Special Assessment to Inform CMS Drug Price Negotiations: Vedolizumab (Entyvio®) for Ulcerative Colitis and Crohn's Disease

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Jeffrey A. Tice served as the lead author for the report. Shahariar Mohammed Fahim and Abigail Wright led the systematic review and authorship of the comparative effectiveness section of this report with assistance from Finn Raymond and Sol Sanchez. Marina Richardson developed the cost-effectiveness model and authored corresponding sections of the report with support from Woojung Lee. Daniel Ollendorf provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Becca Piltch and Anna Geiger for their contributions to this report.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit:
https://icer.org/assessment/special-assessment-cms-2026/#overview

Conflict of Interest Disclosures for the Report

Table 1. ICER Staff and External Collaborators Conflict of Interest Disclosures

ICER Staff and External Collaborators	Conflict of Interest
Shahariar Mohammed Fahim, PhD, Senior Research Lead, Institute for Clinical and Economic Review	No conflicts to disclose.
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Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
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Sara Lewin, MD, Associate Professor of Medicine, University of California, San Francisco	Dr. Lewin receives research funding through her institution. Dr. Lewin has served as a Principal Investigator on studies run and funded by Takeda Pharmaceuticals, but not for any of the drugs within the scope of this review.
Alan Moss, MD, Chief Scientific Officer, Crohn's & Colitis Foundation	Dr. Moss has no conflicts to disclose. The Crohn's & Colitis Foundation receives 30% of annual funding from health care companies, including, Takeda Pharmaceutical Company, AbbVie Inc., Amgen, Celltrion, Pfizer, and Janssen Pharmaceuticals.
Matthijs Versteegh, PhD, MA, MSc, Founder, Huygens and Versteegh	Dr. Versteegh developed the Crohn treatment sequence model for the Dutch Health Care Institute (ZIN). Dr. Versteegh is the co-owner of Huygens and Versteegh, which receives 95% of annual funding from health care companies, including, Merck & Co., Optimax Systems, ICER US, Pfizer, Santen Pharmaceutical, iMTA, and Erasmus Medical Center.

This page includes conflict of interest disclosures for ICER staff, external collaborators, and expert reviewers of the report.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

AIAN	American Indian or Alaskan Native
ACG	American College of Gastroenterology
ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program Participant
ADA	adalimumab
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ASP	Average Sales Price
AZA	Azathioprine
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CRD	Clinical Trial Diversity Rating
CMS	Centers for Medicare and Medicaid Services
CrL	Credible Interval
CRP	C-Reactive Protein
EIMs	Extraintestinal Manifestations
EQ-5D-5L	EuroQol-5 Dimensions
ER	Emergency Room
ESR	Erythrocyte Sedimentation R
evLY	Equal-Value Life Year
FDA	Food and Drug Administration
GI	Gastrointestinal
HCUP NIS	Healthcare Cost and Utilization Project National Inpatient Sample
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IFX	Infliximab
IL	Interleukin
IMM	Immunomodulators
IRA	Inflation Reduction Act
IRR	Incident Rate Ratio
IV	Intravenous
JAK	Janus Kinase
Kg	Kilogram
LTS	Long-Term Study
MCID	Minimal Clinically Important Difference
MCS	Mental Component Summary
Mg	Milligram
Mg/dL	Milligram per Deciliter
MS-DRG	Medicare Severity Diagnosis Related Group
N	Number
NMA	Network Meta-Analysis
NR	Not Reported
NC	Not Calculated
NE	Not Estimated
NHPI	Native Hawaiian or Pacific Islander
OL	Open Label
OR	Odds Ratio
PDRR	Participant to Disease-prevalence Representation Ratio
PBO	Placebo

PCS	Physical Component Summary
RCT	Randomized Controlled Study
RoB 2	Cochrane Risk of Bias Assessment Tool Version 2
RR	Risk Ratio
SC	Subcutaneous
SF-36	36-Item Short Form Survey
SMR	Standardized Mortality Ratio
TIMs	Targeted Immune Modulators
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
US	United States
UST	Ustekinumab
VEDO	Vedolizumab
WAC	Wholesale Acquisition Cost
WPAI	Work Productivity and Activity Impairment Questionnaire

Executive Summary

Under the Inflation Reduction Act (IRA), the Centers for Medicare and Medicaid Services (CMS) has initiated drug price negotiations on selected Medicare Part B and D drugs with participating drug manufacturers. In October of 2023, the Institute for Clinical and Economic Review (ICER) published a special report on two of the 10 drugs selected for the first cycle of drug price negotiations, apixaban and rivaroxaban.[1] In March of 2025, ICER published a special report on two of the 10 drugs selected for the second cycle of drug price negotiations, Trelegy Ellipta® and Breo Ellipta®.[2] CMS released draft guidance for the third cycle of negotiations in May of 2025 and this ICER special report focuses on vedolizumab (Entyvio®), which is subject to price negotiations in this cycle.[3]

Ulcerative colitis (UC) and Crohn's disease (CD) are the two different types of immune-mediated inflammatory bowel diseases (IBD). UC primarily affects the mucosa, the innermost lining of the intestinal wall in the large bowel (i.e., the colon and rectum).[4] Crohn's disease, on the other hand, can affect the entire GI (gastrointestinal) tract from the mouth to the anus and can involve the full thickness, not just the mucosa. These diseases cause long-lasting inflammation and ulcers in the digestive tract and are typically marked by periods of remission and recurrence of symptoms. Symptoms may include frequent diarrhea, sometimes with blood or pus, abdominal and/or rectal pain, weight loss, and fatigue.[5] It is estimated that approximately 2.4 to 3.1 million individuals in the United States (US) have IBD.[6] Most individuals are diagnosed between the ages of 15 and 35.[7] However, there is an increasing incidence of IBD among older adults.[8] Among 25 million Medicare fee-for-service beneficiaries, there are approximately 100,000 people with CD (0.40%) and 160,000 people with UC (0.64%).[9] The economic burden of IBD is significant, with recent estimates of $50 billion per year in the United States.[10]

Both UC and CD are diagnosed based on symptoms of the disease and confirmed by colonoscopy with biopsy.[11] The management of IBD in adults is dependent on the severity of symptoms. Those with moderate to severe disease are candidates for targeted immune modulators (TIMs) to induce and/or maintain remission, including the tumor necrosis factor (TNF) inhibitors adalimumab (Humira®, AbbVie as well as biosimilars), golimumab (Simponi®, Janssen), infliximab (Remicade®, Janssen as well as biosimilars), the $\alpha_4\beta_7$ integrin inhibitor vedolizumab (Entyvio®, Takeda), the Janus kinase (JAK) inhibitor tofacitinib (Xeljanz®, Pfizer), the interleukin (IL)-12 and IL-23 inhibitor ustekinumab (Stelara®, Janssen, as well as biosimilars), and the IL-23 inhibitors (Skyrizi® [risankizumab], Omvoh® [mirikizumab], and Tremfya® [guselkumab]).

Entyvio is indicated for moderate to severe active UC and CD. The recommended dosage is 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks (i.e., "induction therapy"), then every eight weeks thereafter (i.e., "maintenance therapy").

Additionally, a subcutaneous (SC) formulation of Entyvio is available for maintenance therapy, which can be initiated as early as six weeks after the initial two intravenous (IV) infusions. The recommended dosage is 108 mg subcutaneously every two weeks.

Major therapeutic alternatives were determined following consultation with clinical experts and current clinical guidelines. Because our focus was on the comparative effectiveness of Entyvio with other biologic therapies, we focused on guideline-directed monotherapy for patients with moderate to severe disease (infliximab, adalimumab, ustekinumab), rather than combinations with additional immunosuppressive therapies like azathioprine.

Infliximab (Remicade®, Janssen as well as biosimilars) is a TNF blocker administered by intravenous infusion. Infliximab can also be administered subcutaneously (Zymfentra®, Celltrion). Ustekinumab (Stelara®, Janssen, as well as biosimilars) is a human interleukin-12 and -23 antagonist administered intravenous infusion. Adalimumab (Humira®, Abbvie) is a TNF blocker administered by subcutaneous injection.

Table ES1. Evidence Ratings Ulcerative Colitis

Treatment	Comparator	Evidence Rating
Adults with Moderate to Severe Ulcerative Colitis		
Entyvio	Ustekinumab	C-
	Infliximab	C+
	Adalimumab	C+

C+: 'Comparable or Incremental', Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit; C-: 'Comparable or Inferior', Moderate certainty that the net health benefit is either comparable or inferior, with high certainty of at best a comparable net health benefit

We rated Entyvio as comparable or inferior to ustekinumab (C-). For the patient-important outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences, nor were there any important differences in observational data. However, the trend was for higher rates of response, remission, and fewer discontinuations due to adverse events (AEs) with ustekinumab. In the absence of head-to-head randomized trials, we cannot rule out a small net health benefit for ustekinumab relative to Entyvio.

Entyvio was rated comparable or better than the anti-TNF drugs infliximab and adalimumab (C+). For the patient-important outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences. However, there were fewer serious infections with Entyvio in observational data, and both infliximab and adalimumab carry black box warnings for serious infections and malignancies. In the absence of head-to-head randomized trials, we cannot rule out a small net health benefit for Entyvio.

Table ES2. Evidence Ratings Crohn's Disease

Treatment	Comparator	Evidence Rating
Adults with Moderate to Severe Crohn's Disease		
Entyvio	Ustekinumab	C
	Infliximab	C+
	Adalimumab	C+

C: 'Comparable', High certainty of a comparable net health benefit; C+: 'Comparable or Incremental', Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit

Entyvio is comparable to ustekinumab (C). For the outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences, nor were there any important differences in observational data other than one study reporting lower rates of serious infection with ustekinumab. This was not observed in a second observational study, nor was it seen in studies comparing ustekinumab with Entyvio in patients with UC.

Entyvio is comparable or better than the anti-TNF drugs infliximab and adalimumab (C+). For the patient-important outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences. However, there were fewer serious infections with Entyvio in observational data, and both infliximab and adalimumab carry black box warnings for serious infections and malignancies. In the absence of head-to-head randomized trials, we cannot rule out a small net health benefit for Entyvio.

We used decision-analytic modeling to assess the lifetime projected effectiveness and cost of Entyvio compared to infliximab and ustekinumab for UC and CD. We report price premiums at various cost-effectiveness thresholds for Entyvio relative to the prices that CMS pays for therapeutic alternatives (infliximab and ustekinumab) to inform drug price negotiations alongside other considerations. These price premiums are a weighted average of the price premiums calculated for use of Entyvio in UC and CD, assuming that 45% of Entyvio use in the Medicare population is for UC, and 55% of use is for CD. CMS can add these 30-day price premiums to the 30-day price currently paid for infliximab and ustekinumab to determine the calculated value-based price for Entyvio at each threshold. We do not stipulate a specific cost-effectiveness threshold as most appropriate but note for CMS that academic health economics research supports consideration of pricing between $100,000-$150,000 per equal-value life years (evLY) gained.

Entyvio resulted in fewer colectomies, increased life years, increased evLYs, increased years in remission and lower non-intervention health care sector costs compared to infliximab when used to treat UC (Table ES3). Compared to ustekinumab in UC, and when used to treat CD compared to ustekinumab and infliximab, Entyvio resulted in a greater number of colectomies (UC) and surgeries (CD), decreased life years, decreased evLYs, fewer years in remission, and higher non-intervention health care sector costs (Table ES3 and ES4).

Table ES3. Incremental Lifetime Discounted Results for Entyvio versus Therapeutic Alternatives (Ulcerative Colitis)

Treatment	Years in Remission	Number of Colectomies	Life Years	evLYs	Non-Intervention Health Care Sector Costs*
Entyvio vs. Infliximab	0.0785	-0.0011	0.0005	0.0198	-$8,054
Entyvio vs. Ustekinumab	-0.509	0.006	-0.003	-0.114	$46,924

evLYs: equal-value life years

*Non-Intervention Health Sector Costs include the cost of AEs, health state costs, and colectomy costs.

Table ES4. Incremental Lifetime Discounted Results for Entyvio versus Therapeutic Alternatives (Crohn's Disease)

Treatment	Years in Remission	Number of Surgeries	Life Years	evLYs	Non-Intervention Health Care Sector Costs*
Entyvio vs. Infliximab	-0.364	0.014	-0.007	-0.108	$40,097
Entyvio vs. Ustekinumab	-0.210	0.008	-0.004	-0.065	$24,204

evLYs: equal-value life years

*Non-Intervention Health Sector Costs include the cost of AEs, health state costs, and colectomy costs.

