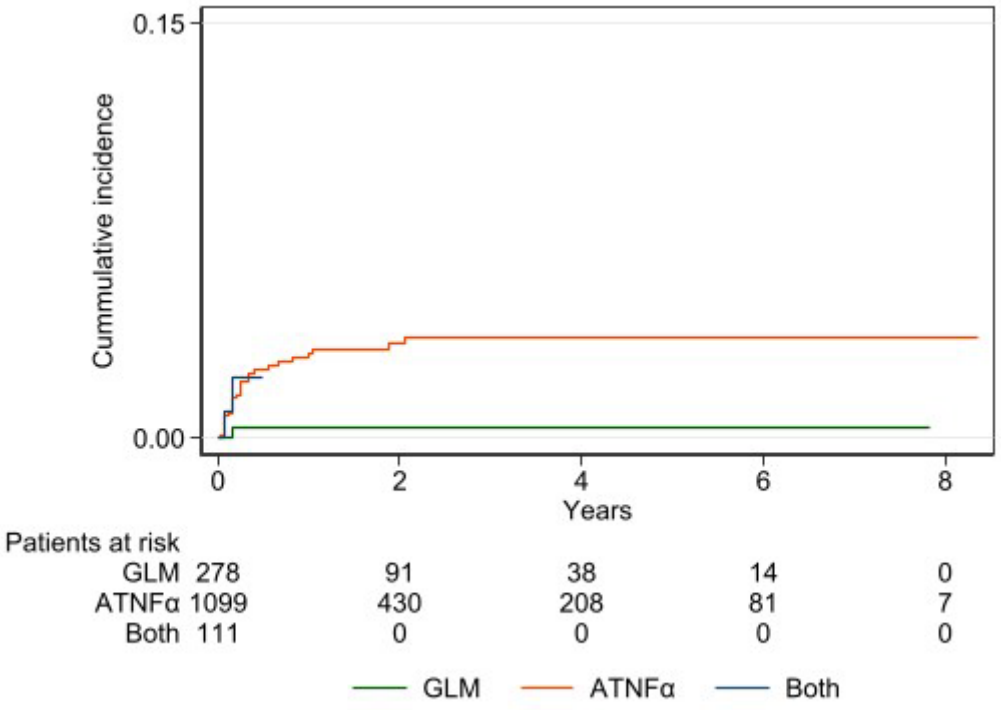
Analysis Figure 1.5.4.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: History of UC Hospitalization or Cyclosporine Use: No



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; UC, ulcerative colitis.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

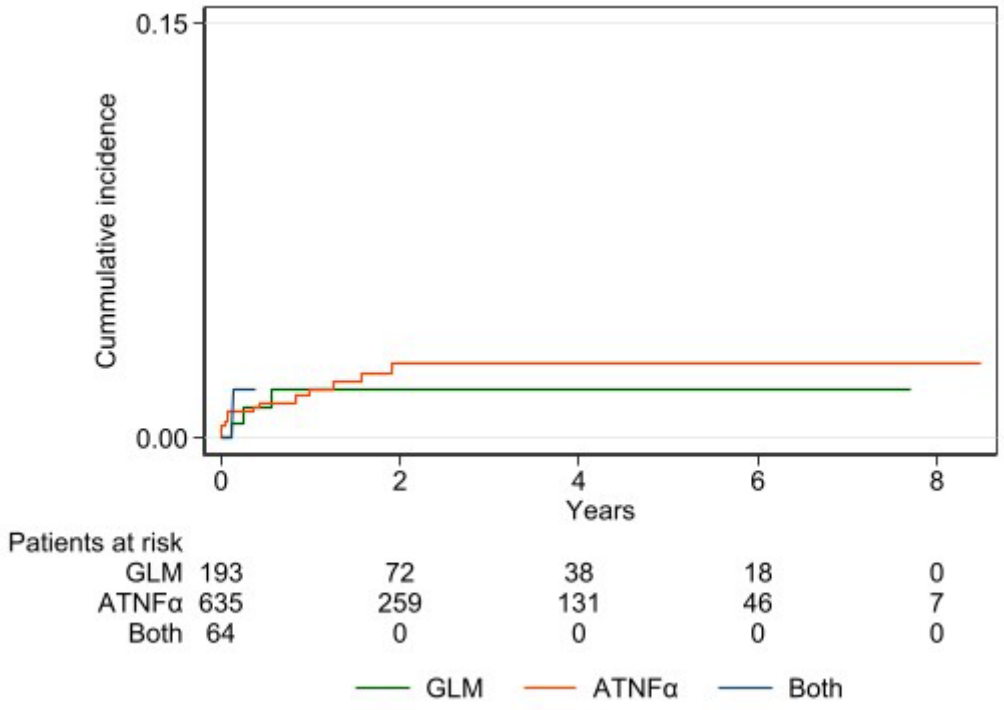
Analysis Figure 1.5.5.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Previous Use of Systemic Steroids: Yes



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

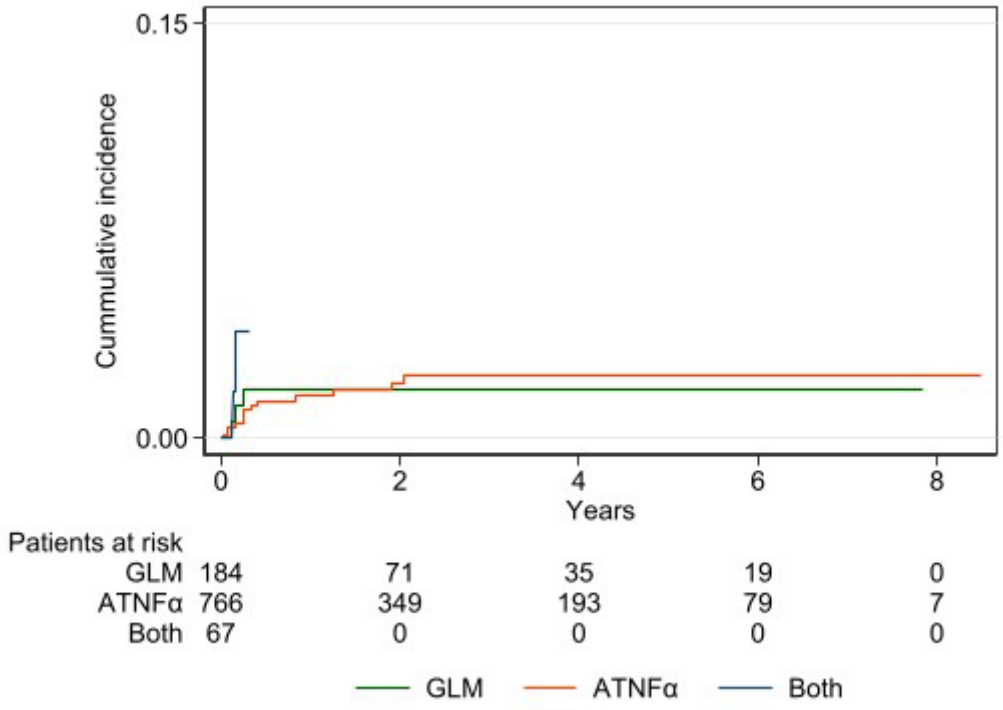
Analysis Figure 1.5.5.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Previous Use of Systemic Steroids: No



