Clinical Study Protocol

EU PAS Number: EUPAS1000000767

Title: Infection Outcomes among Advanced Therapy-naive Older Adult US Patients with UC/CD Initiating ENTYVIO, TNF-alpha Inhibitors, or Ustekinumab: A Retrospective Observational Matched-Cohort Study Using Medicare Claims Data, 2016-2025

Study Number: Vedolizumab-4081

Document Version and Date: Version 1.0, 2 Dec 2025

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

NON-INTERVENTIONAL SAFETY STUDY PROTOCOL

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Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature Page

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MAH (Marketing Authorization Holder):

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EU QPPV:

Role	European Union (EU) Qualified Person responsible for Pharmacovigilance (QPPV)	**Printed Name**	[redacted] MD [redacted] EU-QPPV Office, Patient Safety and Pharmacovigilance
Signature	Signed by: [redacted]	**Date**	13-Dec-2025 | 05:32:50 JST

Study Information

Title	Infection Outcomes among Advanced Therapy-naive Older Adult US Patients with UC/CD Initiating ENTYVIO, TNF-alpha inhibitors, or Ustekinumab: A Retrospective Observational Matched-Cohort Study Using Medicare Claims Data, 2016-2025
Protocol number	Vedolizumab-4081
Protocol version identifier	V1.0
Date of last version of protocol	Not applicable
EU PAS register number	TBD
Active substance	1. ENTYVIO (vedolizumab) 2. Adalimumab 3. Infliximab 4. Golimumab 5. Certolizumab pegol 6. Ustekinumab
Medicinal product	ENTYVIO (vedolizumab)
Product reference	ENTYVIO (vedolizumab)
Procedure number	Not applicable
Joint PASS	No
Research question and objectives	**Research Question** Do rates of overall, serious, and non-serious infections differ between Medicare beneficiaries aged 65 years and older diagnosed with UC/CD who are new users of advanced therapy with ENTYVIO, TNF-alpha inhibitors, or ustekinumab? **Research Objective** This study aims to compare the rates of overall, serious, and non-serious infections among Medicare beneficiaries aged 65 years and older diagnosed with UC/CD who are new users of Entyvio versus new users of anti–TNF alpha antagonists or ustekinumab.
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2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
aHR	Adjusted Hazard Ratios
AMT	Advanced medical therapies
CD	Crohn's disease
CI	Confidence interval
cIR	Crude incidence rates
CMS	Centers for Medicare and Medicaid Services
EC	Ethics committee
DUA	Data use agreement
FFS	Fee-for-service
HCPCS	Healthcare Common Procedural Coding System
IBD	Inflammatory bowel disease
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IL-12/23	Interleukin 12/23
IRB	Institutional Review Board
NDC	National drug code
PAC	Post-acute care
PASS	Post-authorization safety study
PDE	Prescription drug event
PSM	Propensity score matching
RWE	Real-world evidence
SMRW	Standardized morbidity ratio weights
TNF-alpha	Tumor necrosis factor-alpha
UC	Ulcerative colitis
US	United States

3.0 RESPONSIBLE PARTIES

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4.0 ABSTRACT

Title

Infection Outcomes among Advanced Therapy-naive Older Adult US Patients with UC/CD Initiating ENTYVIO, TNF-alpha Inhibitors, or Ustekinumab: A Retrospective Observational Matched-Cohort Study Using Medicare Claims Data, 2016-2025

[redacted] *Outcomes Research IBD, US Medical*

Protocol v1.0

Rationale and background

ENTYVIO (vedolizumab) was approved in the US and EU in 2014 for the treatment of moderate-to-severe UC and CD. Prior to its approval, patients relied on TNF-alpha inhibitors for treatment, which, while effective, carry risks such as systemic immunosuppression and often lose efficacy over time. ENTYVIO provides patients with an alternative to TNF-alpha inhibitors[1], and has been associated with a potentially improved safety profile as compared to TNF-alpha inhibitors.[2] However, data on treatment safety among the older adult population using ENTYVIO and TNF-alpha inhibitors are limited.[3,4] More recently-approved treatment options for UC/CD, such as ustekinumab, are commonly used but also lack robust treatment safety information among the older adult population. As older adults may be potentially more

vulnerable to IBD- and treatment-related complications[5], generation of comparative safety evidence for treatment options is needed. The urgency of this need is compounded by a growing prevalence of IBD among older adults worldwide, both due to aging of the population and increasing incidence of IBD globally.[6]

Research question and objectives

This study aims to compare the rates of overall, serious, and non-serious infections among Medicare beneficiaries aged 65 years and older diagnosed with UC/CD who are new users of Entyvio versus new users of anti–TNF alpha medications or ustekinumab. The objective is to estimate the rates of overall, serious, and non-serious infections among ENTYVIO-, TNF-alpha inhibitor-, and ustekinumab-treated patients with UC/CD by disease, index AMT, and other key subgroups.

Study design

This will be a retrospective, observational, matched-cohort study which will be conducted within two separate Medicare data sources. The analysis for the first source, Medicare FFS claims data, will span from from 01 January 2016 to 31 December 2023. The analysis for the second source, Optum Clinformatics data, will span from 01 January 2016 to March 31, 2025.

Population

The study will include Medicare beneficiaries aged 65 years and older who are diagnosed with UC/CD and who used at least one AMT during the patient observation period.

Variables

The key exposure will be AMT, which will include the following medications and biosimilars where applicable: ENTYVIO; adalimumab; infliximab; ustekinumab; golimumab (UC only); and certolizumab pegol (CD only). Safety outcomes will include overall, non-serious, and serious infections.[2] Other study variables will include patient demographic and clinical characteristics. Additionally, several planned sensitivity analyses will be completed.