Compared to infliximab in UC, 30-day price premiums relative to the cost to CMS of infliximab were $420 at $50,000/evLY, $460 at $100,000/evLY, $510 at $150,000/evLY, and $550 at $200,000/evLY. Compared to infliximab in CD, 30-day price premiums were $0 at all thresholds as Entyvio was found to be more costly and less effective in these analyses. Compared to ustekinumab, Entyvio was not associated with health gains in UC or CD, and therefore decision analytic modeling confirmed that the evidence does not support a price premium for Entyvio above CMS pricing for ustekinumab. Overall estimated 30-day threshold price premiums for Entyvio relative to therapeutic alternatives, weighted by the percentage of Entyvio use in UC and CD, are reported in Table ES5.

Table ES5. Estimated 30-Day Threshold Price Premiums for Entyvio Compared to Therapeutic Alternatives Across a Range of Cost-Effectiveness Benchmarks for UC and CD

	30-Day Threshold Price Premiums for Entyvio			
Therapeutic Alternative	**$50,000/evLY**	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
Infliximab*	$190	$210	$230	$250
Ustekinumab†	No price premium	No price premium	No price premium	No price premium

evLYs: equal-value life years

Note: 30-day prices are rounded to the nearest $10

*Price premiums are calculated as a weighted average of price premiums for Entyvio compared to infliximab in UC and CD and assuming 55% of Entyvio use is for CD and 45% for UC.

†No price premium because Entyvio resulted in fewer evLYs gained relative to ustekinumab.

1. Background

1.1. Introduction

Under the Inflation Reduction Act (IRA), the Centers for Medicare and Medicaid Services (CMS) has initiated drug price negotiations on selected Medicare Part B and D drugs with participating drug manufacturers. In October 2023, the Institute for Clinical and Economic Review (ICER) published a special report on two of the 10 drugs selected for the first cycle of drug price negotiations, apixaban and rivaroxaban.[1] In March of 2025, ICER published a special report on two of the 10 drugs selected for the second cycle of drug price negotiations, Trelegy Ellipta® and Breo Ellipta®.[2] CMS released draft guidance for the third cycle of negotiations in May of 2025 and this ICER special report focuses on vedolizumab (Entyvio®), which is subject to price negotiations in this cycle.[3]

Ulcerative colitis (UC) and Crohn's disease (CD) are the two different types of immune-mediated inflammatory bowel diseases (IBD). UC primarily affects the mucosa, the innermost lining of the intestinal wall in the large bowel (i.e., the colon and rectum).[4] Crohn's disease, on the other hand, can affect the entire GI (gastrointestinal) tract from the mouth to the anus and can involve the full thickness, not just the mucosa. These diseases cause long-lasting inflammation and ulcers in the digestive tract and are typically marked by periods of remission and recurrence of symptoms. Symptoms may include frequent diarrhea, sometimes with blood or pus, abdominal and/or rectal pain, weight loss, and fatigue.[5] When the disease affects children, it can have a detrimental impact on growth, nutritional status, and psychosocial development.[12] It is estimated that approximately 2.4 to 3.1 million individuals in the United States (US) have IBD.[6] Most individuals are diagnosed between the ages of 15 and 35.[7] However, there is an increasing incidence of IBD among older adults.[8] Among 25 million Medicare fee-for-service beneficiaries, there are approximately 100,000 people with CD (0.40%) and 160,000 people with UC (0.64%).[9] The economic burden of IBD is significant, with recent estimates of $50 billion per year in the United States.[10]

Both UC and CD are diagnosed based on symptoms of the disease and confirmed by colonoscopy with biopsy. Other disease processes that may cause similar symptoms, such as infection and cancer, need to be excluded.[11] The management of IBD in adults is dependent on the severity of symptoms. In patients with mild disease, the use of oral and rectal aminosalicylates may induce and maintain remission. Those with moderate to severe disease are candidates for targeted immune modulators (TIMs) to induce and/or maintain remission, including the tumor necrosis factor (TNF) inhibitors adalimumab (Humira®, AbbVie as well as biosimilars), golimumab (Simponi®, Janssen), infliximab (Remicade®, Janssen as well as biosimilars), the $\alpha_4\beta_7$ integrin inhibitor vedolizumab (Entyvio®, Takeda), the Janus kinase (JAK) inhibitor tofacitinib (Xeljanz®, Pfizer), the interleukin (IL)-

12 and IL-23 inhibitor ustekinumab (Stelara®, Janssen, as well as biosimilars), and the IL-23 inhibitors (Skyrizi® [risankizumab], Omvoh® [mirikizumab], and Tremfya® [guselkumab]).

Elective colectomy (surgical removal of the colon) may be considered in patients with UC whose disease does not respond to maximal medical management.[11] Colectomy is not routinely used for treatment in patients with CD, but they frequently need surgery to correct complications of the disease, such as perianal fistulae and intestinal strictures. Patients with IBD are at increased risk for colon cancer and require regular colonoscopies from a young age. Other important outcomes include preventing emergency room visits and hospitalizations due to disease flares. Finally, there are extraintestinal manifestations of IBD, such as arthritis, uveitis, pyoderma gangrenosum, and primary sclerosing cholangitis that can significantly impact patients' quality of life.

1.2. Entyvio for Ulcerative Colitis and Crohn's Disease

Ulcerative Colitis

Entyvio is indicated for moderate to severe active UC. The recommended dosage is 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks (i.e., "induction therapy"), then every eight weeks thereafter (i.e., "maintenance therapy").

Additionally, a subcutaneous (SC) formulation of Entyvio is available for maintenance therapy, which can be initiated as early as six weeks after the initial two intravenous (IV) infusions. The recommended dosage is 108 mg subcutaneously every two weeks.

Crohn's Disease

Entyvio is indicated for moderate to severe active CD. The recommended dosage is 300 mg infused intravenously over approximately 30 minutes at zero, two, and six weeks for induction, then every eight weeks thereafter for maintenance.

Additionally, a subcutaneous formulation of Entyvio is available for maintenance therapy, which can be initiated as early as six weeks after the initial two IV infusions. The recommended dosage is 108 mg subcutaneously every two weeks.

2. Potential Therapeutic Alternatives

2.1. Therapeutic Alternatives for Entyvio

2.1.1. Ulcerative Colitis and Crohn's Disease

We focused on biologics approved by the Food and Drug Administration (FDA) for UC and CD, as well as FDA-approved biosimilars (Table 2.1). Major therapeutic alternatives were determined following consultation with clinical experts, patient representatives, and other key stakeholders. Because our focus was on the comparative effectiveness of monotherapy with Entyvio and other biologic therapies, we focused on guideline-directed monotherapy for patients with moderate to severe disease (infliximab, adalimumab, ustekinumab), rather than combinations with additional immunosuppressive therapies like azathioprine.

Infliximab

Infliximab (Remicade®, Janssen as well as three biosimilars as listed in Table 2.1) is a TNF blocker administered by intravenous infusion for at least two hours with an in-line filter. For UC, the induction dose is 5 mg/kg at zero, two, and six weeks followed by a maintenance dose of 5 mg/kg every eight weeks.[13] For CD, the induction dose is 5 mg/kg at zero, two, and six weeks for induction, then every eight weeks for maintenance dose.[13] Patients who initially respond but later lose response may increase their dose to 10 mg/kg or shorten the interval between infusions.[13] Infliximab can also be administered subcutaneously using Zymfentra® (Celltrion), a "biobetter" of Inflectra® (biosimilar to Remicade), as the originator product and its biosimilars are available only in IV form.[14] Zymfentra is indicated as maintenance treatment only, following a 10 week IV induction.[13] The dose for CD is 120 mg subcutaneously once every two weeks. For patients switching from IV maintenance therapy, Zymfentra replaces the next scheduled IV infusion and is then administered every two weeks.

Ustekinumab

Ustekinumab (Stelara®, Janssen, as well as eight biosimilars as listed in Table 2.1) is a human interleukin-12 and -23 antagonist. Induction dose is administered by a single intravenous infusion using weight-based dosing for induction for both UC and CD: 260 mg (two vials) for those up to 55 kg, 390 mg (three vials) for those between 55 kg and 85 kg, and 520 mg (four vials) for those greater than 85 kg. Maintenance therapy is a 90 mg subcutaneous dose every eight weeks following induction.[15]

Adalimumab

Adalimumab (Humira®, Abbvie, as well as 10 biosimilars as listed in Table 2.1) is a TNF blocker. It is administered by subcutaneous injection only. For adults with UC, the dose is 160 mg on day one (can be split over two days) and 80 mg on day 15 as the induction period. After an initial induction period, the maintenance dose is 40 mg every other week starting on day 29. If patients did not experience clinical remission by eight weeks, discontinuation is advised; patients with a partial response may be tried on 40 mg weekly or 80 mg every other week. For children five years of age and older with UC, a weight-based dosing is used. Those 20 kg to 40 kg, the dose is 80 mg on day one, 40 mg on day eight, 40 mg on day 15, and 40 mg every other week (or 20 mg every week) starting on day 29. Those 40 kg and greater, the dose is 160 mg on day one (can be split over two days), 80 mg on day eight, 80 mg on day 15, and 80 mg every other week (or 40 mg every week) starting on day 29.[16] For adults with CD, the dose is 160 mg on day one (can be split over two days), 80 mg on day 15, and 40 mg every other week starting on day 29.[16] For children five years of age and older with CD, a weight-based dosing is used. Those 17 kg to 40 kg, the dose is 80 mg on day one, 40 mg on day 15, and 20 mg every other week starting on day 29. Those 40 kg and greater, the dose is 160 mg on day one (can be split over two days), 80 mg on day 15, and 40 mg every other week starting on day 29.[16]

Table 2.1. Food and Drug Administration (FDA)-Approved Biologics and Biosimilars

FDA Approved Biologics	FDA Approved Biosimilars
• **Infliximab (Remicade®, Janssen)**	• Infliximab-abda (Renflexis®, Merck) • Infliximab-axxq (Avsola®, Amgen) • Infliximab-dyyb (Inflectra®, Celltrion) • Infliximab-qbtx (IXIFI®, Pfizer)
• **Adalimumab (Humira®, Abbvie)**	• Adalimumab-aacf (Idacio®, Fresenius Kabi) • Adalimumab-aaty (Yuflyma®, Celltrion) • Adalimumab-adaz (Hyrimoz®, Sandoz/Cordavis) • Adalimumab-adbm (Cyltezo®, Boehringer Ingelheim) • Adalimumab-afzb (Abrilada®, Pfizer) • Adalimumab-atto (Amjevita®, Amgen) • Adalimumab-aqvh (Yusimry®, Meitheal) • Adalimumab-bwwd (Hadlima®, Organon/Samsung Bioepis) • Adalimumab-fkjp (Hulio®, Biocon Biologics) • Adalimumab-ryvk (Simlandi®, Alvotech/Teva)
• **Ustekinumab (Stelara®, Janssen)**	• Ustekinumab-aauz (Otulfi®, Fresenius Kabi) • Ustekinumab-aekn (Selarsdi®, Alvotech) • Ustekinumab-auub (Wezlana, Amgen) • Ustekinumab-hmny (Starjezma®, Bio-Thera Solutions) • Ustekinumab-kfce (Yesintek®, Biocon) • Ustekinumab-srlf (Imuldosa®, Accord BioPharma)

FDA Approved Biologics	FDA Approved Biosimilars
	• Ustekinumab-stba (Steqeyma®, Celltrion) • Ustekinumab-ttwe (Pyzchiva®, Samsung Bioepis Co.)

2.2. Clinical Outcomes

2.2.1. Ulcerative Colitis

We focused on patient-important outcomes, based on the American College of Gastroenterology (ACG) guidelines and conversations with focus groups of UC and CD patients.[17] The optimal goals of UC management include clinical remission and response, maintaining or improving health-related quality of life (HRQoL) and function, prevention of morbidity such as UC-related hospitalization and surgery (colectomy), and prevention of colorectal cancer.[17] We sought data on these outcomes, as well as endoscopic evidence of improvement and remission, corticosteroid-free remission, histologic healing, and use of rescue medication (see definitions in the sections that follow). We included normalization of C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), and fecal calprotectin as outcomes in our review. Decrease in these markers has been shown to predict response and remission,[18] and their use is recommended to assess response to therapy.[17]

Clinical Efficacy

Clinical response and remission in randomized controlled trials (RCTs) of Entyvio and its comparators for UC were assessed using the Mayo Clinic score, a composite measure of disease severity. The Mayo Clinic score has four components: stool frequency, rectal bleeding, endoscopic disease activity, and physician global assessment, each rated 0-3 for a total score of 0-12. Higher scores indicate more severe disease. Clinical response is defined as a reduction of at least three points in the total Mayo Clinic score, with a decrease of at least one point on the rectal bleeding subscale or an absolute rectal bleeding score of zero or one. Clinical remission is defined as a total score of two or less, with no subscore greater than one. These outcomes are particularly important to patients as they are associated with improvements in HRQoL, employment, and productivity.[19] Because corticosteroids are not recommended for maintenance of remission,[17] corticosteroid-free remission (remission among patients who were using oral corticosteroids at baseline and subsequently discontinued corticosteroids) was also assessed in clinical trials.