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

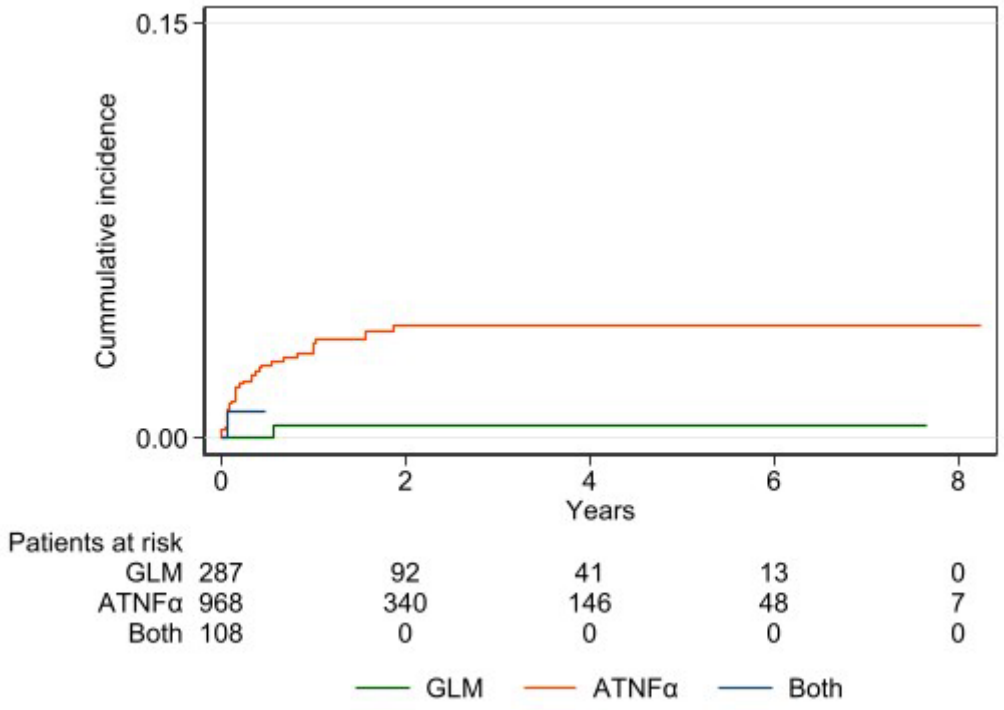
Analysis Figure 1.5.6.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Overlapping Use of Thiopurines: Yes



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

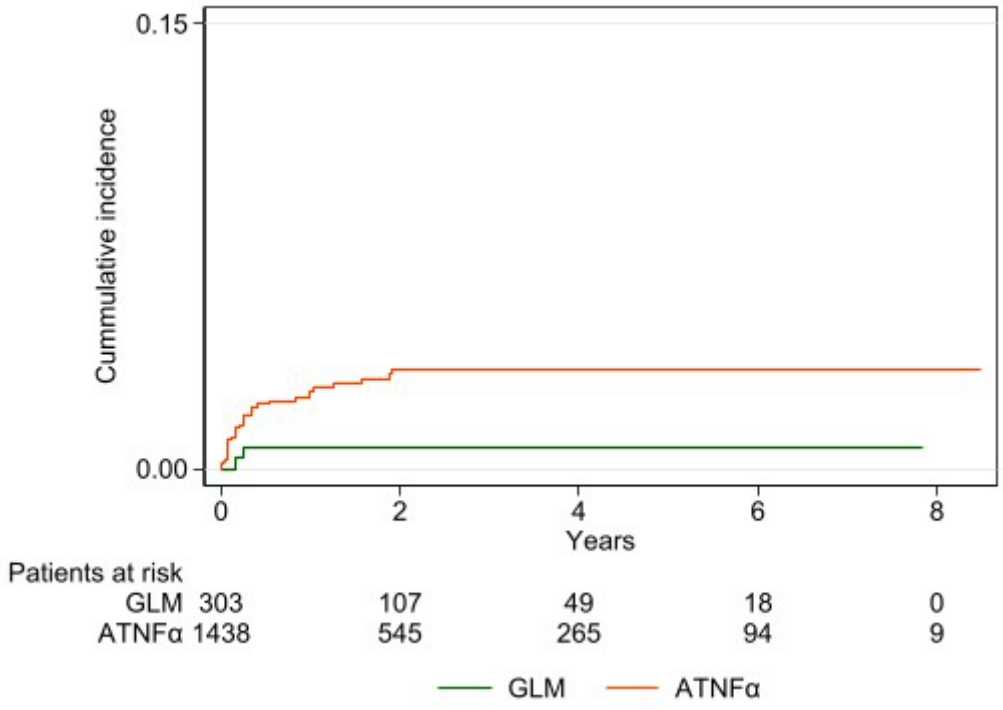
Analysis Figure 1.5.6.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Overlapping Use of Thiopurines: No



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

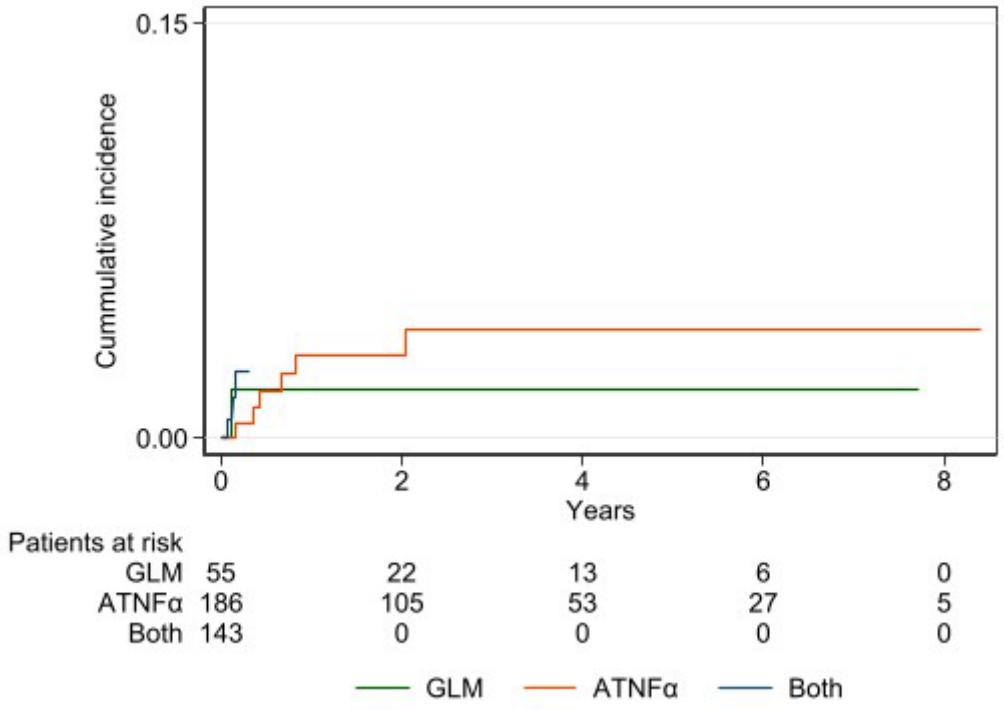
Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