Data sources

This study will use two data sources. The first will be Medicare FFS Part A, B, and D claims data, accessed via Inovalon under a DUA with CMS. The dataset includes 100% of Medicare FFS claims and Part D drug event data, covering hospitalizations, outpatient visits, physician office visits, prescription drug claims, and durable medical equipment use for Medicare beneficiaries across the US.

The second data source will be Optum Clinformatics claims data. This dataset will contain claims from Medicare Advantage patients, which are not represented in Medicare FFS data. This data source captures prescription drug claims, hospitalizations, outpatient visits, and physician office visits for Medicare beneficiaries who use Medicare Advantage plans across the US.

Study size

All eligible patients identified in the source data will be included.

Data analyses

Descriptive statistics will summarize patient characteristics. Select covariates will be used to estimate propensity scores for receiving vedolizumab within UC or CD, and SMRW will be used to ensure covariate distribution in the comparator arms are like that of the ENTYVIO group.

We will calculate cIRs and aHRs with 95% confidence intervals (CIs) using standardized morbidity ratio-weighted Cox proportional hazard models with robust variance estimators to account for weighting.

Milestones

Authors aim to have a completed report by the end of Q1 2026.

5.0 AMENDMENTS AND UPDATES

None

6.0 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	15 DEC 2025	TBD	The data is retrospective claims data.
End of data collection	15 DEC 2025	TBD	This data is retrospective claims data.
Registration in the Catalogue of RWD Studies	TBD	TBD	
Final report of study results	31 MAR 2026	TBD	

7.0 RATIONALE AND BACKGROUND

ENTYVIO (vedolizumab), a first-in-class gut-selective integrin antagonist, was approved in 2014 for the treatment of moderate to severe UC and CD. Prior to its approval, patients relied on TNF-alpha inhibitors, such as infliximab and adalimumab, which, while effective, carry risks such as systemic immunosuppression, and often lose efficacy over time due to anti-drug antibody formation. ENTYVIO provides patients with alternatives to TNF-alpha inhibitors, especially for patients who do not respond to or have previously failed TNF inhibitor therapy.[1] Additionally, ENTYVIO has been suggested to have an improved safety profile when compared to TNF-alpha inhibitors, particularly related to a reduced infection risk.[2] This improved safety profile may be of particular importance for older adults, who are among those most susceptible to and at the greatest risk of harm from treatment-related infections.[4] However, limited information exists regarding comparative safety of these medications for older adults with IBD.[4]

There is a paucity of both randomized controlled trial and real-world evidence related to comparative safety of AMTs among older adults with IBD, especially within the US population. The most pronounced manifestation of this is the lack of population-specific treatment

recommendations in clinical guidelines for IBD.[7] Current clinical guidelines list "older adult" status as an implementation consideration for IBD AMT but make no direct claims regarding first-line therapy for this specific patient population.[7] Despite this lack of guideline-driven consensus around safety of IBD AMT among older adults, there is limited evidence to support utilization of ENTYVIO as a safe treatment option for this group.[3,8] For example, Kochar et al 2022 found that older adult IBD patients initiating ENTYVIO versus TNF-alpha inhibitors had a significantly lower risk of infection leading to hospitalization.[3] A meta-analysis performed by Kirchgesner et al in 2022 found that, among patients with UC, ENYTVIO was associated with a significantly decreased risk of serious infection compared to TNF-alpha inhibitors.[8] However, this same study found no difference in infection-related outcomes for IBD patients overall, or for patients with CD.[8]

Heterogeneity in existing findings, and the general lack of US-specific evidence, drives a need for further exploration of comparative safety of AMTs among the US older adult IBD population. The importance of evidence-based treatment recommendations for this group is compounded by the growing incidence and prevalence of IBD among older adults worldwide.[6,7] This study aims to fill this gap by estimating comparative rates of serious infections, an important safety endpoint, for older adults with IBD. Generation of this evidence can help to inform physician practice and guideline recommendations and will serve to improve outcomes among older adults with IBD.

8.0 RESEARCH QUESTION AND OBJECTIVES

This study will be conducted to generate evidence on comparative safety of ENTYVIO versus other AMTs (advance medical therapy) among Medicare beneficiaries. We hypothesize that Entyvio will have a lower rate of overall, serious, and non-serious infections compared to TNF-alpha inhibitors and ustekinumab.

Research Question

Do overall, serious, and non-serious infection rates differ between Medicare beneficiaries aged 65 and older diagnosed with UC/CD who initiate advance therapy treatment with ENTYVIO versus TNF-alpha inhibitors or ustekinumab?

Research Objective

Estimate the incidence of overall, serious, and non-serious infections during the follow-up period by disease, index AMT, and key advanced therapy-naive Medicare subgroups aged 65 and older.

9.0 RESEARCH METHODS

9.1 Study design

While two data sources are used and time periods between studies differ, the study design will remain the same.

A retrospective, observational, matched-cohort study design will be employed using (1) 100% sourced Medicare FFS secondary claims data from Parts A and B, standalone Part D PDE data, and enrollment data between 01 January 2016 and 31 December 2023; and (2) Optum Clinformatics Medicare Advantage claims data between 01 January 2016 and March 2025. The study will assess safety outcomes among continuously enrolled US adult patients diagnosed with UC or CD who initiated ENTYVIO or other AMTs. Patients will be identified using a claims-based algorithm incorporating ICD-10-CM codes, NDC, and HCPCS codes. Key study terms and temporal anchors can be found below.