ACG guidelines report that endoscopic improvement (Mayo endoscopic score of zero or one) is associated with a greater likelihood of sustained steroid-free remission and a reduced risk of hospitalizations and surgery; thus, it is a key treatment goal in UC management.[17] Mucosal healing or endoscopic remission (Mayo endoscopic score of zero) was also evaluated as an outcome of interest in our review.[17]

The Inflammatory Bowel Disease Questionnaire (IBDQ), the 36-item Short Form survey (SF-36), the Work Productivity and Activity Impairment Questionnaire (WPAI), and EuroQol-5 Dimensions (EQ-5D-5L) are the most commonly used measures of health-related quality of life in studies of patients with UC. The IBDQ is a 32-item questionnaire that measures the overall health-related quality of life in patients with IBD. The minimal clinically important difference (MCID) is considered to be an improvement of at least 16 points from baseline.[20] The SF-36 is a self-reported, generic tool to assess health related quality of life. It consists of 36 questions across eight domains. It has two summary components: a physical component summary (PCS) and mental component summary (MCS). There is no established MCID for patients with UC, but, in Crohn's disease, anchor-based estimates linked to IBDQ suggest that the MCID for SF-36 PCS and MCS is approximately four points from baseline, with a broader estimated range.[21] The WPAI is a six-item questionnaire that measures the impact of health problems on absenteeism, presenteeism, and unpaid labor activity. The scores range from 0% (no impairment) to 100% (total loss of productivity). There is no universally established MCID for patients with UC, but the MCID in Crohn's disease has been reported as an absolute reduction of 6.1%-8.5% from baseline for each subdomain.[22] Finally, the EQ-5D-5L is used to generate a health utility score that varies from zero (death) to one (perfect health) with non-disease specific MCID estimates of approximately 0.07.[23] The tool includes a visual analogue scale (EQ-5D VAS) that varies from zero to 100 (worst to best). The EQ-5D VAS MCID for UC has not been established but, in Crohn's disease, the MCID for the EQ-5D VAS is approximately 9.2 points from baseline, with a broader estimated range.[21]

Safety

Serious infections are rare, but are serious complications of all immune-modulating UC treatments and are included as safety warnings in the FDA label for Entyvio, as well as "black box" warnings for some therapeutic alternatives (i.e., adalimumab and infliximab).[13,16,24] Increased risks of lymphomas and other malignancies are also listed as black box warnings for infliximab and adalimumab. Studies report an increased risk of malignancies, thrombotic events, hepatic events, and anti-TNF induced psoriasis in patients with UC receiving TIMs.[25,26] In addition, patient-reported fatigue was a common side effect that impacted daily functioning.

Observational Data

High-quality observational data were sought to supplement evidence from RCTs. Avoidance of surgery and other UC-related hospitalizations are important to patients and caregivers; because these outcomes were not reported in clinical trials, we sought data from observational studies. Given reports from prior observational studies of increased risk of malignancies, thrombotic events, and hepatic events, we also sought long-term observational data on these safety outcomes.

2.2.2. Crohn's Disease

According to ACG guidelines, the goals of CD therapy include achieving clinical and endoscopic remission, improving overall quality of life, and minimizing treatment-related adverse effects.[27] Consistent with this guidance, we sought data on these and other patient-important outcomes, e.g., clinical endoscopic response and remission, corticosteroid-free remission, histologic healing, and use of rescue medication. We also included normalization of C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin as outcomes in our review. Decreases in these biomarkers can predict response and remission.[18]

Clinical Efficacy

Clinical response and remission in trials of Entyvio and its potential therapeutic comparators were measured using the Crohn's Disease Activity Index (CDAI), a composite score that measures symptom severity. The CDAI includes variables such as frequency of stools, well-being, abdominal pain, hematocrit, among others. Scores can range from 0-600, with scores of 150–219 categorized as mildly active disease, 220–450 as moderately active disease, and scores above 450 as severe disease. Clinical response is typically defined as a reduction of either 70 or 100 points (CDAI) from baseline. More recent studies have favored the CDAI 100-point response as it reflects a more robust and clinically meaningful improvement. Clinical remission is defined as a score <150 points on the CDAI. Because corticosteroids are not recommended for long-term use beyond three months,[27] corticosteroid-free remission was also assessed.

Endoscopic response/remission (i.e., mucosal healing) has emerged as an important treatment target in CD and is defined as the absence of ulceration visualized during endoscopy.[27] Achievement of mucosal healing has been associated with clinical remission and reduced rates of surgery and hospitalizations.[27] Trials of the comparators reported endoscopic response/remission rates,[28] but no comparative mucosal healing data were available for Entyvio.

The IBDQ (see MCID above), SF-36, WPAI, and EQ-5D are the most commonly used measures of health-related quality of life in studies of patients with CD. In Crohn's disease, anchor-based estimates linked to IBDQ suggest that the MCID for SF-36 PCS and MCS is approximately four points

from baseline and MCID for the EQ-5D VAS is approximately 9.2 points from baseline, both with a broader estimated range.[21] The MCID for WPAI has been reported as an absolute reduction of 6.1%-8.5% from baseline for each subdomain.[22]

Safety

Safety and black box warnings are reported above. Studies report an increased risk of malignancies, thrombotic events, hepatic events, and anti-TNF-induced psoriasis in patients with CD receiving TIMs.[26,29] In addition, patients with CD reported fatigue as a common side effect that impacted their daily functioning.

Observational Data

High-quality observational data were sought to supplement evidence from RCTs. CD-related surgery and hospitalization are clinically important but are not typically reported in clinical trials of short duration. Thus, we reviewed data from observational studies to inform these outcomes. We also sought long-term observational evidence for safety concerns, including malignancies, thrombotic events, and hepatic events.

3. Comparative Clinical Evidence

3.1. Interventions and Therapeutic Alternatives

We focused on patients with moderate to severe UC or CD who have not responded to conventional systemic therapy. We compared Entyvio with other immune-modulating drugs recommended as monotherapy by current guidelines as well as in consultation with multiple clinical experts, including both branded and biosimilar forms.

Ulcerative Colitis

We updated a systematic literature review and network meta-analysis (NMA) published by ICER in 2020 to evaluate the comparative effectiveness and safety of Entyvio with infliximab, adalimumab, ustekinumab, or conventional systemic therapy in patients with moderate to severe UC.[30] We also evaluated direct comparative evidence from Entyvio trials and observational studies of Entyvio in patients with UC.[30]

Crohn's Disease

We updated the systematic literature review and NMA published by Versteegh et al. (2025) and Ungaro et al. (2020) to evaluate the comparative effectiveness and safety of Entyvio with infliximab, adalimumab, ustekinumab, or conventional systemic therapy in patients with moderate to severe CD.[31,32] We also evaluated direct comparative evidence from Entyvio trials and observational studies in patients with CD.

3.2. Ulcerative Colitis

Methods Overview

Detailed methods for the systematic literature review assessing evidence on Entyvio for the treatment of adults with moderate to severe UC are available in Supplement Section D1.

Evidence Base

NMA Evidence

In addition to ICER's 2020 NMA, our search identified three systematic reviews and NMAs.[33-35] Following pre-specified inclusion and exclusion criteria, a total of 12 trials from previous systematic reviews were included in the NMA evidence for this report. Our updated search identified three new studies: EFFICACI, Naganuma et al. (2025), and LIBERTY UC.[36-38] Details about design and baseline characteristics of these studies are available in Supplement Tables D3.1-D3.2.

Using the Cochrane Risk of Bias Assessment Tool Version 2 (RoB 2), we rated trials for the primary endpoint of response and remission in the induction and maintenance phase. During the induction phase, four trials were rated as having "high risk" of bias, three as having "some concerns", and five as having "low risk" of bias. During the maintenance phase, six trials were rated as having "high risk" of bias, five as having "some concerns", and one as having "low risk" of bias. In all cases, increased risk of bias was caused by missing outcome data due to high drop-out rate in the comparator arms of these trials. This pattern is common in trials of chronic inflammatory diseases where patients are more likely to discontinue placebo and remain on effective treatment.[39]

Additional details about the prior NMAs and our methods can be found in Supplement Section D1.

Clinical Trial Evidence

Our clinical trial evidence comes from three head-to-head trials and three placebo-controlled trials of Entyvio. The three head-to-head trials were: VARSITY, EFFICACI, and Naganuma et al. (2025).[36,37,40] VARSITY was a Phase III trial comparing Entyvio with adalimumab. It was a treat-through trial, meaning patients randomized during the induction period (six weeks) would remain on therapy for the maintenance period (52 weeks) as well.[40] The two additional head-to-head trials, EFFICACI and Naganuma et al. (2025), were limited to the induction phase only. EFFICACI (14 weeks) compared Entyvio with infliximab, whereas Naganuma et al. (2025) (12 weeks) was designed as a three-arm trial comparing Entyvio, ustekinumab, and infliximab.[36,37] The three placebo-controlled trials were: GEMINI 1, NCT02039505, and VISIBLE 1.[41-43] GEMINI 1 included a double-blind, randomized cohort and a separate open-label single-arm cohort in the trial of induction therapy. Participants who had a response to Entyvio at week six in either cohort were later re-randomized to Entyvio or placebo in the trial of maintenance therapy (52 weeks).[41] NCT02039505 was a Japanese Phase III trial which followed an identical study design to GEMINI 1.[42] Finally, VISIBLE 1 was a maintenance trial only (52 weeks) in which participants received Entyvio for two weeks and responders were re-randomized to Entyvio IV, Entyvio SC, and placebo with a follow-up period of 52 weeks.[43]

All clinical trials of Entyvio included adults with moderate to severe active UC, primarily defined as a Mayo score of six to 12 and an endoscopic subscore of ≥2. Participants had an inadequate response to, loss of response to, or intolerance of conventional systemic therapies, including corticosteroids and immunomodulators. The majority of the trial participants (57-72%) had concomitant glucocorticoids and immunosuppressants. In trials that reported disease localization, around 30-43% of the participants had left-sided colitis, meaning their inflammation extended from the rectum to the splenic flexure, and 34-70% experienced inflammation extending to the entire colon. Most trials predominantly included "biologic-naïve" participants (i.e., those who had not previously used a biologic treatment, such as those in focus for this review previously) (49-79%), while Naganuma et al. (2025) included only biologic-naive participants and the EFFICACI trial included only biologic-experienced participants. The induction phases were generally 6-14 weeks long, and the maintenance phases extended up to 60 weeks. The GEMINI long-term study (LTS) reported safety data over a two-year period.[44] Overall, baseline characteristics were similar across arms and trials. See Supplement Tables D2.1 and D3.2.

Observational Studies

For UC, we included 13 observational studies of Entyvio, with two coming from the 2020 ICER review and 11 identified in the updated search.[45-57] Nine of these 13 evaluated Entyvio against anti-TNF drugs,[45-50,52,53,55] two evaluated Entyvio against ustekinumab,[51,54] and two were Entyvio single-arm studies.[56,57] The majority of these studies were conducted in the US and focused on the long-term safety of Entyvio. The baseline characteristics of these observational studies, with respect to age and sex at birth, were largely similar to the trial populations. See Supplement Tables D2.2 and D3.16.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the six Entyvio trials for UC using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[58] Among the trials conducted in the US, all were rated as "fair" for racial and ethnic diversity, with an underrepresentation of Black/African American and Hispanic patients.[58] Most trials were also rated as "fair" in terms of female representation. Data on the inclusion of older adults were limited. See Supplement D1 for full details of CDR methods and results (Tables D1.15-D1.17).

Results

Clinical Benefits

We first summarize levels of clinical response and clinical remission from NMAs comparing all listed treatments, followed by evidence of endoscopic improvement from NMAs and a review of HRQoL outcomes directly from the Entyvio trials. The NMA model fits were largely similar even after accounting for placebo response rates and different durations of follow-up. To account for these factors and broader heterogeneity, we selected random-effects unadjusted models for both the induction and maintenance phases and present these results separately. We also summarize the evidence from high-quality observational studies after the clinical benefits and harms sections.