Analysis Figure 1.5.7.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: 0



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

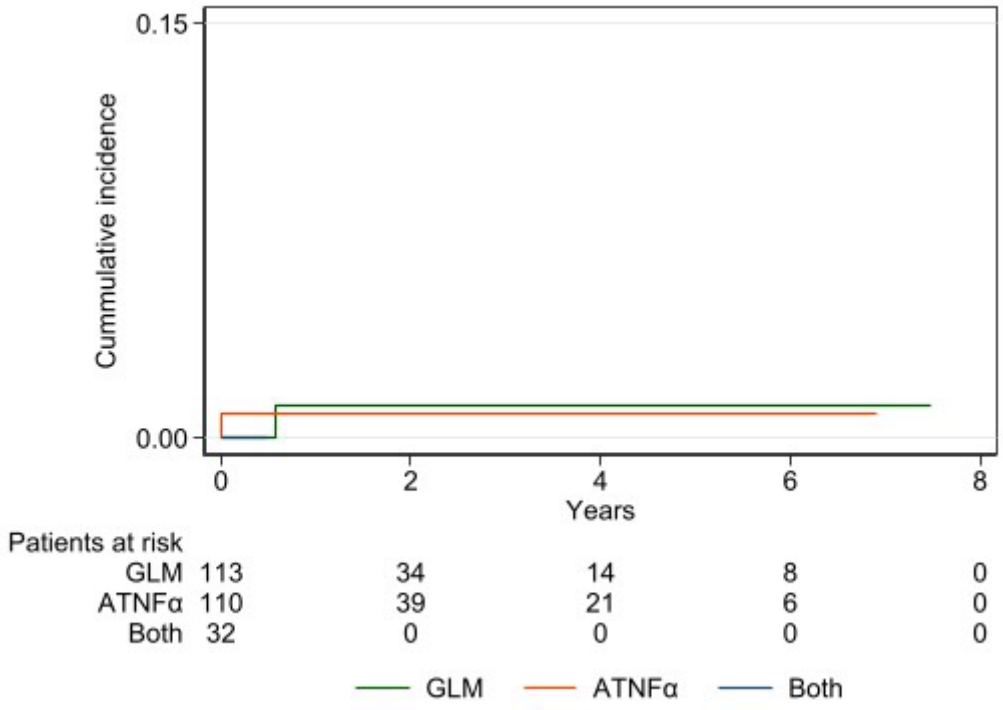
Analysis Figure 1.5.7.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: 1



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

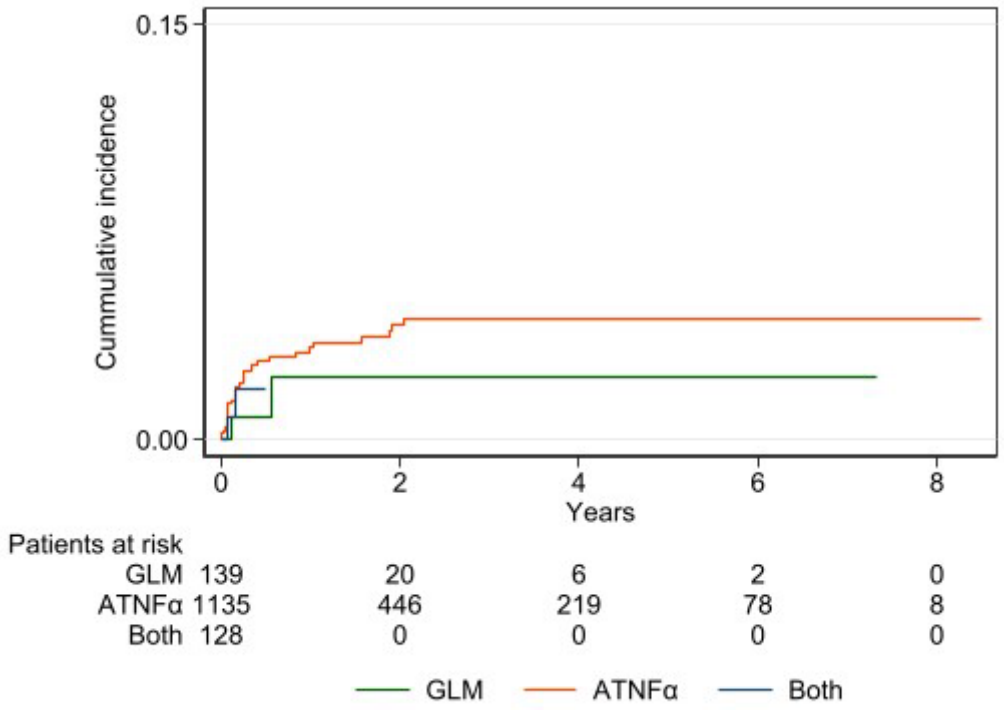
Analysis Figure 1.5.7.3: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: >1



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

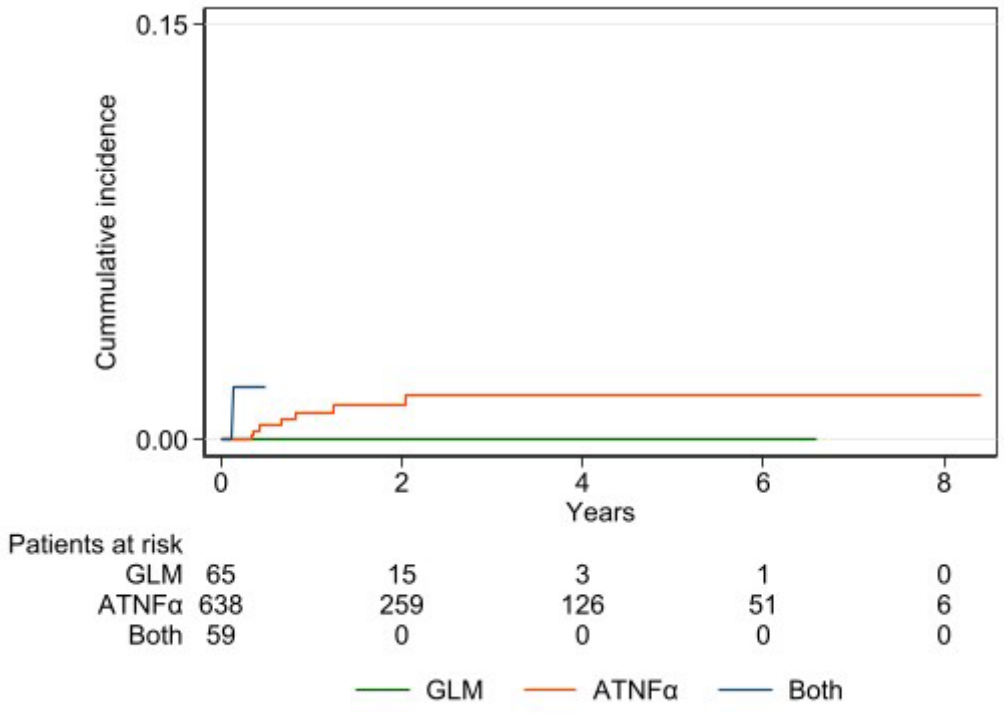
Analysis Figure 1.5.8.1: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Patients Exposed to an Other Anti-TNFα Agent for Which Entry Into the Cohort Was Qualified by the Initiation of Infliximab: Yes