- Study Period: Medicare FFS data: 01 JAN 2016 – 31 DEC 2023; Optum Clinformatics data: 01 JAN 2016 - 31 MAR 2025

- Index Date: Date of the first claim for an approved AMT for UC or CD occurring during the study period

- Patient Identification Period: Medicare FFS data: 01 JAN 2018 – 30 NOV 2023; Optum Clinformatics data: 01 JAN 2018 - 28 FEB 2025

- Baseline Period: This will include the 24 months prior to and including the Cohort entry date

- Follow-up Period: This will be a variable period following and including the Index Date, which will end on the first occurrence of any of the following:

    - Beneficiary date of death (if applicable)

    - End of the Study Period

    - Occurrence of the study outcome

    - Discontinuation of Index AMT
      Discontinuation will be defined as having no treatment claim for at least two cycle lengths of treatment plus days supply since last fill date, where a cycle length is equal to the typical administration for the medication.

        - A cycle length will be equal to the typical administration interval for a medication; for example, a cycle length for ENTYVIO IV would be 8 weeks (56 days).

        - For oral medications, the cycle length will be the last fill's days supply or imputed days supply based on quantity and US FDA-approved dosing information.

- Combination Therapy with AMT
  Combination therapy with AMT will be considered to occur if a patient initiates a second treatment without discontinuing the Index AMT, defined as an overlap of at least two cycle lengths between therapies.

- Switching of AMT
  Switching of AMT will be defined by either of the following scenarios: (1) a patient initiates a second AMT before discontinuation of the first and has an overlap of less than 2 cycle lengths between therapies; or (2) a patient initiates a second AMT that does not overlap with the Index AMT with less than 2 cycle lengths between the Index AMT and the second AMT

- Data Extraction date: Data will include the most recently available Medicare FFS claims data, which ends Q2 of 2024 for Medicare Parts A and B and Q4 2024 for Medicare Part D; for Optum Clinformatics data, the most recent data available will be used.

A study design flow chart for Medicare FFS data analysis is presented in Figure 1.

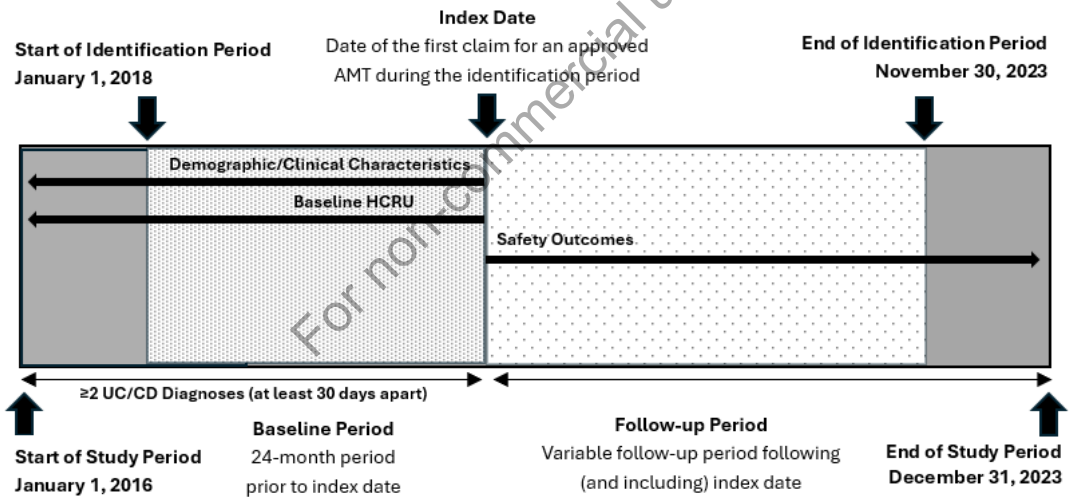

Figure 1. This is a visualization of the study design using Medicare FFS data

9.2 Setting

9.2.1 Study population

This study will use 100% samples of Medicare FFS beneficiary enrollment and demographic data, Medicare FFS parts A and B medical encounter data, and Medicare Part D retail and mail order pharmacy PDE data, as well as Optum Clinformatics Medicare Advantage claims data. Medicare Advantage is a privately-administered health plan which offers alternative coverage

from traditional or original Medicare plans in the United States. As of 2025, over half of all Medicare beneficiaries are covered by Medicare Advantage plans.

Thus, the sampling frame will include all Medicare beneficiaries in the United States who have used inpatient care, outpatient care, or generated pharmacy claims in the United States covered by original Medicare insurance and will also include patients who have opted for privately-administered Medicare Advantage plans. The study will include Medicare beneficiaries who are diagnosed with UC or CD who had continuous enrolment in Medicare Parts A, B, and D or in Medicare Advantage across the Baseline Period and Follow-up Period, and who used at least one AMT during the Patient Identification Period.

9.2.2 Inclusion criteria

Participants will be included in the study if they are eligible to be included in the UC or CD Study Cohorts, which are detailed below. Notably, analyses for UC or CD will be completed separately.