NMA Evidence of Clinical Response and Remission During Induction Period

A total of 13 RCTs were available for data on induction phase (6-14 weeks). All treatments were significantly better than placebo, (risk ratios [RR] 1.3 to 1.9 for clinical response; RR 1.6 to 3.3 for clinical remission). During the induction period, there were no significant differences between Entyvio and either ustekinumab or infliximab. However, Entyvio and ustekinumab were superior to adalimumab for both measures (see Tables 3.1 and 3.2).

Table 3.1. Risk Ratios for Response at the End of Induction Phase in Moderate to Severe UC Patients

Ustekinumab				
1.08 (0.82, 1.40)	**Entyvio**			
1.11 (0.84, 1.47)	1.03 (0.83, 1.30)	**Infliximab**		
1.44 (1.04, 2.07)	**1.34 (1.001, 1.86)**	1.29 (0.996, 1.73)	**Adalimumab**	
1.91 (1.47, 2.43)	**1.77 (1.46, 2.14)**	**1.71 (1.38, 2.09)**	**1.32 (1.01, 1.763)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table 3.2. Risk Ratios for Remission at the End of Induction Phase in Moderate to Severe UC Patients

Ustekinumab				
1.16 (0.68, 2.01)	**Entyvio**			
1.24 (0.72, 2.19)	1.07 (0.698, 1.65)	**Infliximab**		
2.01 (1.08, 3.96)	**1.73 (1.004, 3.07)**	1.62 (0.99, 2.72)	**Adalimumab**	
3.27 (1.96, 5.21)	**2.81 (1.97, 4.00)**	**2.62 (1.76, 3.82)**	**1.62 (1.01, 2.57)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Clinical Response and Remission During Maintenance Period

Eight RCTs were available that focused on the maintenance phase (52-60 weeks). All treatments were significantly better than placebo (RR 1.5 to 1.9 for clinical response; RR 1.8 to 2.5 for clinical remission). There were no statistically significant differences between Entyvio and any of the three therapeutic alternatives. (See Tables 3.3 and 3.4.)

Table 3.3. Risk Ratios for Response at the End of Maintenance Phase in Moderate to Severe UC Patients

Ustekinumab				
1.14 (0.79, 1.91)	**Entyvio**			
1.17 (0.85, 1.80)	1.03 (0.59, 1.65)	**Infliximab**		
1.26 (0.95, 1.85)	1.11 (0.65, 1.89)	1.08 (0.67, 1.71)	**Adalimumab**	
1.92 (1.53, 2.37)	**1.67 (1.02, 2.33)**	**1.64 (1.11, 2.16)**	**1.52 (1.02, 2.07)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table 3.4. Risk Ratios for Remission at the End of Maintenance Phase in Moderate to Severe UC Patients

Ustekinumab				
1.22 (0.69, 2.53)	**Entyvio**			
1.27 (0.78, 2.35)	1.04 (0.47, 2.11)	**Infliximab**		
1.16 (0.54, 2.51)	1.16 (0.54, 2.51)	1.11 (0.56, 2.18)	**Adalimumab**	
2.52 (1.8, 3.42)	**2.05 (1.03, 3.40)**	**1.99 (1.16, 2.97)**	**1.78 (1.03. 2.82)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Endoscopic Improvement

All treatments were significantly more likely to achieve endoscopic improvement compared to placebo during the induction and maintenance phases (Table 3.5 and 3.6). During the induction phase, ustekinumab was superior to Entyvio. However, there were no statistically significant differences between Entyvio and the three therapeutic alternatives during the maintenance phase. See Tables 3.5 and 3.6.

Table 3.5. Risk Ratios for Endoscopic Improvement at the End of Induction Phase in Moderate to Severe UC Patients

Ustekinumab				
1.23 (0.87, 1.75)	Infliximab			
1.52 (1.04, 2.24)	1.24 (0.90, 1.70)	Entyvio		
1.75 (1.20, 2.61)	**1.43 (1.06, 1.91)**	1.15 (0.81, 1.62)	Adalimumab	
2.23 (1.62, 3.11)	**1.81 (1.49, 2.22)**	**1.46 (1.12, 1.92)**	**1.27 (1.03, 1.58)**	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table 3.6. Risk Ratios for Endoscopic Improvement at the End of Maintenance Phase in Moderate to Severe UC Patients

Infliximab				
1.02 (0.54, 2.02)	Entyvio			
1.35 (0.63, 2.98)	1.33 (0.72, 2.39)	Ustekinumab		
1.42 (0.72, 2.81)	1.39 (0.96, 1.93)	1.04 (0.56, 1.92)	Adalimumab	
2.53 (1.43, 4.60)	**2.47 (1.81, 3.35)**	**1.86 (1.12, 3.13)**	**1.79 (1.29, 2.51)**	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Direct Evidence on Health-Related Quality of Life

Only one trial reported data on HRQoL during the induction period for Entyvio versus placebo.[59] GEMINI 1 reported numerically higher mean scores of the IBDQ, SF-36, and EQ-5D at week six for Entyvio compared to placebo, but no statistical tests were conducted. No data compared to the therapeutic alternatives of interest were available. See Supplement Table D3.6.

Three trials reported data on HRQoL during the maintenance period.[43,59,60] In the VARSITY head-to-head trial, the rates of achieving IBDQ response (a change from baseline of ≥16 points in IBDQ total score) and IBDQ remission (IBDQ total score ≥170) were statistically significantly higher with Entyvio (52% and 50%) compared to adalimumab (42% and 40%) at the end of the week 52. The VISIBLE 1 trial reported that both the IV and SC dosage forms of Entyvio demonstrated statistically significant improvements compared to placebo and achieved MCID thresholds in changes from baseline in IBDQ total scores, EQ-5D VAS scores, WPAI work productivity and activity impairment scores. Finally, the GEMINI 1 trial reported greater proportions of patients (7-20%) meeting the MCID across all HRQoL measures compared to placebo. See Supplement Table D3.7.

Harms

In this section, we first summarize harms evidence from an NMA comparing all listed treatments, followed by a review of direct evidence from Entyvio trials and a summary of evidence from observational studies. Safety outcomes of interest include discontinuations due to adverse events, serious infections, malignancies, thrombotic events, and hepatic events.

Black Box Warnings

Both anti-TNFs (infliximab and adalimumab) carry a black box warning in their FDA labels for increased risk of serious infections and risk of lymphomas and other malignancies.[16,61]

Other Warnings and Precautions

FDA labels suggest that patients treated with Entyvio and ustekinumab are at increased risk of developing infections.[15,24]

NMA Evidence for Discontinuation Due to Adverse Events

For the induction and maintenance phases, the NMA showed no significant differences in discontinuation due to AEs between Entyvio and any of its therapeutic alternatives. However, Entyvio and ustekinumab showed significantly lower risks of discontinuation compared to placebo See Table 3.7 and Supplement Table D2.5.

Table 3.7. Risk Ratios for Discontinuations Due to Adverse Events at the End of Maintenance Phase

Ustekinumab				
0.51 (0.1, 2.61)	**Entyvio**			
0.30 (0.05, 1.63)	0.59 (0.16, 1.92)	**Infliximab**		
0.28 (0.05, 1.30)	0.56 (0.22, 1.21)	0.95 (0.28, 3.01)	**Adalimumab**	
0.24 (0.05, 0.94)	**0.46 (0.21, 0.95)**	0.79 (0.3, 2.08)	0.84 (0.44, 1.68)	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence for Serious Infections

As mentioned in the outcomes Section 2.2, serious infections are a particular concern for treatments in individuals with moderate to severe UC. We were unable to conduct an NMA for the induction phase due to data limitations. A total of nine trials were included in the maintenance phase (44-60 weeks) NMA; however, there were no statistically significant differences between Entyvio and any of its therapeutic alternatives as well as in comparisons of any of these to placebo. (Supplement Table D2.6).

Direct Evidence from Clinical Trials on Additional Harms

Among six trials, two reported harms data for the induction phase (6-14 weeks)[41,42] and four reported data for the maintenance phase (44-60 weeks).[40-43]

Adverse event rates were higher during the maintenance phase compared to the induction phase, but they were comparable across trials and arms. Most adverse events appeared to be mild-to-moderate in severity. Within each phase, rates of serious adverse events and malignancies were comparable across all trials and treatment arms. VISIBLE 1 reported the only hepatic event with Entyvio, and two patients treated with Entyvio developed thrombotic events compared to one in the placebo group across all trials.[40]

Finally, around 17% of UC patients (N=894) experienced ≥1 UC-related hospitalization, colectomy or UC-related procedure and less than 20% of UC patients experienced any extraintestinal manifestations in the GEMINI LTS.[44] In the VISIBLE open-label extension, participants who completed 52 weeks and then received Entyvio SC had few UC-related hospitalizations (6%) and no colectomies.[62] Additional details are available in the Supplement Section D2 (Additional Harms) and Tables D3.11-D3.15.

Observational Studies

Observational studies were primarily used to assess long-term safety outcomes, with the emphasis on serious infections, malignancies, and colectomy.

A large observational study evaluating risks of serious infections was reported by Kirchgesner et al. (2022), which used two US-based claims databases for anti-TNF naïve patients and added a French insurance database for anti-TNF experienced patients (N=14,459). Entyvio patients were propensity-matched to anti-TNF patients on a 1:4 basis, yielding a total sample size of 35,424. Entyvio was associated with a statistically significant 32% reduction in the risk of serious infections compared with anti-TNFs in the overall UC population (HR 0.68; 95% CI: 0.50 to 0.93).[52] Singh et al. (2022) analyzed claims data from OptumLabs and reported a statistically significantly 46% reduction

in serious infections (HR 0.54; 95% CI: 0.35 to 0.83) for UC patients treated with Entyvio (N=671) compared to those treated with anti-TNFs (N=1950).[48] However, another study in Sweden (N=44,012) found similar rates of serious infections between treatment with Entyvio (3.74 per 100-person years) and anti-TNF (3.42 per 100 person-years) in UC.[53] Kocchar et al. (2023) evaluated long-term efficacy and safety of Entyvio, ustekinumab, and tofacitinib as a second line therapy after anti-TNF exposure in the US (N=2,141). Although fewer patients receiving ustekinumab developed malignancies (2% vs. 3%) and colectomies (2% vs. 3%) compared to Entyvio, these differences were not statistically significant.[51] Similarly, Singh et al. (2022) found no statistically significant difference in the rates of malignancy between Entyvio and anti-TNFs.[49,51]

Finally, data from US-based claims analyses suggested that treatment with Entyvio was associated with a similar risk of developing any extraintestinal manifestations compared to anti-TNF therapies.[46] Additional outcomes from observational studies are presented in the Supplement Section D2 (See Additional Evidence from Observational Studies) and Table D3.19.

Uncertainty and Controversies

There are several important uncertainties regarding the comparative effectiveness of Entyvio versus ustekinumab, infliximab, and adalimumab for the treatment of patients with ulcerative colitis. First, there are few head-to-head randomized trials, so the analysis rests on network meta-analyses relying on placebo groups as the common comparator. This is particularly true for the subcutaneous formulations of these drugs, and we have assumed that they are as effective as the IV formulations when used for maintenance therapy. The clinical trial data and patient-reported experience support equivalence for disease maintenance, but uncertainty remains.

Second, there are limited data in subgroups of interest to Medicare, including older patients and those with end-stage renal disease. There were some subgroup analyses by age that did not detect any effect modification, but these analyses are often underpowered. In addition, older patients and patients with end-stage renal disease are at higher risk for the rare but serious complications of immunosuppressive therapies, such as serious infections and malignancies.

Finally, there was scant data on outcomes that matter to patients. The randomized trials are often too short to evaluate outcomes like emergency room (ER) visits, hospitalizations, extraintestinal manifestations, and rates of colectomy, as well as serious infections and malignancies. Longer observational studies provided some data on infections, malignancy, hospitalizations, and UC-related surgeries, but comparative evidence is very limited and future studies are warranted to confirm the findings.

3.3. Crohn's Disease

Methods Overview

Detailed methods for the systematic literature review and NMA for the treatment of adults with moderate to severe CD are available in Supplement Section D1.

Evidence Base

NMA Evidence

We updated two NMAs evaluating Entyvio and its therapeutic alternatives in moderate to severe CD patients: Versteegh et al. (2025) for clinical trials and Ungaro et al. (2023) for observational studies.[31,32] No additional clinical trials of Entyvio were found in our updated search. One new trial of subcutaneous infliximab 120 mg was included in our updated NMA.[38] Details about design and baseline characteristics of these studies are available in Supplement Tables D3.20-D3.21.