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

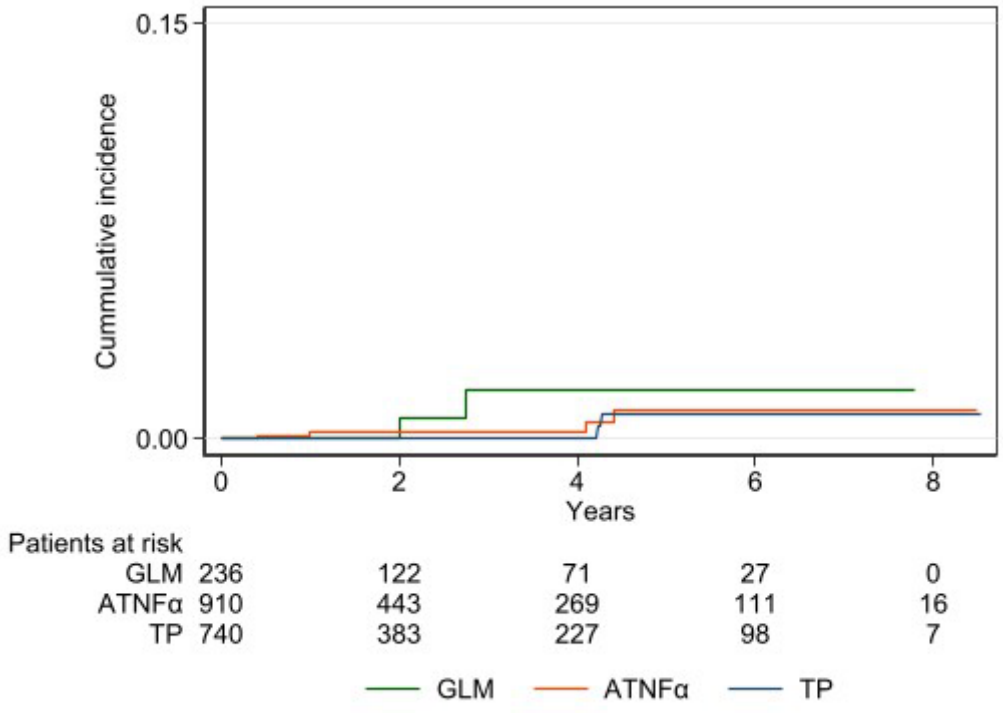
Analysis Figure 1.5.8.2: Cumulative Incidence of Colectomy Due to Intractable Disease, by Exposure Category; Subgroup: Patients Exposed to an Other Anti-TNFα Agent for Which Entry Into the Cohort Was Qualified by the Initiation of Adalimumab: Yes



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

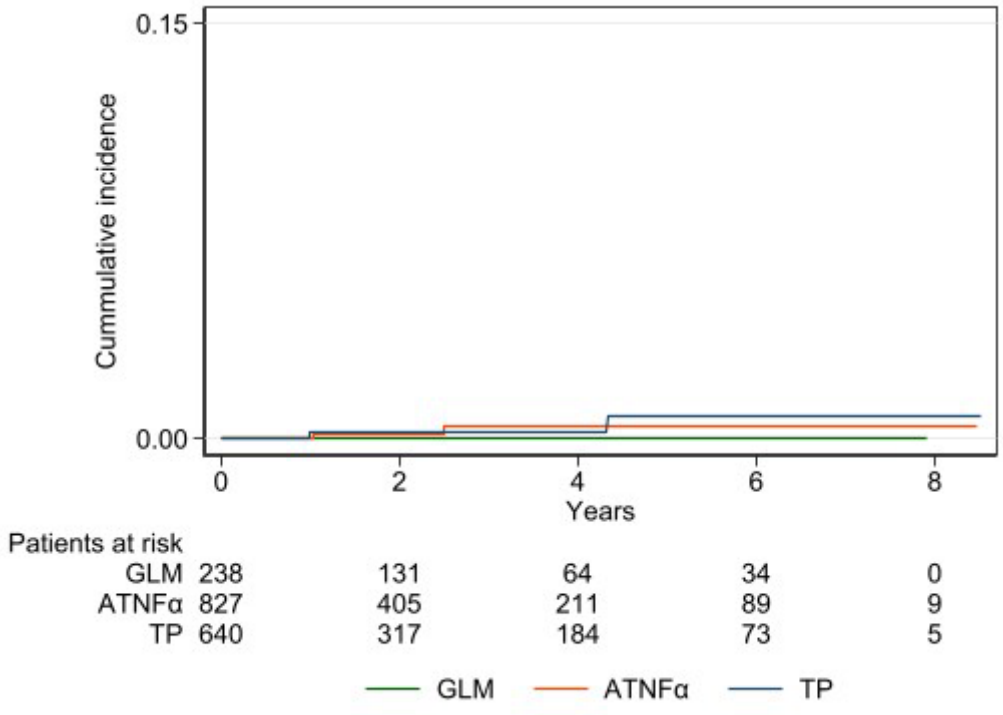
Note: "Both" refers to patients at risk and events occurring while exposed to both GLM and other anti-TNFα agents.

Analysis Figure 1.6.1.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Sex: Male



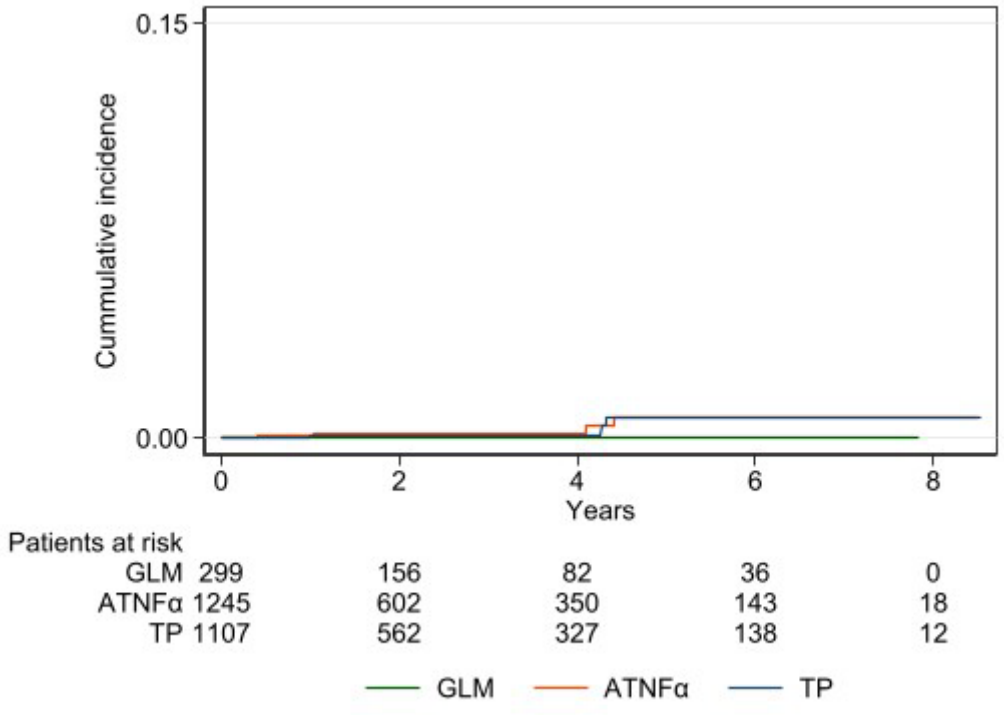
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.1.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Sex: Female



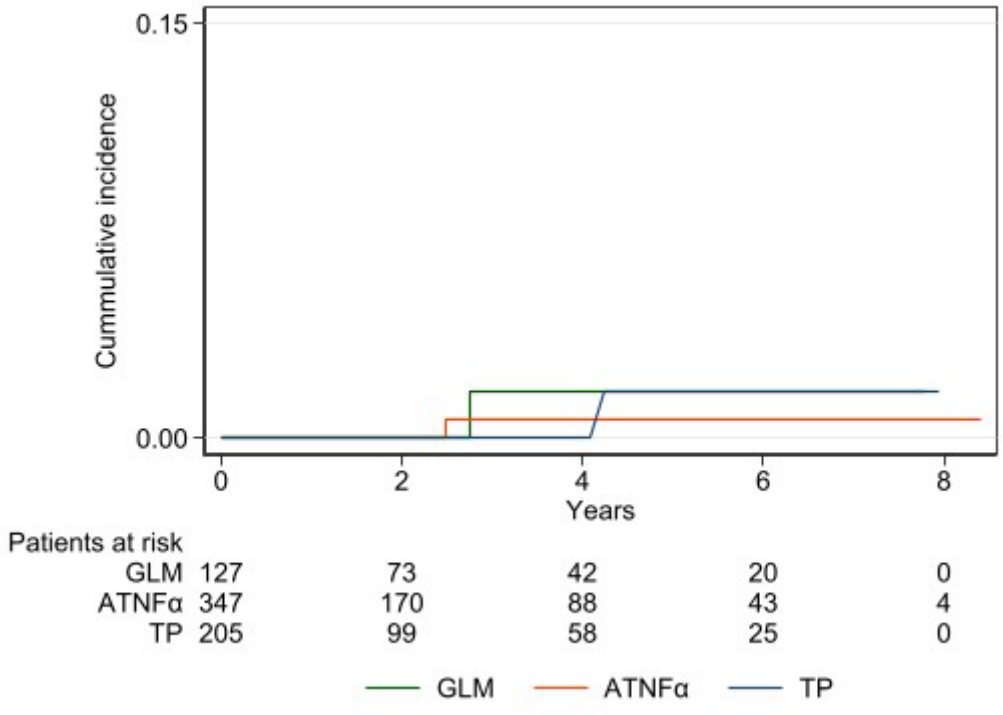
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.2.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Time Since Initial UC Diagnosis: <10 years