UC Study Cohort
Patients will be included if they had:

- ≥1 medical (for Medicare FFS, Part A/B) or pharmacy claim (for Medicare FFS, Medicare Part D) for an approved AMT for UC during the Patient Identification Period;
    - Note: Claim should be on or after the FDA treatment-specific approval dates for each drug
    - The date of the first claim during the Patient Identification Period will be designated the Index Date, and the corresponding AMT, the index AMT
- ≥2 medical (for Medicare FFS, Part A/B) claims, at least 30 days apart, with an ICD-10-CM code for UC during the Baseline Period or on the Index Date;
- Continuous enrollment in either Medicare FFS or Medicare Advantage medical and pharmacy benefits during the Baseline Period

CD Study Cohort
Patients will be included if they had:

- ≥1 medical (for Medicare FFS, Part A/B) or pharmacy claim (for Medicare FFS, Part D) for an approved AMT for CD during the Patient Identification Period;
    - Note: Claim should be on or after the FDA treatment-specific approval dates for each drug
    - The date of the first claim during the Patient Identification Period will be designated the Index Date, and the corresponding AMT, the index AMT
- ≥2 medical (for Medicare FFS, Part A/B) claims, at least 30 days apart, with an ICD-10-CM code for CD during the Baseline Period or on the Index Date;
- Continuous enrollment in either Medicare FFS or Medicare Advantage medical and pharmacy benefits during the Baseline Period

If a patient has both a UC and CD diagnosis during the baseline period or on the index date, the diagnosis most proximate to or on the index date will be used to categorize the patient as having UC or CD.

9.2.3 Exclusion criteria

Patients with any of the following will be excluded from the analysis:

- Any evidence of AMT utilization during the Baseline Period
- Patients with at least 2 ICD-10-CM codes for rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, hidradenitis suppurativa, juvenile idiopathic arthritis, non-infectious uveitis, or psoriatic arthritis during the Baseline Period
- Patients with 2 or more ICD-10-CM codes for non-dermatologic malignancy during the Baseline Period

9.3 Variables

9.3.1 Exposures

Focal Exposure

The focal exposure will be initiation of an AMT, as identified by any HCPCS or NDC claim for any of the TNF-alpha inhibitors or ustekinumab (see Table 1 below). Where applicable, AMTs will include both reference and biosimilar products. AMTs of interest are outlined in Table 1 below.

Table 1. Index AMTs of Interest by Disease State

Condition	Index AMT Cohort	Mechanism	Type
UC	ENTYVIO	α4β7 integrin inhibitor	Biologic
	Humira & biosimilars	TNF-α inhibitor	Biologic
	Remicade & biosimilars	TNF-α inhibitor	Biologic
	Any TNF-α inhibitor (i.e., Humira & biosimilars, Remicade & biosimilars, Simponi)	TNF-α inhibitor	Biologic
	Stelara & biosimilars	IL-12/23 inhibitor	Biologic
CD	ENTYVIO	α4β7 integrin inhibitor	Biologic
	Humira & biosimilars	TNF-α inhibitor	Biologic
	Remicade & biosimilars	TNF-α inhibitor	Biologic
	Any TNF-α inhibitor (i.e., Humira & biosimilars, Remicade & biosimilars, Cimzia)	TNF-α inhibitor	Biologic
	Stelara & biosimilars	IL-12/23 inhibitor	Biologic

In addition to head-to-head agent comparisons for ENTYVIO with ustekinumab and and other TNF-alpha inhibitors in Table 1, comparisons of ENTYVIO versus any TNF-alpha inhibitor (adalimumab, infliximab, golimumab (UC only), and certolizumab pegol (CD only) will be performed pending sample size required to produce adequate power.

9.3.2 Outcomes

All outcomes will be identified using HCPCS, NDC, and ICD-10 coding in Medicare claims or Optum Clinformatics Medicare Advantage data, depending on the nature of the outcome. Identification and classification of outcome events will be guided by prior literature and input from medical colleagues.

Serious, Non-serious, and Overall Infection Occurrence:
The proportion of patients (n [%]) experiencing serious, non-serious, and overall infections during the follow-up period as well as the crude incidence (i.e., number of events per X person-months of treatment) of safety event outcomes will be reported. The primary outcome will be a hospitalization for an infection, i.e. a "serious infection" (defined by the primary ICD code for the

hospitalization) per Grijalva et al, 2011, which includes infections of the respiratory tract, skin and soft tissue, genitourinary tract, gastrointestinal tract, central nervous system, and septicemia/sepsis.[2] Notably, this operationalization excludes intraabdominal infections, perianal infections, tuberculosis, and other opportunistic infections.[2,4] The first secondary outcome will be non-serious infections, which will include any primary diagnosis of infection that is not associated with hospitalization.[5] The second secondary outcome will be overall infections, which will be a composite measure of any hospitalized or non-hospitalized infection, using the Grijalva 2011 algorithm.

9.3.3 Covariates

Baseline Patient Characteristics
Baseline patient characteristics will include:

1. Age (at index): continuous and categorical (e.g., 18-39, 40-64, 65-69, 70-74, 75-79, ≥80)
2. Sex: categorical (male, female, unknown)
3. Geographic region: categorical (Northeast, Midwest, West, South, Unknown)
4. Race/ethnicity: categorical (White, Black, Asian, Hispanic, North American Native, Other)
5. Dual-eligibility status: categorical (full eligibility, partial eligibility, no eligibility, unknown)
6. Low-income Part D subsidy laboratory information system ("LIS") eligibility: categorical (full eligibility, partial eligibility, no eligibility, unknown)
7. Original reason for entitlement to Medicare: categorical (age, disability, both, other)

Baseline Clinical Characteristics
Baseline clinical characteristics will include:

8. Use of prior IBD conventional treatments
   - Immunomodulators
   - 5-ASA
   - Corticosteroids
   - Budesonide
9. Other immunological conditions
   - Psoriasis
   - Rheumatoid arthritis
   - Ankylosing spondylitis
   - Psoriatic arthritis
   - Hidradenitis suppurativa
   - Juvenile idiopathic arthritis
   - Non-infectious uveitis
10. Frailty index (Kim et al., 2018)[11]
11. IBD severity indices (Chen et al., 2020)[12]
12. Prior serious infections
13. Charlson Comorbidity Index (CCI): continuous and categorical (0, 1, 2, 3, 4, 5, 6, 7+)