Using the Cochrane RoB 2 tool, we rated one trial as having "some concerns" and nine as having "low" risk of bias during the induction phase for the primary endpoint of response and remission. During the maintenance phase, four trials were at "high" risk of bias, four were at "some concerns", and one was at "low" risk of bias. In all cases, increased risk of bias was caused by missing outcome data due to high drop-out rate in the comparator arms. This pattern is common in trials of chronic inflammatory diseases where patients are more likely to discontinue placebo and remain on effective treatment.[39]

Additional details about our methods can be found in Supplement Section D1.

Clinical Trial Evidence

Our clinical trial evidence comes from four placebo-controlled RCTs: GEMINI 2, GEMINI 3, VISIBLE 2, and Watanabe et al. (2020).[63-66] GEMINI 2 was a Phase III, multinational study comparing intravenous Entyvio 300 mg with placebo. GEMINI 2 included two separate cohorts: cohort 1 (N=368) randomized patients to either Entyvio or placebo and cohort 2 (N=747) was an open-label group receiving Entyvio only. Participants from these two cohorts who had a response at week six (N=461) were then re-randomized to intravenous Entyvio 300 mg every eight weeks, intravenous Entyvio 300 mg every four weeks, and placebo until week 52.[63] GEMINI 3 was another multinational trial that enrolled a total of 416 patients with CD and compared intravenous Entyvio 300 mg with placebo during the induction period only (i.e., 10 weeks).[64] VISIBLE 2 was also a Phase III, multinational trial involving an open label induction period of six weeks with intravenous Entyvio,

followed by randomization of responders (N=412) to either subcutaneous Entyvio 108 mg or placebo for every two weeks until week 52.[65] Finally, Watanabe et al. (2020) was a Japanese, Phase III trial that randomized a total of 157 patients with moderate to severe CD to intravenous Entyvio 300 mg or placebo.[65] After six weeks of the induction phase (N=24), those who responded were re-randomized to Entyvio and placebo until week 52.[66]

All four trials included adult patients with moderate to severe CD, defined as having a score of 220 to 450 on the CDAI scale and one of the following: a C-reactive protein level greater than 2.87 mg/L, a colonoscopy showing ulcerations, or a fecal calprotectin greater than 250 mcg/g stool plus evidence of ulcers. Baseline characteristics were comparable across these trials. Participants enrolled in these trials had a mean age ranging from 33-38 years, with women representing 34-57% of participants. Around 27-44% of participants had undergone prior surgery related to CD and a majority of the trial participants (57-78%) were anti-TNF experienced. Lesions were present in the ileum in 14-21% of participants, in the colon in 19-28% of participants, and at both locations in 48-67% of participants. See Supplement Tables D2.3 and D3.21.

Observational Studies

For CD, we included 13 observational studies of Entyvio, most of which focused on Entyvio's long-term safety.[46,48,49,52,53,56,57,67-72] Seven evaluated Entyvio versus anti-TNF drugs,[46,48,49,52,53,68,69] two evaluated Entyvio versus ustekinumab,[67,72] two evaluated Entyvio against both anti-TNF and ustekinumab,[70,71] and two were Entyvio single-arm studies.[56,57] Slightly more than half of these studies were conducted using US-based databases. Baseline characteristics of these observational studies, with respect to age and sex at birth, were largely similar to the trial populations. Details can be found in the Supplement Section D2 and Table D2.4.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the four Entyvio trials in CD using the ICER's CDR Tool.[58] Among the trials conducted in the US, all were rated as "fair" for racial and ethnic diversity, with an underrepresentation of Black/African American and Hispanic patients.[58] Most trials were rated as "good" in terms of female representation. When data were available for inclusion of older adults, trials were rated as "poor" or "fair". See Supplement D1 for full details of CDR methods and results. (Tables D1.18-.20)

Results

Clinical Benefits

We first summarize clinical response and clinical remission from NMA comparing all listed treatments, followed by evidence of endoscopic improvement and HRQoL outcomes directly from Entyvio trials. NMA model fits were largely similar even after accounting for different placebo responses and follow-up periods. As such, we selected random-effects unadjusted models for both induction and maintenance phases and presented results separately. We also discuss evidence from high-quality observational studies at the end of clinical benefits and harms section.

NMA Evidence of Clinical Response and Remission During Induction Period

A total of 10 trials informed the induction phase (6-14 weeks) data, with no clinical trial evaluating IV infliximab monotherapy that met our criteria for study inclusion. There were no significant differences in achieving clinical response and remission between Entyvio and the two remaining therapeutic alternatives, although all three were statistically superior to placebo. See Tables 3.8 and 3.9.

Table 3.8. Risk Ratios for Response at the End of Induction Phase in Moderate to Severe CD Patients

Adalimumab			
1.02 (0.82, 1.32)	**Ustekinumab**		
1.22 (0.90, 1.74)	1.20 (0.90, 1.66)	**Entyvio**	
1.82 (1.46, 2.31)	**1.78 (1.47, 2.14)**	**1.49 (1.15, 1.86)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1. Following pre-specified inclusion and exclusion criteria, there was no trial of infliximab in this updated NMA. Additional details are available in the Supplement Section D.

Table 3.9. Risk Ratios for Remission at the End of Induction Phase in Moderate to Severe CD Patients

Adalimumab			
1.03 (0.75, 1.47)	**Ustekinumab**		
1.32 (0.87, 2.13)	1.28 (0.87, 2.01)	**Entyvio**	
2.25 (1.46, 2.31)	**2.18 (1.68, 2.80)**	**1.70 (1.21, 2.31)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1. Following pre-specified inclusion and exclusion criteria, there was no trial of infliximab in this updated NMA. Additional details are available in the Supplement Section D.

NMA Evidence of Clinical Response and Remission During Maintenance Period

Nine RCTs were available on maintenance phase (52-60 weeks). There were no significant differences in achieving clinical response and remission between Entyvio and any of the three therapeutic alternatives, although all four were statistically superior to placebo. See Table 3.10 and 3.11.

Table 3.10. Risk Ratios for Response at the End of Maintenance Phase in Moderate to Severe CD Patients

Infliximab				
1.01 (0.59, 1.48)	**Adalimumab**			
1.16 (0.64, 1.86)	1.15 (0.84, 1.64)	**Ustekinumab**		
1.31 (0.69, 2.01)	1.3 (0.82, 1.9)	1.13 (0.66, 1.7)	**Entyvio**	
1.90 (1.14, 2.63)	**1.88 (1.43, 2.42)**	**1.64 (1.11, 2.24)**	**1.45 (1.05, 2.04)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table 3.11. Risk Ratios for Remission at the End of Maintenance Phase in Moderate to Severe CD Patients

Infliximab				
1.01 (0.54, 1.61)	**Adalimumab**			
1.19 (0.59, 2.11)	1.18 (0.82, 1.78)	**Ustekinumab**		
1.38 (0.65, 2.27)	1.36 (0.79, 2.12)	1.16 (0.62, 1.86)	**Entyvio**	
2.11 (1.16, 3.16)	**2.09 (1.52, 2.82)**	**1.78 (1.13, 2.59)**	**1.53 (1.06, 2.3)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Direct Evidence of Endoscopic Improvement

No clinical trials reported endoscopic improvement or mucosal healing in moderate to severe CD patients comparing Entyvio with the three therapeutic alternatives. We were unable to conduct an NMA due to limited data availability. However, treatment with Entyvio led to endoscopic remission in 17% of patients at both week 14 and week 52 in a Phase III, open-label, single group trial.[73] Additionally, around 29% of CD patients (N=24) achieved endoscopic healing in the GEMINI LTS.[74] See Supplement Table D3.24.

Direct Evidence on Health-Related Quality of Life

Only two out of four clinical trials evaluating Entyvio reported data on HRQoL versus placebo.[65,75] GEMINI 2 trial reported greater numerical improvements with Entyvio in IBDQ total score, SF-36 PCS and MCS scores, and EQ-5D scores compared to placebo at week six. However, none of the differences were statistically significant. Entyvio demonstrated statistically significant improvements and achieved MCID thresholds in most of these measures compared to placebo during the maintenance phase, except for SF-36 mental component summary scores.[75] Although favorable HRQoL scores were observed in VISIBLE 2 at week 52, there were no statistically significant differences between Entyvio and placebo.[65] See Supplement Tables D3.25-D3.26.

Harms

In this section, we first summarize harms evidence from an NMA comparing all listed treatments, followed by a review of direct evidence from Entyvio trials. Safety outcomes of interest include discontinuations due to adverse events, serious infections, malignancies, thrombotic events, and hepatic events.

Black Box Warnings

Both anti-TNFs (infliximab and adalimumab) carry a black box warning in their FDA labels for increased risk of serious infections and risk of lymphomas and other malignancies.[16,61]

Other Warnings and Precautions

FDA labels suggest that patients treated with Entyvio and ustekinumab are at increased risk of developing infections.[15,24]

NMA Evidence for Discontinuations Due to Adverse Events

For the induction and maintenance phases, NMAs showed no statistically significant differences in discontinuations due to AEs between Entyvio and any of its therapeutic alternatives, as well as in comparisons of any of these to placebo. See Supplement Section D2 (Additional Harms) and Tables D2.8-D2.9.

NMA Evidence for Serious Infections

For the induction and maintenance phases, there were no statistically significant differences in rates of serious infections between Entyvio and its therapeutic alternatives. See Supplement Section D2 (Additional Harms) and Tables D2.10-D2.11.

Direct Evidence from Clinical Trials on Additional Harms

Three out of four clinical trials evaluating Entyvio reported harms data during the induction phase.[63,64,66] The rates of serious infections were <1% for both Entyvio and placebo groups. There was one case of malignancy with Entyvio in the GEMINI 2 study. No thrombotic or hepatic events were reported during induction.

Long-term data on harms primarily comes from the GEMINI 2 and VISIBLE 2 studies during the maintenance phase.[63,65] Serious adverse events were comparable between Entyvio (8-18%) and placebo (10-15%). Serious infections were reported among 2-4% patients treated with Entyvio and 3-5% treated with placebo. The rates of malignancies were generally low (1%) and comparable across treatment arms and trials. Although no hepatic or thrombotic cases were reported in the 52-week GEMINI 2 study, GEMINI LTS reported 5% of CD patients treated with Entyvio experiencing hepatic events and 2% experiencing thromboembolic events during data collected over eight years.[44]

Finally, around 28% of CD patients (N=1,349) experienced ≥1 CD-related hospitalization, bowel resection or CD-related procedure and fewer than 33% of CD patients experienced any extraintestinal manifestations in the GEMINI LTS.[44] In the VISIBLE open-label extension, 12% of participants who completed 52 weeks and then received Entyvio SC required CD-related hospitalizations and 3% of participants required bowel surgeries.[62] Additional details are available in the Supplement Section D2 (Additional Harms) and Tables D3.27-D3.29.

Observational Studies

Observational studies were primarily used to assess long-term safety outcomes, with the emphasis on serious infections, and malignancies. In a propensity score matched cohort (N=2,965) derived from five health systems in California, ustekinumab demonstrated 80% lower risk of serious infections (HR 0.20; 95% CI: 0.07 to 0.60) compared to Entyvio.[70] However, another study comparing Entyvio and ustekinumab after anti-TNF failure showed similar safety profile for both treatments including serious infections.[67] Data from four US-based studies showed no statistical differences in the risk of serious infections between Entyvio and anti-TNF therapies.[48,52,68,70] There was also no statistical difference in the rates of malignancy between Entyvio and anti-TNFs.[49]

Finally, data from US-based claims analyses suggested that treatment with Entyvio was associated with a higher risk of developing any extraintestinal manifestations compared to anti-TNF therapies (Incident rate ratio [IRR] 1.49; 95% CI: 1.18 to 1.88).[46] Additional outcomes from observational studies are presented in the Supplement Section D2 (See Additional Evidence from Observational Studies) and Table D3.32.

Uncertainty and Controversies

There are several important uncertainties regarding the comparative effectiveness of Entyvio versus ustekinumab, infliximab, and adalimumab for the treatment of patients with Crohn's disease. First, there are few head-to-head randomized trials, so the analysis rests on network meta-analyses relying on placebo groups as the common comparator. This is particularly true for the subcutaneous formulations of these drugs, and we have assumed that they are as effective as the IV formulations when used for maintenance therapy. The clinical trial data and patient-reported experience support equivalence for disease maintenance, but uncertainty remains.