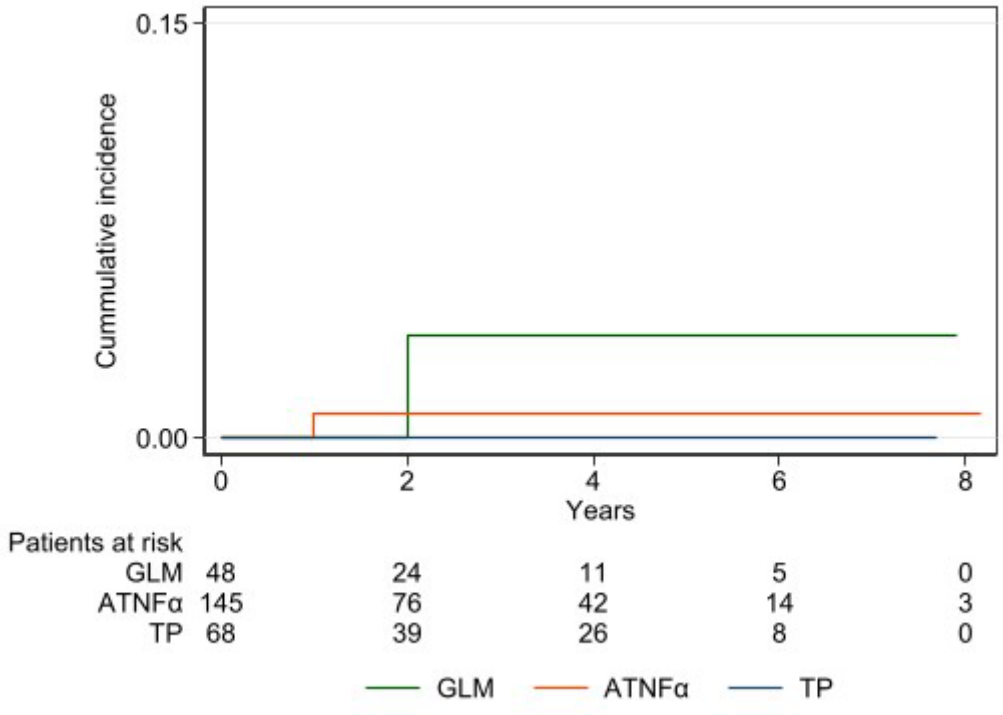
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine; UC, ulcerative colitis.

Analysis Figure 1.6.2.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Time Since Initial UC Diagnosis: 10 to <20 Years



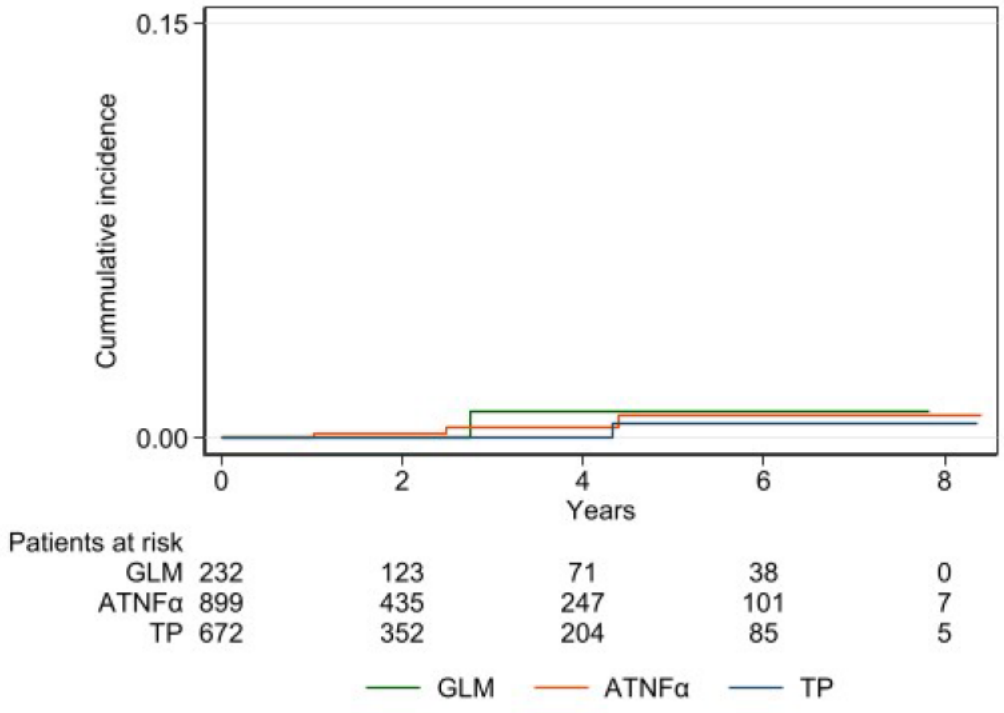
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine; UC, ulcerative colitis.

Analysis Figure 1.6.2.3: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Time Since Initial UC Diagnosis: ≥20 Years



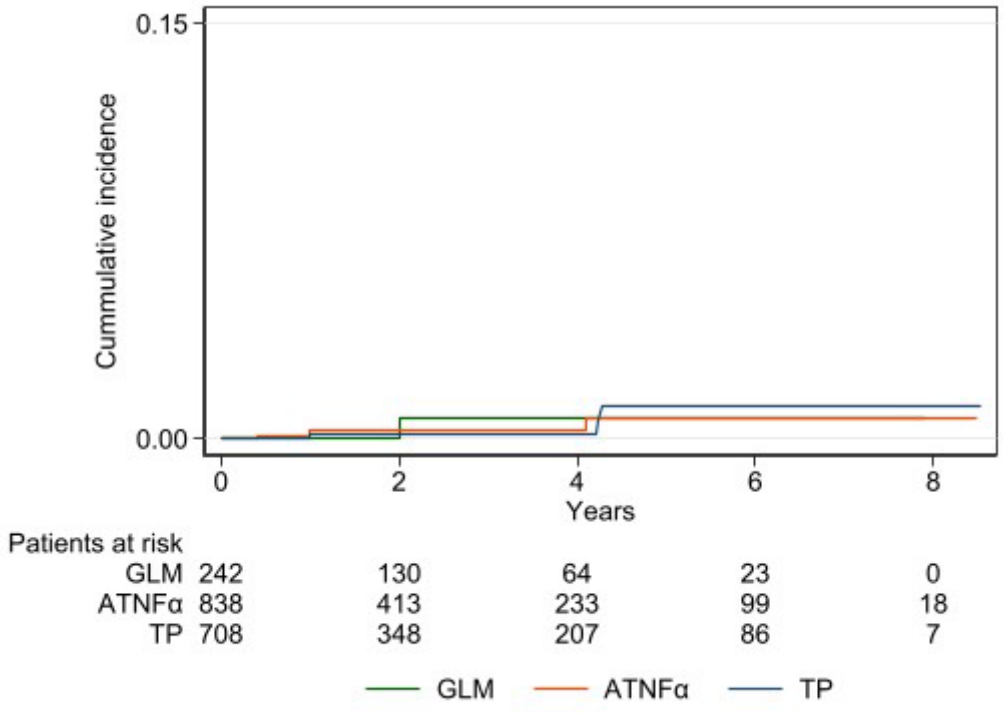
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine; UC, ulcerative colitis.