14. Comorbidities
    - Myocardial infarction
    - Congestive heart failure
    - Peripheral vascular disease
    - Cerebrovascular disease
    - Dementia
    - Chronic pulmonary disease
    - Connective tissue disease
    - Peptic ulcer disease
    - Liver disease (mild, moderate, severe)
    - Diabetes mellitus, without complications
    - Diabetes mellitus with end-organ damage
    - Hemiplegia
    - Renal disease (moderate, severe)
    - Any tumor without metastasis
    - Metastatic solid tumor
    - Leukemia
    - Lymphoma
    - AIDS/HIV
15. Healthcare utilization in the Baseline Period
    - All-cause and UC/CD-related HCRU (by setting of care) will be measured during the baseline period
        - Settings of care across which HCRU is evaluated will include:
            - Hospitalizations
            - ER visits
            - Outpatient visits
            - Physician office visits
            - PAC (including long-term acute care hospitals, inpatient rehabilitation facilities, skilled nursing facilities, and home health agencies)
16. IBD surgeries in the Baseline Period

9.3.4 Variables for Determining Follow-up

The first day of follow-up will be the Index Date detailed in **9.1 Study Design.** This will be the date on which the first AMT claim occurs during the Patient Identification Period. After Index Date, patients will be followed until the first occurrence of any of the following: (1) beneficiary date of death; (2) the end of the Study Period; (3) occurrence of the study outcome; or (4) discontinuation of Index AMT. Discontinuation of index AMT will be determined as occurring when a patient has no treatment claim for at least two cycle lengths of treatments plus days supply since last fill date, where a cycle length is equal to the FDA-approved administration interval for a medication.

9.3.5 Planned Sensitivity Analyses

9.3.5.1 Stratifications by Key Subgroup

In addition to focal exposure outlined above, there will be planned stratifications of the analysis by key patient subgroups as part of sensitivity analyses. These subgroups, and the study variables which characterize them, are detailed below.

Post-Surgical Subgroup (Major). Patients will be included if they have:

- ≥1 claim for a qualifying major surgery during the 90-day period prior to the index date

Post-Surgical Subgroup (IBD-Related). Patients will be included if they have:

- ≥1 claim for a qualifying IBD-related surgery (e.g., abscess drainage, bowel resection, fistula removal/repair, ostomy, proctocolectomy, strictureplasty, etc.) during the 90-day period prior to the index date

Frailty Stratification. Stratify by frailty index (tertiles or other cut-point) by Kim et al, 2018.[11]

IBD Severity Stratification. Stratify the analysis into 3 strata based on tertiles of IBD severity score by Chen et al., 2020.[12]

9.3.5.2 Addition of Patients with Comorbid Autoimmune Conditions

In this sensitivity analysis, we will not exclude patients with at least 2 ICD-10-CM codes for rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, or psoriatic arthritis. Instead, we will stratify the analysis based on the presence of comorbid autoimmune conditions.

9.4 Data sources

9.4.1 Medicare FFS Claims Data

The study will utilize 100% samples of Medicare FFS beneficiary enrollment and demographic data, Medicare FFS Parts A and B medical encounter data (“medical claims”), and Medicare Part D retail and mail order pharmacy PDE data (“pharmacy claims”), accessed by Avalere via a research collaboration with Inovalon, Inc., and governed by a research-focused CMS DUA (“Medicare 100% FFS Database”). Medicare Parts A/B data are refreshed quarterly (six-month lag), and Part D data are updated annually. The study will use the most recent available data cut, including full 2023 Part D data. A summary of data elements for Medicare 100% FFS Database are highlighted in Table 2.

The DUA with CMS has two requirements with which this study must comply. First, this study will analyze no more than a 20% cohort of total Medicare population in any given year. Second, all cells with a sample size less than 11 will be suppressed when sharing results of our analyses.

This is to protect the confidentiality of beneficiaries by avoiding the release of information that could be used to identify them.

While CMS limits final cohort sizes to no more than 20% of total Medicare beneficiaries in any given year, we do not anticipate any concerns with that threshold for this study given that patients meeting the inclusion and exclusion criteria will not exceed 20% of total Medicare beneficiaries. The study cohort will be derived from the 100% sample of Medicare FFS Research Identifiable Files. The Part D Event file contains all pharmacy encounters for this population. The Medicare Master Beneficiary Summary File will be used to determine beneficiary monthly eligibility for Part A/B services, patient demographics, and where applicable, date of death.

Table 2. Summary of Data Elements Included in Medicare FFS Data

Data Files	Data Elements
Beneficiary Enrollment Details & Demographics	• Beneficiary FFS enrollment and coverage dates • Reason for FFS eligibility (e.g., age, disability, end-stage renal disease) • Gender, age, race/ethnicity, geographic region, low-income subsidy status • Validated date of death
Medical Claims (Part A and B)	• Hospitalizations, including readmissions (note: no visibility into drug utilization except ICD-10 procedure codes) • Emergency department visits • Post-acute care services, including skilled nursing and rehabilitation • Outpatient services, including surgical procedures, physician-administered treatments, office visits • Medicare payment amounts, secondary payments, out of pocket contributions
Pharmacy Claims (Part D)	• Fill date, drug name, class, strength, formulation, days' supply • Medicare payment amounts, secondary payments, foundation contributions and patient out of pocket contributions • Part D benefit phase (e.g., pre-catastrophic, catastrophic)

9.4.1 Optum Clinformatics Claims Data

The Optum Clinformatics data mart is a large, de-identified, longitudinal claims dataset containing information from both commercially insured and Medicare Advantage members. It contains information regarding enrollees' from demographic, enrollment, inpatient medical, outpatient medical, and pharmacy claims. Like Medicare FFS data, these data robustly support analyses of healthcare utilization, treatment patterns, and health outcomes. Medicare Advantage

beneficiaries will be identified within Optum Clinformatics claims data using the member enrollment files, where these individuals have a business products line as Medicare.