One specific uncertainty is the comparative risk for serious infections between Entyvio and ustekinumab. No differences were reported in the randomized trials, but one observational study suggested that there were 80% fewer serious infections with ustekinumab compared with Entyvio. However, at least three other studies did not find any difference in the rates of serious infections between the two drugs. This merits further careful study.

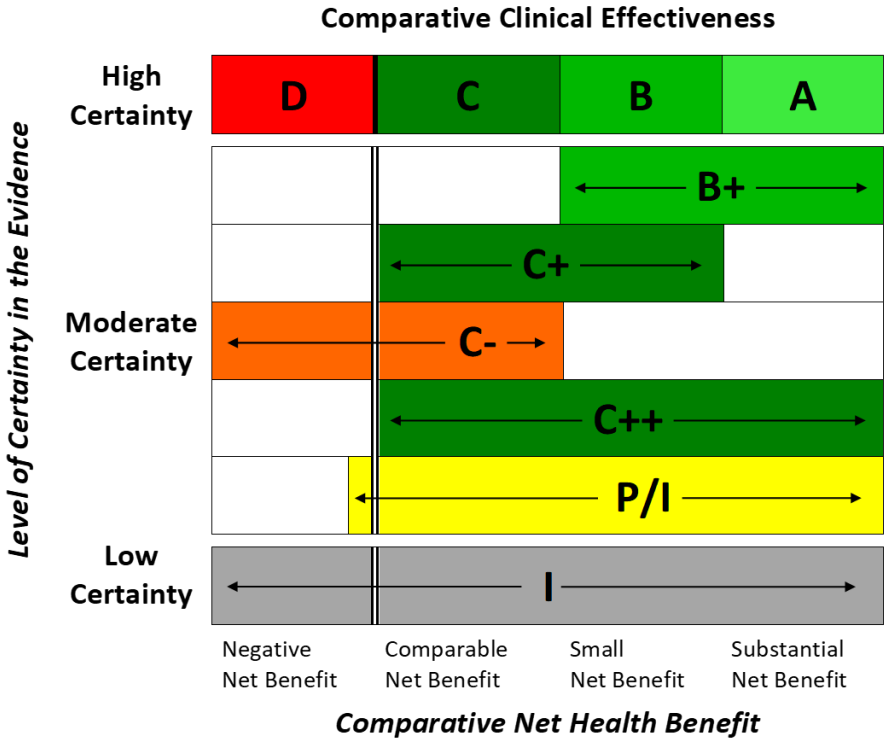
Second, there are limited data in subgroups of interest to Medicare, including older patients and those with end-stage renal disease. There were some subgroup analyses by age that did not detect any effect modification, but these analyses are often underpowered. In addition, older patients and patients with end-stage renal disease are at higher risk for the rare but serious complications of immunosuppressive therapies, such as serious infections and malignancies.

Finally, there was scant data on outcomes that matter to patients. The randomized trials are often too short to evaluate outcomes like ER visits, hospitalizations, extraintestinal manifestations, and rates of surgeries for perianal fistulae and strictures, as well as serious infections and malignancies. Longer observational studies provided some data on infections, malignancy, hospitalizations, and CD-related surgeries, but comparative evidence is very limited and future studies are warranted to confirm the findings.

3.4. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" - *Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Ulcerative Colitis

Benefits

Among patients with moderate to severe ulcerative colitis, there were no significant differences between Entyvio and its three therapeutic alternatives in our NMAs with one exception. This was true for analyses of both response and remission in both the induction and maintenance phases, except that Entyvio was slightly better than adalimumab during the induction phase. In all comparisons, there was a trend towards ustekinumab having the greatest relative benefit.

In a secondary outcome, endoscopic improvement, ustekinumab was significantly better than Entyvio.

Harms

Similarly, in our NMAs, there were no differences between the drugs in discontinuations due to AEs. In one observational study, Entyvio was associated with fewer serious infections compared to the two anti-TNF drugs. In a second observational study, Entyvio and ustekinumab had similar rates of serious infections and malignancies. The anti-TNF drugs infliximab and adalimumab both carry black box warnings for serious infections and malignancies, particularly lymphomas.

Summary

We have rated Entyvio as comparable or inferior to ustekinumab (C-). For the patient-important outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences, nor were there any important differences in observational data. However, the trend was for higher rates of response, remission, and fewer discontinuations due to AEs with ustekinumab. In the absence of head-to-head randomized trials, we cannot rule out a small net health benefit for ustekinumab relative to Entyvio.

Entyvio was rated comparable or better than the anti-TNF drugs infliximab and adalimumab (C+). For the patient-important outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences. However, there were fewer serious infections with Entyvio in observational data, and both infliximab and adalimumab carry black box warnings for serious infections and malignancies. In the absence of head-to-head randomized trials, we cannot rule out a small net health benefit for Entyvio. See Table 3.12.

Table 3.12. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Moderate to Severe Ulcerative Colitis		
Entyvio	Ustekinumab	C-
	Infliximab	C+
	Adalimumab	C+

C+: 'Comparable or Incremental', Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit; C-: 'Comparable or Inferior', Moderate certainty that the net health benefit is either comparable or inferior, with high certainty of at best a comparable net health benefit

Crohn's Disease

Benefits

Among patients with moderate to severe Crohn's disease, there were no significant differences between Entyvio and its three therapeutic alternatives in our NMAs. This was true for analyses of both response and remission in both the induction and maintenance phases. In all comparisons, there was a trend towards the anti-TNF agents infliximab and adalimumab having the greatest benefit, although infliximab was not included in the NMAs of the induction phase.

Harms

Similarly, in our NMAs, there were no differences between the drugs in discontinuations due to AEs. In one observational study, Entyvio was associated with fewer serious infections compared to the two anti-TNF drugs. In one observational study, ustekinumab had fewer serious infections than Entyvio. However, in a second observational study, Entyvio and ustekinumab had similar rates of serious infections and malignancies and there were no differences in serious infections between the two drugs in observational studies among patients with UC. The anti-TNF drugs infliximab and adalimumab both carry black box warnings for serious infections and malignancies, particularly lymphomas.

Summary

Entyvio is comparable to ustekinumab (C). For the outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences, nor were there any important differences in observational data other than one study reporting lower rates of serious infection with ustekinumab. This was not observed in a second observational study, nor was it seen in studies comparing ustekinumab with Entyvio in patients with UC.

Entyvio is comparable or better than the anti-TNF drugs infliximab and adalimumab (C+). For the patient-important outcomes of response, remission, and discontinuations due to serious adverse events, there were no significant differences. However, there were fewer serious infections with Entyvio in observational data, and both infliximab and adalimumab carry black box warnings for serious infections and malignancies. In the absence of head-to-head randomized trials, we cannot rule out a small net health benefit for Entyvio. See Table 3.13.

Table 3.13. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Moderate to Severe Crohn's Disease		
Entyvio	Ustekinumab	C
	Infliximab	C+
	Adalimumab	C+

C: 'Comparable', High certainty of a comparable net health benefit; C+: 'Comparable or Incremental', Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit

4. Specific Populations and Patient Experience

4.1. Comparative Clinical Effectiveness – Subgroup Analyses and Heterogeneity

NMA Evidence for Biologic-Naïve versus Biologic-Experienced Subgroups on Response and Remission

We also conducted clinical response and clinical remission NMAs separately for patients without evidence of prior biologic use (biologic-naïve) and those with such evidence (biologic-experienced). For UC, Entyvio demonstrated superiority over adalimumab and placebo at the end of both the induction and maintenance phases among biologic-naïve subgroup. This was true for biologic-experienced subgroup as well during the induction phase but there was no difference between Entyvio and adalimumab during the maintenance phase. For CD, all treatments were statistically better than placebo at the end of the induction period; however, there were no statistical differences between Entyvio and the two other treatment alternatives with data available (ustekinumab and adalimumab). Results were largely similar for both biologic-naïve and biologic-experienced subgroups. During the maintenance phase, all treatments were more likely to achieve clinical response and clinical remission compared to placebo among the biologic-naïve subgroup. Additionally, adalimumab was statistically better than Entyvio. In contrast, only ustekinumab and Entyvio were statistically significantly superior to placebo among the biologic-experienced group, and ustekinumab was statistically better than Entyvio. See Supplement Section D2 (Additional Evidence on Subgroup Analyses and Heterogeneity) and Supplement Tables D2.11-D2.26.

Data on Medicare-Aged Patients with UC or CD

A total of 2,218 patients with UC or CD aged ≥70 years old were included in the Entyvio Global Post-marketing dataset collected over four years by the manufacturer. A total of 16% and 15% of UC and CD patients reported experiencing serious adverse events, respectively. The rate of infections was 8% for both UC and CD patients. These proportions appear to be similar to the data reported from patients aged <70 years old, suggesting a similar safety profile for both subgroups.[56]

4.2. Patient Experience

Engaging with the patient community was an essential part of our assessment of Entyvio. We held focused discussions with patients from the UC and CD community as well as patient advocacy organizations to inform both the clinical and economic components of our assessment. Focused

clinical discussions took place to understand the perspectives of those living with UC or CD, specific challenges, unmet needs, and outcomes of most relevance. Following the clinical discussions, a subset of these patients, and one additional patient from the UC community were engaged in conversations on our planned approach to the cost-effectiveness analysis and to discuss draft findings. Details of these discussions and the impact on our economic model development are reported in Supplement E. Below we summarize the key themes from these discussions.

There were consistent themes we heard when speaking with patients. First, patients wanted relief from the diarrhea and bleeding: "I want to be able to have a formed bowel movement. I'm looking for symptom relief." Part of this included feeling like they couldn't move around in their community: "my biggest concern is that when I'm out, I need to know where the bathrooms are." Patients reported having to work from home due to the need for frequent bathroom breaks and mentioned that they carry a spare change of clothes in case an accident happens. Remission means freedom: "the minute I was in remission, we were going everywhere. I can travel. I can eat."

The second theme that was noted was on dietary restrictions. We heard from patients:

- "I was hoping to have a diet where I can eat anything. My goal was to be able to go back to eating whatever I wanted."
- "I want to be able to lead a normal life – eat what I want to eat."
- "Even in remission, I still have to follow a strict diet, and you never know how I'm going to feel."
- "The food restriction is crazy – you feel like you're walking on a tight rope. I've been mostly stable, but I can't eat things beyond salt and garlic. My diet is very plain Jane."

Fatigue was highlighted by almost all of the patients: "I was hoping to feel more energetic. I have a lot of fatigue and arthritis and pain."

We heard that the challenges described above often lead to mental health issues:

- "My life has slowly become smaller and smaller because I'm limited in what I can do."
- "Being faced with your own mortality at this age is not a fun thing to go through."
- "I've battled extreme depression and not wanted to be alive anymore."
- "I struggled with suicidal thoughts because I didn't know how to deal with it all. I constantly felt like I was letting everyone else down."

Patients highlighted the challenges with IV infusions:

- "It was incredibly time consuming going into the hospital for infusion."
- "Every four weeks going in and getting infusions. They were very hard on the veins."

They were optimistic about the switch to subcutaneous formulations of their drugs: "but when the pen came out, I absolutely wanted to try that. I love it, and the transfer to the pen was easy." But they also acknowledged some of the limitations of home therapy: "injections are way easier, but I forget to do it. So downside is the consistency. Once I start flaring, then I know it is time for my injection."

Finally, patients spoke about the financial burdens and their struggles to get therapies approved by their insurance. They spoke about co-pays, the cost of regular blood draws, and the cost of special diets to avoid flares. But issues with insurance were first and foremost in their minds: "for me, it has been an insurance battle." However, we heard positive experiences with Medicare: "insurance approval is an issue, though it seems to be easier once transitioned to Medicare."

Patient organizations highlighted the need to include evidence on the impact of treatment sequencing on disease progression, as limited access to certain treatments may lead to worsening IBD and put patients at higher risk for IBD-related hospitalization or surgery. The reasons for hospitalization include disease flares requiring IV corticosteroids, bowel obstruction, fistulas, abscesses, *Clostridioides difficile* infection, cytomegalovirus infection, toxic megacolon, bowel perforation, venous thromboembolism, malnutrition, and opiate dependence in the setting of poorly controlled pain. Patient organizations also emphasized the heterogeneity of the patient population and the importance of considering factors such as comorbidities, side effects, route of administration, and costs when choosing treatments. Additionally, patient organizations spoke of the extraintestinal manifestations, such as arthritic symptoms, psychological effects, fatigue, and brain fog, that can further impact patients' quality of life in addition to the typical IBD symptoms.