Analysis Figure 1.6.3.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Disease Extent: Extensive



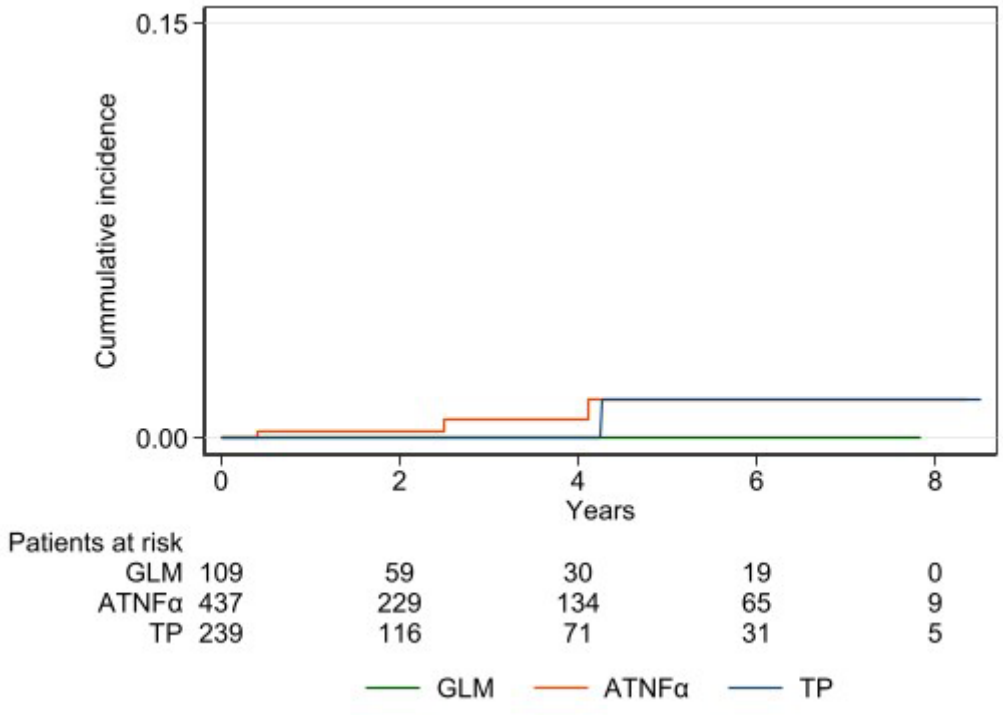
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.3.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Disease Extent: Other



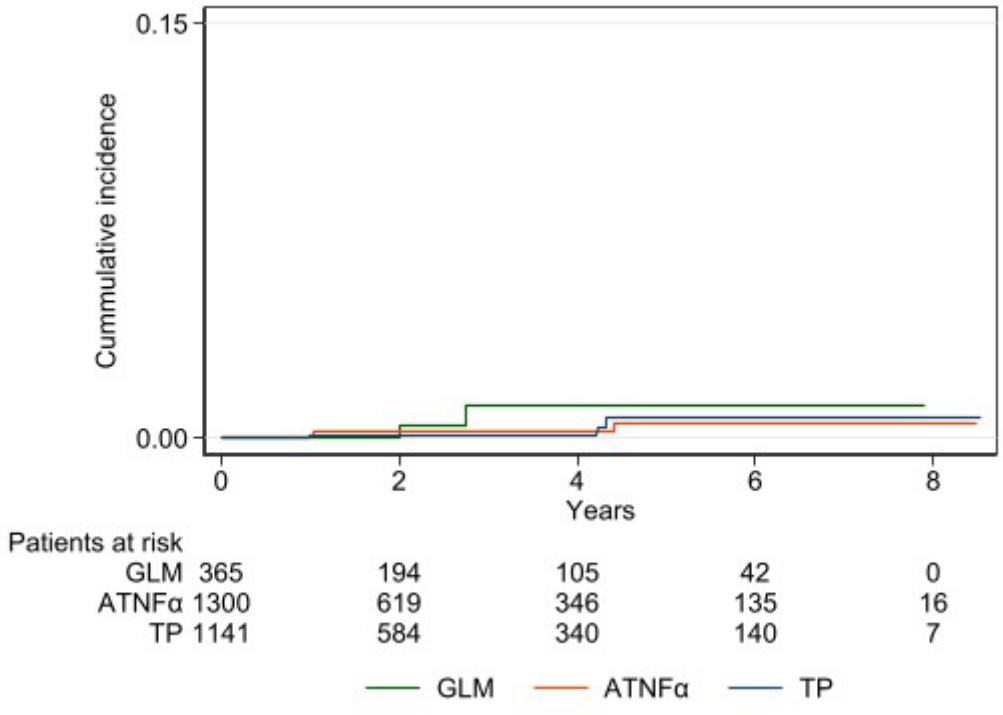
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.4.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; History of UC Hospitalization or Cyclosporine Use: Yes



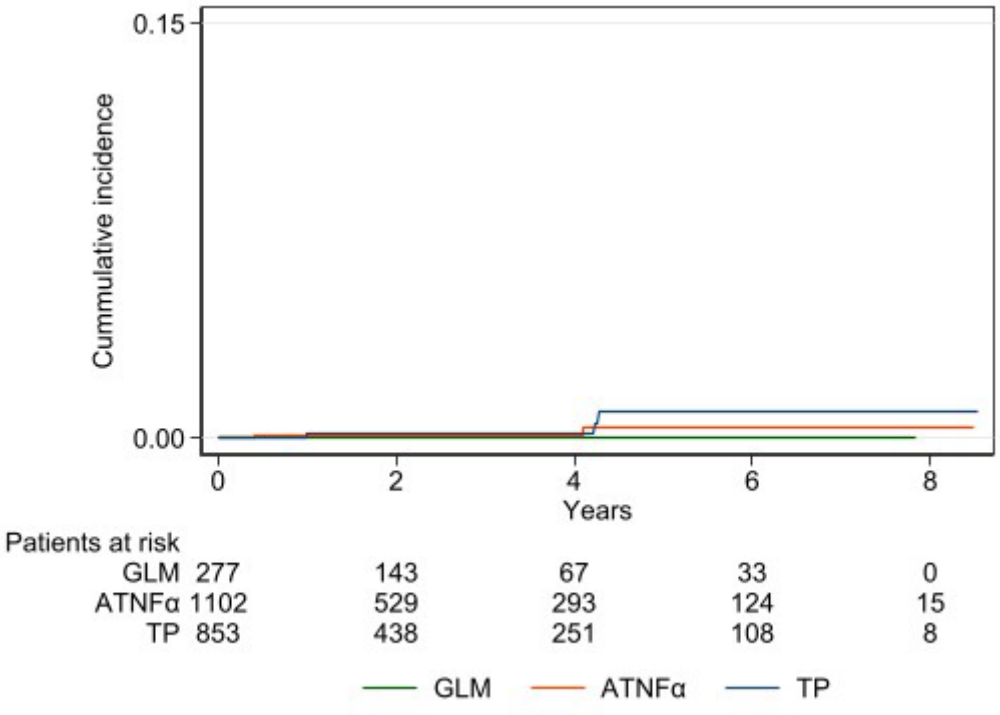
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine; UC, ulcerative colitis.