9.5 Study size

9.5.1 Medicare FFS Data
This study will analyze no more than a 20% cohort of total Medicare population in any given year. Additionally, all cells with a sample size <11 will be suppressed when sharing results of our analyses. This is to protect the confidentiality of beneficiaries by avoiding the release of information that could be used to identify them.

While CMS limits final cohort sizes to no more than 20% of total Medicare beneficiaries in any given year, we do not anticipate any concerns with that threshold for this study given that patients meeting the inclusion and exclusion criteria will not exceed 20% of total Medicare beneficiaries. The study cohort will be derived from the 100% sample of Medicare FFS Research Identifiable Files. The Part D Event file contains all pharmacy encounters for this population. The Medicare Master Beneficiary Summary File will be used to determine beneficiary monthly eligibility for Part A/B services, patient demographics, and where applicable, date of death.

9.5.2 Optum Clinformatics Claims Data
While above rules on Medicare cell size suppression do not apply to Optum Clinformatics data, Optum's minimum cells-size thresholds will be observed in the reporting of the analysis per Takeda's DUA with Optum.

9.5.3 Sample Size Calculations
Sample size calculations will be based on historical claims data and estimated incidence rates of healthcare utilization and safety events. Including all individuals from the database who meet the selection criteria maximizes the sample size.

Table 3 summarizes sample size estimates based on power calculations with a range of effect sizes. Based on Kochar 2022[3,4], we hypothesize an event rate of 5.0% during a 12-month follow-up period anda relative hazard of 0.6 for ENTYVIO versus TNF-alpha inhibitors for the primary outcome. Based on work performed using the same dataset by the vendor, we anticipate roughly the following sample sizes for each group of interest.

Among UC patients, we estimate the following:
- N = 4,700 eligible ENTYVIO users
- N = 1,200 eligible adalimumab (and biosimilar) users
- N = 3,500 eligible infliximab (and biosimilar) users
- N = 600 eligible ustekinumab (and biosimilar) users

Among CD patients, we estimate the following:
- N = 4,200 eligible ENTYVIO users
- N = 2,100 eligible adalimumab (and biosimlar) users
- N = 5,000 eligible infliximab (and biosimilar) users

- N = 2,600 eligible ustekinumab (and biosimilar) users

Given these estimates and information in Table 3, we anticipate that we may reach the number of events needed if the effect size is pronounced (HR = 0.6) or if the outcomes of interest are more common among the cohort (P_{event} = 5% to 7.5%). However, final sample sizes are not yet determined. Comparisons not adequately powered will be identified and results described with nominal p-values where necessary.

Table 3. Sample Size Estimates at Different Effect and Event Rate Estimates

Sample size estimation			
	Effect size		
	HR=0.8	**HR=0.7**	**HR=0.6**
Events needed	631	247	121
P-event	Total sample size needed*		
2.5%	25,240	9,880	4,840
5.0%	12,620	4,940	2,420
7.5%	8,413	3,293	1,613
*Parameters include α=0.05, β=0.2, and equal group sizes HR=hazard ratio of vedolizumab versus comparator on safety outcomes			

9.6 Data management

Data collection will involve extracting relevant information from administrative claims databases maintained by various healthcare payers, including Medicare FFS commercial insurance, Medicare Advantage, and Managed Medicaid plans. These databases contain records of medical claims, procedures, prescriptions, and demographic information, which will allow for the capture of all relevant study outcomes. As administrative claims exist for all adjudicated healthcare claims across all points of service, there will be no need for additional data collection methods such as self-reported or administered questionnaires for the purposes of addressing this study's objectives. The study will encompass a longitudinal design, with data collection occurring continuously over the study period. Follow-up assessments will occur at regular intervals, allowing for the tracking of patients' healthcare journeys over time. The total study duration, from the start of enrollment to the end of the study will be 01 JAN 2016 to 31 DEC 2023 for Medicare FFS data and 01 JAN 2016 to 31 MAR 2025 for Optum Clinformatics Medicare Advantage data.

Study documentation and data will be stored on secure, password protected servers. All management and analyses of the Medicare FFS administrative claims data will be performed by Avalere Health. SQL will be used to construct study cohorts; all descriptive analyses and statistical modeling will be performed using SAS Enterprise (version 8.3). All management and

analyses of the Optum Clinformatics Medicare Advantage claims will be performed by Genesis Research Group on Takeda's secure servers.

9.7 Data analysis

Overall, serious, and non-serious infection occurrence among the ENTYVIO cohort will be compared to each of the weighted comparisons samples identified in **Section 9.3.1 Exposures.** All analyses of the Medicare FFS administrative claims data will be performed by Avalere; all analyses of the Optum Clinformatics Medicare Advantages claims will be conducted by Genesis Research Group. For Medicare FFS analyses, SQL will be used to construct the study cohorts; all statistical analyses will be performed on Takeda's protected servers using SAS 9.4 (SAS Institute, Cary, NC). For Optum Clinformatics analyses, all statistical analyses will be performed using SAS Studio.