4.3. Health Equity Considerations

Inflammatory bowel disease is more common in non-Hispanic White people in the United States. Concerns have been raised that this may lead to delays in diagnosis in non-White populations due to the perception that they are less likely to have IBD. The other health equity concern is that patients living in rural areas, far from large medical centers, may have challenges accessing infusion centers for drugs that require IV infusion.

4.4. Health Insurance Access Considerations

We accessed IPD Analytics Payer & Provider Insights for information on formulary status and coverage criteria for the therapies of interest, with a focus on Medicare Part D and Medicare Advantage plans.[76] From a pharmacy benefit perspective, access to Entyvio is somewhat limited, as the SC version is not listed on approximately 80% of these formularies.[76] Zymfentra, the SC form of infliximab, does not appear on any formulary. SC Ustekinumab appears to be more widely available, although subject to quantity limits and prior authorization requirements in many cases.

IV formulations of Entyvio and its therapeutic alternatives appear to be more widely available through Part B reimbursement, subject to important limitations. Many criteria require step therapy with systemic agents and/or adalimumab (although steps can be skipped in certain clinical situations, including if the patient is biologic-experienced). Criteria generally require reauthorization after 6-12 months of use.

5. Comparative Effectiveness and Cost

5.1. Unmet Need

5.1.1. Qualitative Discussion

CMS defines unmet need as "treating a disease or condition in cases where no other treatment options exist, or existing treatments do not adequately address the disease or condition." For patients with moderate to severe UC or CD who do not respond to systemic therapy, several TIMs are available including the TNF inhibitors such as adalimumab, golimumab, and infliximab, and other drugs with different mechanisms of action including ustekinumab and Entyvio. Despite multiple available agents, many patients do not respond to treatment or may lose response over time. For both UC and CD, surgical procedures are available, but like systemic therapies, these may not always result in sustained remission without complications or treatment, and patients may prefer to avoid surgery despite its potential benefit.

5.1.2. Quantitative Discussion

Decision-analytic models, often used to support estimates of value-based drug pricing, can also produce quantitative assessments of unmet need. Calculations of proportional and absolute health "shortfall" are two different ways of representing society's considerations for severity or burden of illness. They are complementary measures that estimate the reduction in lifetime health due to a specific condition compared with health in the age- and sex-matched general US population. Using the decision-analytic model described below in Section 5.2, we calculated proportional and absolute shortfalls in health using the equal-value life year (evLY) measure.

We attest that all measures of health used throughout this report, most prominently the evLY, do *not* treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. The evLY treats the value of extended life of all individuals in exactly the same way, with each year of life gained from treatment valued identically. The evLY has served for many years as a bedrock of ICER's drug price benchmarks that are used by the Veterans Administration, Medicaid programs, and private insurers. In our public comments on the CMS draft guidance, we provided further rationale for why the evLY is consistent with the IRA and will be helpful to CMS in its deliberations. A detailed description of the evLY calculation can be found in the Supplement Section E1.

To quantify unmet need for patients with at least moderate UC and CD, we present evLY shortfall calculations assuming that patients have received Entyvio. We chose Entyvio to represent the most

relevant therapy because it meets or exceeds the standard of care for patients with at least moderate UC and CD. To calculate the absolute evLY shortfall, we subtracted the lifetime undiscounted evLYs with Entyvio from the evLYs expected for the general population (calculated using age- and sex-adjusted estimates for mortality and a constant utility of 0.851 for quality of life). To calculate the proportional evLY shortfall, we divided the absolute evLY shortfall by the evLY life expectancy for the general population with the same age and sex distribution at baseline.

Ulcerative Colitis

The undiscounted absolute shortfall for Medicare patients with at least moderate UC who have reached the maximum possible therapy (i.e., assumed to be Entyvio) was 2.47 evLYs versus the general age- and sex-adjusted US population. The undiscounted proportional shortfall was 2.47/12.57=19.6%. For context, as shown in Table 5.1, the absolute evLY shortfall for Medicare patients with at least moderate UC treated with Entyvio is similar to that observed with osteoporosis, but substantially less than observed for beta thalassemia. The proportional shortfall was similar to that for patients living with osteoporosis, but substantially less than for patients with multiple myeloma. The shortfalls were calculated assuming that patients are treated with Entyvio, and as such, represent the continued unmet need for patients with UC despite existing therapies.

Crohn's Disease

The undiscounted absolute shortfall for Medicare patients with at least moderate CD who have reached the maximum possible therapy (i.e., assumed to be Entyvio) was 6.2 evLYs versus the general age- and sex-adjusted US population. The undiscounted proportional shortfall was 6.2/16.45=37.7%. For context, as shown in Table 5.1, the absolute evLY shortfall for Medicare patients with at least moderate CD treated with Entyvio is similar to that observed with COPD, but substantially less than observed for beta thalassemia. The proportional shortfall was similar to that for patients living with prostate cancer, but substantially less than for patients with multiple myeloma. The shortfalls were calculated assuming that patients are treated with Entyvio, and as such, represent the continued unmet need for patients with CD despite existing therapies.

Table 5.1. Absolute and Proportional evLY Shortfalls for Ulcerative Colitis and Crohn's Disease

	Absolute evLY Shortfall	Proportional evLY Shortfall
Beta Thalassemia	25.5	52.5%
Multiple Myeloma	18.7	95.7%
Alzheimer's Disease	9.4	71.3%
Chronic Obstructive Pulmonary Disease	6.8	44.8%
Prostate Cancer	3.6	35.6%
High Cholesterol	1.7	10.9%
Osteoporosis	2.6	18.7%
Ulcerative Colitis	2.5	19.6%
Crohn's Disease	6.2	37.7%

evLY: equal value of life years

5.2 Overview and Model Structure

5.2.1. Ulcerative Colitis and Crohn's Disease

We developed two separate *de novo* decision analytic models for this evaluation, one for UC and one for CD to evaluate the lifetime clinical and economic outcomes of Entyvio. The model compared Entyvio to infliximab and ustekinumab which represents a subset of therapeutic alternatives that were reviewed for comparative clinical effectiveness. Infliximab and ustekinumab were selected based on discussions with patient organizations, clinicians, manufacturers, and payers on what represented the most relevant monotherapy alternatives to Entyvio for a Medicare population and based on the availability of biosimilar alternatives. When Entyvio was compared to infliximab, we assumed that the subsequent line of therapy was ustekinumab, and when Entyvio was compared to ustekinumab, we assumed that the subsequent line of therapy was infliximab. Patients who did not respond to or who did not continue to respond to subsequent therapy moved to conventional therapy. Conventional therapy transition probabilities were based on the placebo arms of relevant clinical trials, and for costing purposes and model simplicity, conventional therapy was defined as an induction period of prednisone followed by mercaptopurine or azathioprine. Outcomes assessed included total costs, total evLYs, total years in remission, number of colectomies (UC) or surgeries (CD) and incremental cost per evLY gained. The use of evLYs provides a standardized approach to assessing treatment value, accounting for both survival and overall health impact, while adhering to statutory requirements under the IRA set by CMS. Costs and outcomes were discounted at 3% annually.

Both models focused on a hypothetical cohort of Medicare patients with moderately to severely active UC or CD with and without prior use of biologics and without extraintestinal manifestations (EIMs) at baseline who initiated treatment with Entyvio, infliximab, or ustekinumab. Mean age of

the modeled cohort was 71 years for UC (53% female), and 65 years for CD (60% female). Where IV and SC options for treatment administration were available, we assumed 10% of patients would be on SC based on recent market data as well as clinical expert and payer estimates. Model cycle length was eight weeks based on what was observed in prior published economic models and key clinical trials (i.e., based on timing of clinical endpoint assessment, frequency of treatment administration, and the induction and maintenance periods of treatment). Patients were followed over a lifetime time horizon.

For UC, the Markov model consisted of health states for moderately to severely active disease, clinical response without remission, clinical response with remission, post-colectomy (with and without complications), and death. All patients entered the model receiving an induction period of treatment with Entyvio, infliximab, or ustekinumab. Following induction, patients who achieved clinical response (with or without remission) continued to receive their initial treatment. Patients who did not achieve clinical response during induction, did not continue to respond to treatment during the maintenance phase, or discontinued treatment due to adverse events (AEs) while responding to treatment or in remission, transitioned to subsequent therapy (infliximab or ustekinumab, depending on the comparator). Patients with active disease had a per-cycle probability of colectomy, and after colectomy moved to the post-colectomy health state. The model also included a risk of chronic pouchitis for a percentage of patients following colectomy. All patients in the post-colectomy health state remained in this state until death.

For CD, the Markov model consisted of a similar set of health states as for UC, including moderately to severely active disease, clinical response without remission, clinical response with remission, and death. All patients entered the model receiving an induction period with Entyvio, infliximab, or ustekinumab. Following induction, patients who achieved clinical response (with or without remission) continued to receive their initial treatment. Patients who did not achieve clinical response during induction, did not continue to respond to treatment during the maintenance phase, or discontinued treatment due to AEs while responding to treatment or in remission, transitioned to subsequent therapy. In the absence of infliximab data in the NMA, we used adalimumab data as a proxy given their similar mechanisms of action. Patients with moderately to severely active CD had a risk of surgery in each model cycle, and this was captured as a transient episode with additional costs and associated impacts on health outcomes. Following surgery, patients remained on the same therapy and in the same health state.

For both models, patients remained in the model until they die. All patients could transition to death from all causes from any of the alive health states. In addition, patients had an acute risk of death from colectomy (for patients with UC) and surgery (for patients with CD). For the purposes of threshold price premium calculations, we assumed that the proportion of use in Medicare for treating UC would be 45%, and 55% for CD.[77]

5.2.2. Impact of Patient Involvement on Model Development

During the development of our model analysis plan, we discussed our draft model structure and assumptions with seven members of the patient community to ensure their perspectives and experiences were reflected in our analysis plan. The feedback received informed our model structure (e.g., depiction of post-colectomy with or without complications), outcomes of interest selected (e.g., years in remission and number of surgeries avoided), choice of scenario analyses (e.g., inclusion of the impact of extraintestinal manifestations for CD), and inputs for the societal perspective analysis (e.g., caregiver time required for IV infliximab). Full details of the format of the discussions can be found in the Supplement Section E1, and a full summary of the impact of patient involvement on the model development can be found in the Model Analysis Plan.

5.3 Results

5.3.1 Ulcerative Colitis

Projected Discounted Lifetime Health Outcomes and Health Care Sector Costs for Entyvio versus Infliximab and Ustekinumab

For UC, the total lifetime discounted health outcomes for the intervention and each therapeutic alternative are shown in Table 5.2. Total lifetime discounted intervention (inclusive of acquisition costs, mark-up, and administration costs for first, second, and third lines of therapy) and non-intervention costs (inclusive of costs for treating serious infections, costs of colectomy, and chronic condition costs) for the intervention and each therapeutic alternative are shown in Table 5.3. Disaggregated results for intervention acquisition and related costs can be found in the Supplement (Section E3).

Entyvio versus Infliximab

Compared to infliximab, Entyvio resulted in fewer colectomies, increased life years, increased evLYs, and lower non-intervention health care sector costs (Table 5.2).

Entyvio versus Ustekinumab

Compared to ustekinumab, Entyvio resulted in more colectomies, fewer life years, decreased evLYs, and higher non-intervention health care sector costs (Table 5.2).

Table 5.2. Lifetime Discounted Health Outcomes for Entyvio and Therapeutic Alternatives in UC

Treatment	Years in Remission	Number of Colectomies	Life Years	evLYs
Entyvio vs. Infliximab				
Entyvio	1.965	0.062	10.898	7.997
Infliximab	1.887	0.063	10.897	7.978
Entyvio vs. Ustekinumab				
Entyvio	1.396	0.069	10.895	7.866
Ustekinumab	1.904	0.063	10.898	7.980

evLYs: equal-value life years

Table 5.3. Lifetime Discounted Health Care Sector Costs for Entyvio versus Infliximab and Entyvio versus Ustekinumab in UC

	Intervention Health Care Sector Costs		Non-Intervention Health Care Sector Costs		
Treatment	**Intervention Acquisition Costs***	**Intervention Related Costs***	**Cost of AEs**	**Health State Costs**	**Colectomy Costs**
Entyvio vs. Infliximab					
Entyvio	$131,475	$5,670	$1,146	$578,399	$1,960
Infliximab	$79,648	$2,591	$1,322	$586,243	$1,994
Entyvio vs. Ustekinumab					
Entyvio	$94,453	$6,762	$1,181	$632,262	$2,190
Ustekinumab	$82,707	$2,267	$1,303	$585,414	$1,993

AE: adverse event, evLYs: equal-value life years

*Intervention acquisition costs include the cost of Entyvio, second line treatment costs (i.e., the cost of ustekinumab when Entyvio is compared to infliximab, and the cost of infliximab when Entyvio is compared to ustekinumab), and the cost of conventional therapy in the last line. Intervention-related costs include the mark-up and administration costs for each line of therapy. Fully disaggregated results for intervention acquisition and related costs can be found in the Supplement (Section E3).