Analysis Figure 1.6.4.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; History of UC Hospitalization or Cyclosporine Use: No



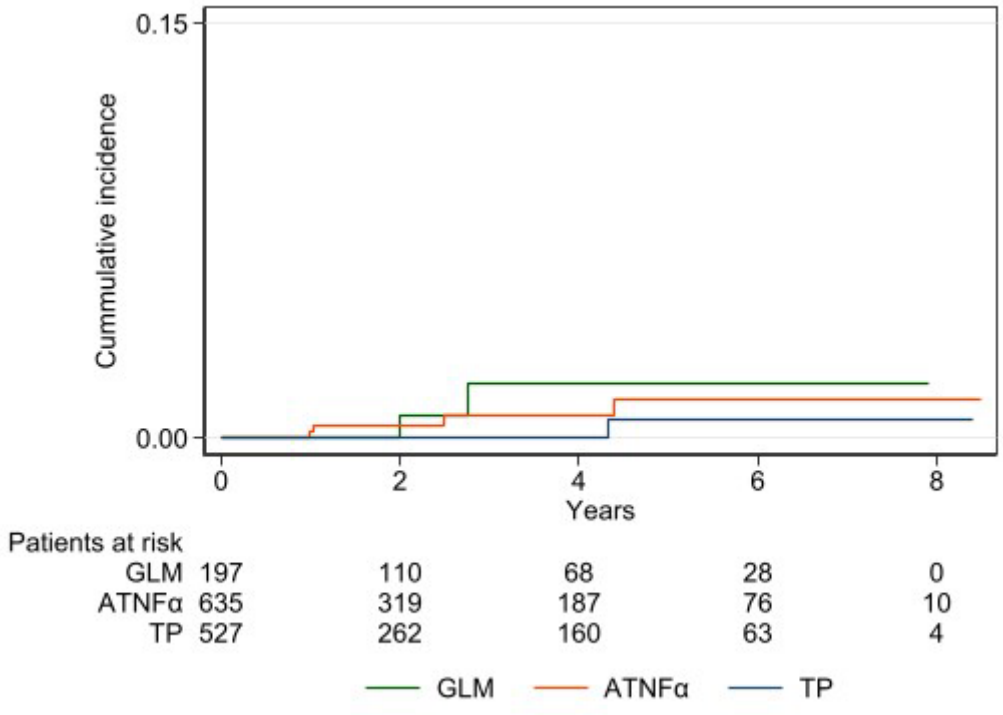
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine; UC, ulcerative colitis.

Analysis Figure 1.6.5.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Previous Use of Systemic Steroids: Yes



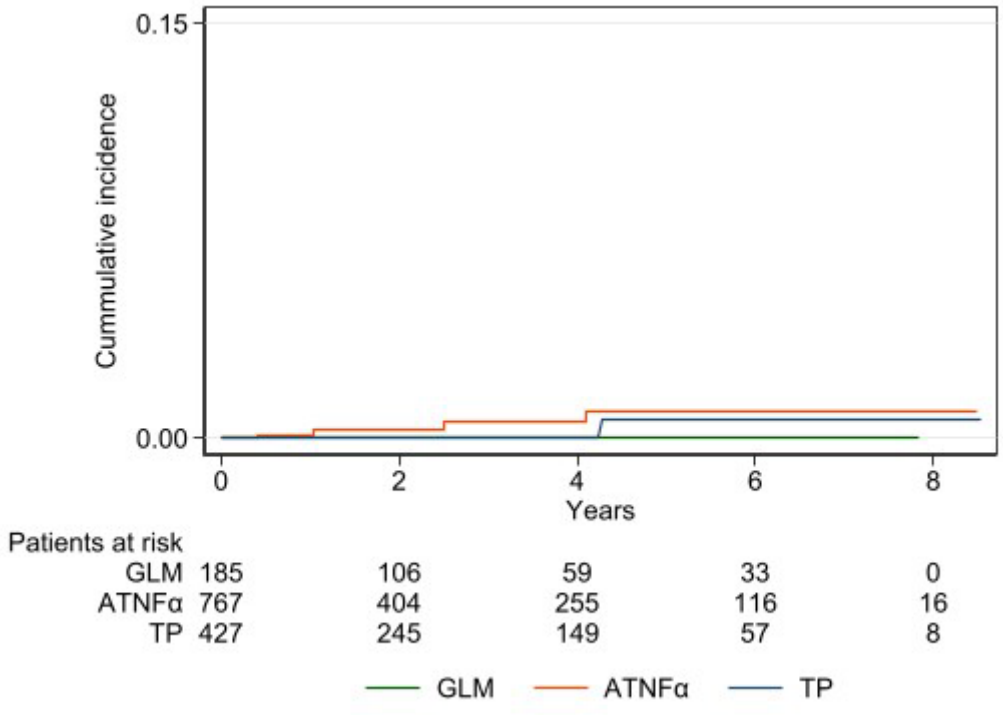
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.5.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Previous Use of Systemic Steroids: No



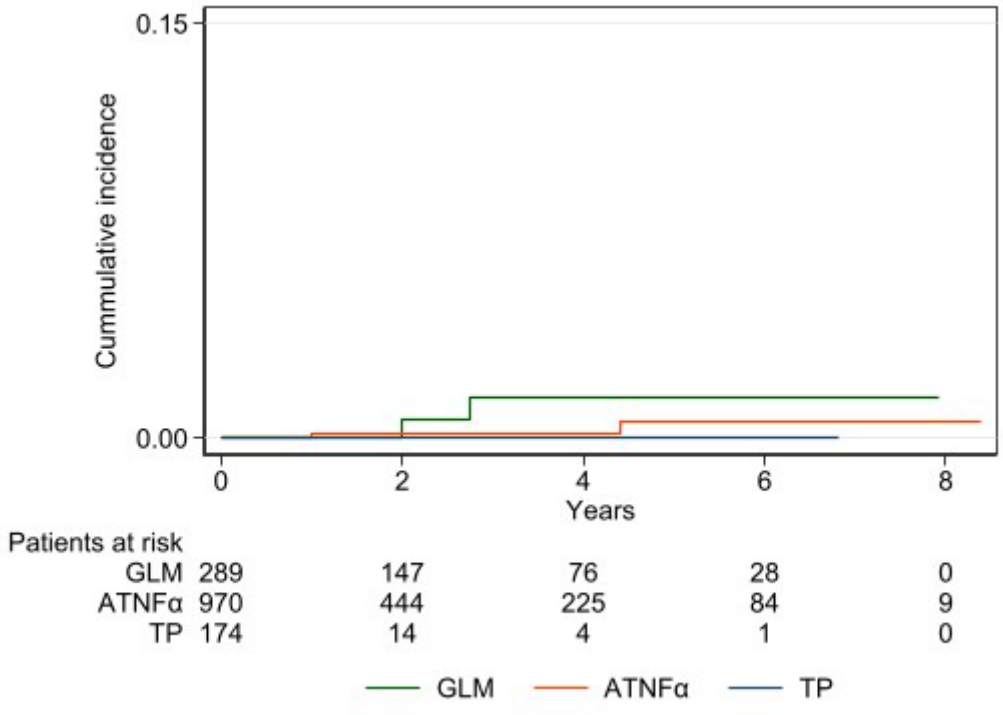
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.6.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Overlapping Use of Thiopurines: Yes