Descriptive Statistics

Descriptive statistics will be conducted to summarize patient characteristics for the number of patients with non-missing data.

- Continuous variables will be reported using means, medians, standard deviations (SD), and interquartile ranges (IQRs)
- Categorical variables will be reported as frequencies and percentages

Weighted Sample Creation

Age, sex, race, other IBD medications, presence of pre-biologic infection, HCRU, and IBD surgeries will be used to estimate propensity scores for receiving vedolizumab within UC or CD, respectively. To compare estimates of serious infections across arms, the covariate distribution of each comparator will be standardized to that of the vedolizumab group by applying standardized morbidity ratio weights (SMRW) calculated using the estimated propensity scores. After weighting the sample, covariate balance will be assessed using standardized mean differences, with a threshold of 0.10 as a meaningful difference between groups.

If the standardized mean differences exceed the threshold, which indicates imbalances exist between groups, the propensity score model specification will be evaluated and the model potentially re-specified to ensure correctness and completeness in propensity score calculation. If resulting standardized mean differences after propensity score model respecification still exceed the threshold, direct propensity score matching and double-adjustment, which involves adjusting for variables which are imbalanced between groups after matching or weighting during outcome assessment, will be explored.

Outcome Assessment

We will calculate crude incidence rates (cIRs) and estimated adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) using standardized morbidity ratio-weighted Cox proportional hazard models with robust variance estimators to account for weighting. Prior to model development, both the Schoenfeld residuals test and visual inspection of graphs (Kaplan-Meier curves and log-log plots) will be used to evaluate the proportional hazards assumption. A

statistically significant result (p value < 0.05) for the Schoenfeld test will indicate violation of the proportional hazards assumption. For visual inspection, non-parallel curves will be used to identify violations of the proportional hazards assumption. If the proportional hazards assumption is violated, alternative modeling approaches, such as utilization of stratified Cox models or the calculation of incidence rate ratios using generalized linear models, will be explored.

Planned analyses will be conducted separately for UC/CD and for each dataset in question. Comparisons of interest will include: ENTYVIO vs. ustekinumab and ENTYVIO vs. TNF-alpha inhibitors (see Table 4) for UC; and ENTYVIO vs. usekinumab for and ENTYVIO vs. TNF-alpha inhibitors (see Table 5). All analyses are based on feasibility numbers and are expected to be adequately powered (see Table 3).

Table 4. Planned Comparisons for Entyvio UC/CD in Medicare Study Among the Ulcerative Colitis Group

SMRW Comparison	ENTYVIO (Vedolizumab) Cohort	Comparator Cohort
UC PS	Patients with UC receiving ENTYVIO	Patients with UC receiving Humira (adalimumab) or biosimilars
UC PS	Patients with UC receiving ENTYVIO	Patients with UC receiving Remicade (infliximab) or biosimilars
UC PS	Patients with UC receiving ENTYVIO	Patients with UC receiving any TNF-a inhibitors
UC PS	Patients with UC receiving ENTYVIO	Patients with UC receiving Stelara (ustekinumab) or biosimilars

Table 5. Planned Comparisons for Entyvio UC/CD in Medicare Study Among the Crohn's disease Group

SMRW Comparison	ENTYVIO (Vedolizumab) Cohort	Comparator Cohort
CD PS	Patients with CD receiving ENTYVIO	Patients with CD receiving Humira (adalimumab) or biosimilars
CD PS	Patients with CD receiving ENTYVIO	Patients with CD receiving Remicade (infliximab) or biosimilars
CD PS	Patients with CD receiving ENTYVIO	Patients with CD receiving any TNF-a inhibitors
CD PS	Patients with CD receiving ENTYVIO	Patients with CD receiving Stelara (ustekinumab) or biosimilars

9.8 Quality control

9.8.1 Medicare FFS Claims Data

The data will be sourced directly from CMS claims records, ensuring high reliability. To ensure data accuracy and integrity, the study will adhere to strict data quality assurance measures, including:

- Routine validation checks to detect inconsistencies
- Standardized coding practices for diagnosis and procedure codes
- Data cleaning protocols to remove duplicate or erroneous claims

Avalere's programmers will leverage their expertise to ensure data quality of the analytic file generated from the data warehouse and will follow internal processes to ensure quality control of the data analysis and results. The statistical programming and analysis will be independently validated by a second programmer who will review the code (line-by-line), the output, and the outputted program log. The validator will use an internal validation log to confirm completeness of the project folder for the detailed contents. The validation log will contain sufficient information for identifying the project in an archive, as it details the project name and ID, project specification, date, and project team staff (e.g., program manager, team support, subject matter expert, programmer, validator). This validation log will indicate whether the validator and project manager have signed off on the statistical analysis. The validator will be responsible for completing the validation log to confirm the traceability of the project (e.g., documentation, program files), alignment of the deliverable with the analytic plan, accuracy of the results, and archiving of the program files.

9.8.2 Optum Clinformatics Medicare Advantage Data

Data used in this study is saved on the internal Takeda servers, in accordance with Takeda SOPs, and will be documented in a contract or Quality Agreement prior to use.

All programming and data quality standards will adhere to Takeda and Genesis Research Group's internal protocols. Access to data and analytic platform will be provided to Genesis analysts in accordance with Takeda's protocols and procedures.

9.9 Limitations of the research methods

9.9.1 Confounding

Despite SMRW, residual confounding may exist due to unmeasured variables (e.g., lifestyle factors). Sensitivity analyses may be used to assess robustness.