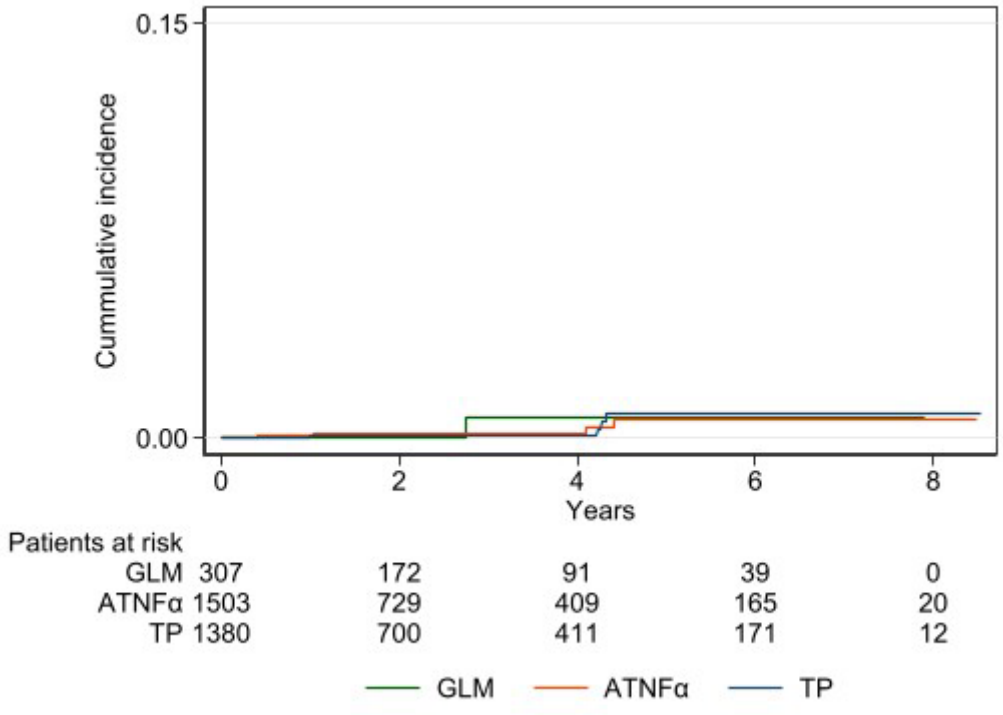
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.6.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Overlapping Use of Thiopurines: No



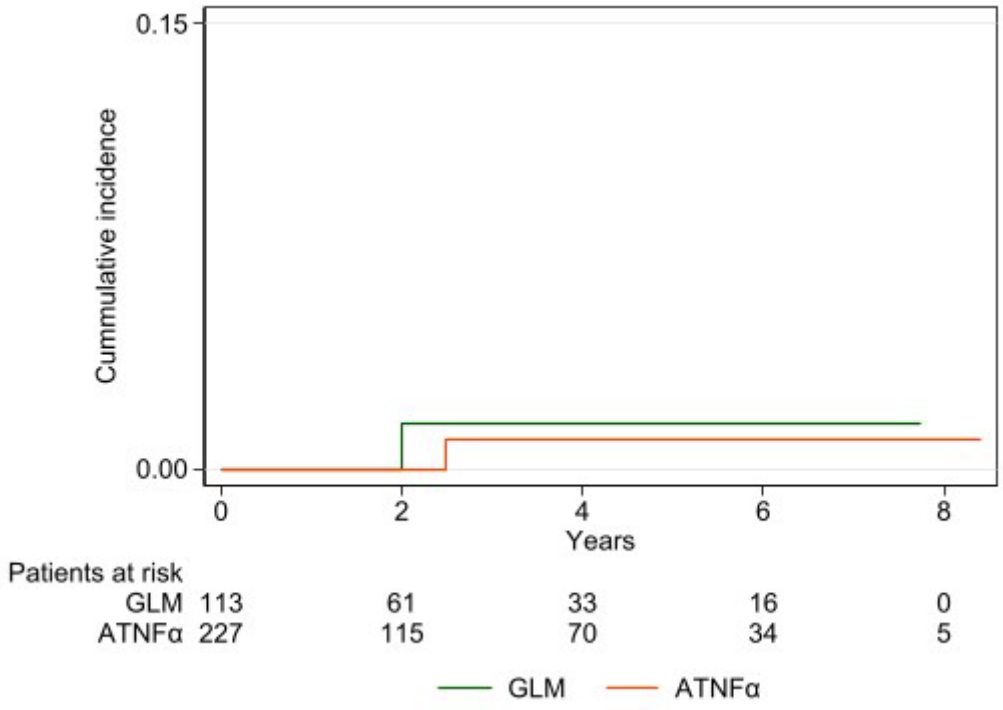
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.7.1: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: 0



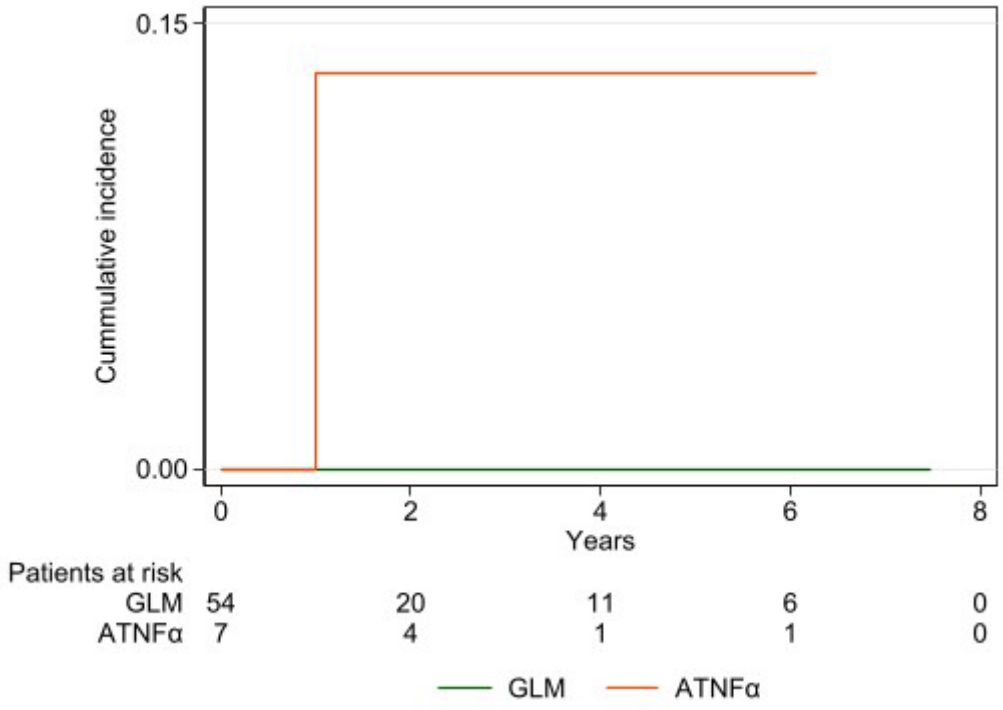
ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab; TP, thiopurine.

Analysis Figure 1.6.7.2: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: 1



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.

Analysis Figure 1.6.7.3: Cumulative Incidence of Advanced Colorectal Neoplasia, by Exposure Category; Subgroup: Number of Previous Anti-TNFα Agents: >1



ATNFα, other anti–tumor necrosis factor alpha; GLM, golimumab.