9.9.2 Selection Bias

Administrative claims data are derived from individuals with healthcare coverage, which may exclude uninsured or underinsured individuals. This bias can result in the underrepresentation of certain demographic groups. Disruption in the continuity of health insurance coverage may result in further attrition. Individuals who lose insurance eligibility or fail to pay insurance premiums may be subject to greater attrition due to discontinuous health insurance enrollment. The tradeoff in requiring continuous enrollment is to allow for ample opportunity to observe or not observe a cancer diagnosis, which would otherwise be another form of information bias.

9.9.3 Information Bias

As a claims-based study, this research relies on administrative coding, which may introduce misclassification bias and there are chances that some of the data that captures medical conditions and outcomes are not documented correctly. This can lead to patient misclassification either due to miscoding or misdiagnosis. Miscoding can occur for a variety of reasons, such as submission of an incorrect code by a provider; use of a less descriptive ICD-10-CM billing code rather than a more specific code; upcoding to maximize reimbursement; and/or deletion of a diagnosis code from the billing form.

9.10 Other aspects

The findings will be generalizable to Medicare FFS and a number of Medicare Advantage beneficiaries but may not fully reflect the broader UC/CD patient population. This study will leverage comprehensive Medicare claims data to analyze UC/CD safety outcomes among patients taking AMTs. A SMRW cohort design ensures robust comparisons. Limitations include missing clinical data and generalizability constraints to non-Medicare populations.

10.0 PROTECTION OF HUMAN SUBJECTS

10.1 Informed Consent

This study only involves the use of anonymized electronic healthcare records. The researchers will not have any access to named or identifiable patient information. Informed consent is not required.

10.2 Institutional Review Board or Ethics Committee

This study only involves the use of anonymized electronic healthcare records. The researchers will not have any access to named or identifiable patient information. IRB/EC review will not be required.

10.3 Privacy and Confidentiality

The privacy rights of individuals and the confidentiality of medical records will be protected in accordance with all applicable laws, regulations, and guidelines.

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 regarding confidentiality and data protection will be followed in connection with all processing of data from US-based subjects.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly year of birth will be recorded. They may be transferred to, and used in, other countries which may not provide the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer and use may include: to support regulatory submissions, to conduct new data analyses, to publish or present the study results, or to answer questions asked by regulatory or health authorities. The sponsor may transfer data collected in this study to its affiliates, collaborators, licensees, or other companies and organizations working with or for the sponsor in connection with these purposes.

11.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definitions

11.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

11.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Healthcare provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

- An SAE may also be any other medically important event that, in the opinion of the Healthcare provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

11.1.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

11.1.4 Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product or device and combination product after it is released for distribution.

11.1.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse, or medication error: All information on medicinal product abuse, misuse, or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label” and “off-label use” for unintended benefit
- Use of falsified medicinal product
- Use of counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- AEs occurring in the pediatric or elderly population, as described in GVP Module VI

An SSR should be reported even if there is no associated AE.

11.2 Collection and notification of Adverse Events, Special Situation Reports and Product Quality Complaints to Takeda Pharmacovigilance or Takeda Quality

- SAEs, AEs, ADRs, SSRs and PQCs in the healthcare record or other applicable source data that are part of the study objectives or endpoints

Events/complaints which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized in aggregate as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance and/or Takeda Quality

- SAEs, AEs, SSRs and PQCs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints

Events/complaints which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

- SAEs, AEs, ADRs, SSRs and PQCs spontaneously reported to the investigator(s) or research team

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQC where the event/complaints pertains to a Takeda product (or unbranded generic), such information should be forwarded to the relevant Takeda Pharmacovigilance and/or Takeda Quality department within 1 business day for fatal or life-threatening SAEs and PQCs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

The Investigator may be contacted by Takeda to obtain additional information on the event or for data clarification.

<u>Contact list for Reporting of Adverse Events and Special Safety Reports (SSRs)</u>

Adverse event reports and SSRs shall be sent to the following contact:

Phone : 1-877-TAKEDA7 (877-825-3327)

Email : PVSafetyAmericas@takeda.com

Fax : 1-224-554-1052

Contact list for Reporting Product and Quality Complaints (PQCs)

Product and Quality Complaints shall be sent to the following contact.

Email: PQC@takeda.com

12.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Public Posting and Disclosure of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. The study will be registered in the Catalogue of RWD Studies and made available on ClinicalTrials.gov as well as Takeda's own clinical trails website, ClinicalTrails.Takeda.com.

Avalere and Inovalon have an obligation based on their DUA with CMS to disseminate certain notable findings of our research. Avalere will complete the project and provide a summary of notable findings and disseminate to the public via an "Avalere Insight" post released on Avalere's website. The post-project dissemination obligation is intended to expand the knowledge base for the broader Medicare research community. As such, the dissemination would aggregate the findings at a cohort, regional, national level, etc. The Project Manager or another designated member of the project management team, will be responsible for disseminating the "Avalere Insight". The client will elect whether to be recognized as the funder of the research on the "Avalere Insight" or not.

12.2 Study Results/Publications

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts, and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

After the research data are finalized and become available, the scope, planning, and development of the publication(s), and how such publication(s) will be reviewed and amended is all in accordance with The International Society for Medical Publication Professionals (ISMPP) Good Publications Practice (GPP3). Unless otherwise required by the scientific journal to which the publication is submitted, or the forum in which it is presented, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

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APPENDICES

Annex 1 List of Stand-Alone Documents

None

Annex 2 ENCePP Checklist for Study Protocols

Not applicable

Annex 3 Additional Information

Not applicable