Table 5.4. Incremental Lifetime Discounted Results for Entyvio versus Infliximab and Entyvio versus Ustekinumab in UC

Treatment	Years in Remission	Number of Colectomies	Life Years	evLYs	Non-Intervention Health Care Sector Costs*
Entyvio vs. Infliximab	0.0785	-0.0011	0.0005	0.0198	-$8,054
Entyvio vs. Ustekinumab	-0.509	0.006	-0.003	-0.114	$46,924

evLYs: equal-value life years

*Non-Intervention Health Sector Costs include the cost of AEs, health state costs, and colectomy costs.

5.3.2 Crohn's Disease

Projected Discounted Lifetime Health Outcomes and Health Care Sector Costs for Entyvio versus Infliximab and Ustekinumab

For CD, the total lifetime discounted health outcomes for the intervention and each therapeutic alternative are shown in Table 5.5. Total lifetime discounted intervention (inclusive of acquisition costs, mark-up, and administration costs for first, second, and third lines of therapy) and non-intervention costs (inclusive of costs for treating serious infections, costs of surgeries, and chronic condition costs) for the intervention and each therapeutic alternative are shown in Table 5.6. Fully disaggregated results for intervention acquisition and related costs can be found in the Supplement (Section E3).

Entyvio versus Infliximab

Compared to infliximab, Entyvio resulted in more surgeries, fewer life years, decreased evLYs, and higher non-intervention health care sector costs (Table 5.5).

Entyvio versus Ustekinumab

Compared to ustekinumab, Entyvio resulted in more surgeries, fewer life years, decreased evLYs, and higher non-intervention health care sector costs (Table 5.5).

Table 5.5. Lifetime Discounted Health Outcomes for Entyvio versus Infliximab and Entyvio versus Ustekinumab in CD

Treatment	Years in Remission	Number of Surgeries	Life Years	evLYs
Entyvio vs. Infliximab				
Entyvio	1.26	0.31	12.82	7.76
Infliximab	1.63	0.30	12.83	7.87
Entyvio vs. Ustekinumab				
Entyvio	1.42	0.31	12.82	7.80
Ustekinumab	1.63	0.30	12.82	7.86

evLYs: equal-value life years

Table 5.6. Lifetime Discounted Health Care Sector Costs for Entyvio versus Infliximab and Entyvio versus Ustekinumab in CD

	Intervention Health Care Sector Costs		Non-Intervention Health Care Sector Costs		
Treatment	Intervention Acquisition Costs*	Intervention Related Costs*	Cost of AEs	Health State Costs	Surgery Costs
Entyvio vs. Infliximab					
Entyvio	$80,600	$3,674	$739	$1,063,246	$8,010
Infliximab	$54,179	$2,436	$687	$1,023,551	$7,660
Entyvio vs. Ustekinumab					
Entyvio	$69,956	$4,832	$517	$1,047,770	$7,879
Ustekinumab	$55,521	$2,341	$586	$1,023,714	$7,661

AE: adverse event, evLYs: equal-value life years

*Intervention acquisition costs include the cost of Entyvio, second line treatment costs (i.e., the cost of ustekinumab when Entyvio is compared to infliximab, and the cost of infliximab when Entyvio is compared to ustekinumab), and the cost of conventional therapy in the last line. Intervention-related costs include mark-up and administration costs for each line of therapy. Fully disaggregated results for intervention acquisition and related costs can be found in the Supplement (Section E3).

Table 5.7. Incremental Lifetime Discounted Results for Entyvio versus Infliximab and Entyvio versus Ustekinumab in CD

Treatment	Years in Remission	Number of Surgeries	Life Years	evLYs	Non-Intervention Health Care Sector Costs*
Entyvio vs. Infliximab	-0.364	0.014	-0.007	-0.108	$40,097
Entyvio vs. Ustekinumab	-0.210	0.008	-0.004	-0.065	$24,204

evLYs: equal-value life years

*Non-Intervention Health Sector Costs include the cost of AEs, health state costs, and colectomy costs.

Price Premium Threshold Analysis

We framed our price threshold calculations as the price premiums that CMS should pay for Entyvio over the pricing of therapeutic alternatives. A range of cost-effectiveness thresholds is recommended, and the most commonly suggested thresholds in the US are $100,000 and $150,000 per additional year of health benefit. We used these same thresholds when using the evLY gained, which would have the effect of increasing the premium prices at each threshold. We have included a wider range of thresholds to provide CMS with additional pricing points for consideration.

Since CMS may want to consider comparative results for Entyvio versus both infliximab and ustekinumab, we present threshold price results versus both these potential therapeutic alternatives. The results are incremental to the price of the therapeutic alternative, and as such, the results remain relevant regardless of the price CMS might pay for infliximab and ustekinumab.

Thirty-day price premiums for Entyvio relative to the cost of infliximab are shown in Table 5.8. Compared to infliximab, 30-day price premiums for Entyvio are $190 at $50,000/evLY, $210 at $100,000/evLY, $230 at $150,000/evLY, and $250 at $200,000/evLY. These price premiums are a weighted average of the price premiums calculated for use of Entyvio in UC ($420 at $50,000/evLY, $460 at $100,000/evLY, $510 at $150,000/evLY, and $550 at $200,000/evLY) and CD ($0 at all thresholds, as Entyvio was found to be more costly and less effective in these analyses) assuming that 45% of Entyvio use in the Medicare population is for UC, and 55% of use is for CD.[77] CMS can add these 30-day price premiums to the 30-day price currently paid for infliximab to determine the calculated value-based price for Entyvio at each threshold. For example, if the cost to CMS of a 30-day supply of infliximab is $1,000, the 30-day threshold price for Entyvio is $1,210 at a $100,000/evLY threshold.

Compared to ustekinumab, Entyvio was not associated with health gains in UC or CD, and therefore decision analytic modeling confirmed that the evidence does not support a price premium for Entyvio above CMS pricing for ustekinumab.

Table 5.8. Estimated 30-Day Threshold Prices for Entyvio Compared to Therapeutic Alternatives Across a Range of Cost-Effectiveness Benchmarks

	30-Day Threshold Price Premiums for Entyvio			
	$50,000/evLY	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
Ulcerative Colitis				
vs. Infliximab	$420	$460	$510	$550
vs. Ustekinumab	No price premium*	No price premium*	No price premium*	No price premium*
Crohn's Disease				
vs. Infliximab	No price premium*	No price premium*	No price premium*	No price premium*
vs. Ustekinumab	No price premium*	No price premium*	No price premium*	No price premium*
Multi-Indication Price†				
vs. Infliximab	$190	$210	$230	$250
vs. Ustekinumab	No price premium*	No price premium*	No price premium*	No price premium*

evLYs: equal-value life years

Note: 30-day prices are rounded to the nearest $10

*Entyvio resulted in fewer evLYs gained relative to therapeutic alternatives.

†Weighted assuming 55% of Entyvio use is for CD and 45% for UC.

Conventional threshold analyses (i.e., inclusive of infliximab pricing assumptions), are reported in the Supplement (Section E4). While we report conventional threshold analyses results in the Supplement for completeness, we recommend that CMS use the Threshold Price Premiums reported in Table 5.8 above because these prices are independent of the price CMS currently pays for infliximab for which we do not have full transparency.

Sensitivity Analyses

Ulcerative Colitis

In one-way sensitivity analyses, compared to infliximab, Entyvio was generally more costly, and more effective when parameters were varied individually across reasonable ranges of uncertainty. The spread between the lower and upper result for each parameter was wide; however, the findings of our sensitivity analyses did not change our conclusions. Compared to ustekinumab, across all parameters, Entyvio was more costly and less effective. In probabilistic sensitivity analyses, Entyvio had less than 10% probability of yielding benefits aligned with the assumed price compared to therapeutic alternatives when all parameters were varied simultaneously. The 95% credible interval for incremental evLYs for Entyvio compared to both infliximab and ustekinumab ranged from less effective to more effective. Details related to sensitivity analyses for the UC model can be found in the Supplement (Section E4).

Crohn's Disease

In one-way sensitivity analyses, compared to infliximab and ustekinumab, Entyvio was more costly and less effective when parameters were varied individually across reasonable ranges of uncertainty. When the relative risk of achieving remission following response in maintenance for Entyvio compared to ustekinumab was varied to the high end (upper 95% credible interval [CrI]: 3.16), Enytvio was more costly and more effective, however the findings of our sensitivity analyses did not change our conclusions. In probabilistic sensitivity analyses, Entyvio had less than 1% probability of yielding benefits aligned with the assumed price compared to therapeutic alternatives when all parameters were varied simultaneously. The 95% credible interval for incremental evLYs for Entyvio compared to both infliximab and ustekinumab ranged from less effective to more effective. Details related to sensitivity analyses for the CD model can be found in the Supplement (Section E4).

Scenario Analyses

Ulcerative Colitis

Across all scenario analyses, results were consistent with the base case. The most impactful scenario was when using alternative utility estimates (incremental evLYs vs. infliximab of 0.049 in the scenario analysis vs. 0.0198 in the base case). Details related to scenario analyses for the UC model can be found in the Supplement (Section E4).

Crohn's Disease

Across all scenario analyses, results were consistent with the base case. Details related to scenario analyses for the CD model can be found in the Supplement (Section E4).

Model Validation

Details related to model validation for UC and CD can be found in the Supplement (Section E4).

Uncertainty and Controversies

No measure of health gain, including IBD-relevant outcomes such as years in remission or surgeries avoided, or summary measures such as the evLY gained, captures all information important in value considerations. Additional considerations such as unmet need are relevant to consider in discussions on value and pricing negotiations.

We recognize that quality of life associated with active disease, or states of response with or without remission vary across individual patients. Our modeling approach aggregates these impacts to find an average projected lifetime benefit to inform threshold pricing estimates. Given that CMS is seeking a single price for consideration as an initial offer, it is reasonable for an aggregated population-based approach to be used.

The intent of our analysis is to inform CMS drug price negotiations for Entyvio and not necessarily determine its most optimal place in therapy amongst other biologic agents. Our model was intentionally simplified to maintain the same subsequent treatment options between intervention and therapeutic alternatives. Further, the effectiveness estimates used in the model were based on results from the NMA that included patients with and without prior use of biologic therapy and therefore our threshold price premiums reflect Entyvio's effectiveness as both a first line and subsequent line of therapy. The effectiveness estimates were applied to conventional therapy transition probabilities which were derived from the placebo arms of the trials included in NMA and two separately published trials. Placebo treatment in the included trials generally included

immunosuppressants, corticosteroids, or no active therapy, and for the purposes of calculating drug costs for conventional therapy, we assumed an induction period of prednisone followed by mercaptopurine or azathioprine. We recognize that our model does not necessarily represent all potential real-world treatment options or patterns; however, subsequent treatment options were selected based on patient, clinician, payer, and manufacturer feedback on what represented the most relevant options for the Medicare population while retaining the focus of the model to be on initial therapy.

The results of our model were highly sensitive to the relative treatment effects derived from the NMAs which were subject to a high level of uncertainty and some gaps in evidence. We used the point estimates for treatment effectiveness to inform the model; however, the credible ranges of the estimates were wide. Distributions based on the credible intervals that informed the probabilistic analysis yielded incremental evLYs that crossed no effect indicating that the joint uncertainty in model parameters could result in situations where Entyvio was more effective and situations where Entyvio was less effective than therapeutic alternatives infliximab and ustekinumab. Our findings are based on the best available evidence and this range of relative treatment effect estimates suggested that differences in health outcomes between treatments in UC and CD, if any, are small.

We did not have data to inform induction response and remission, or rates of serious infection and discontinuation due to AEs for infliximab in the CD model. We used adalimumab data as a proxy for infliximab given their similar mechanisms of action, however we recognize this is an imperfect alternative. Our sensitivity and scenario analyses explored the impact of this uncertainty on model results. Because Entyvio and therapeutic alternatives were found to perform comparably on many clinical parameters, small changes in key measures could have an outsized impact on results and conclusions. Furthermore, the model did not include the effects of endoscopic improvement; however, there was no evidence to suggest differential effects between treatments based on the results from the ICER NMAs. It is unclear how endoscopic improvement may impact patient's experience with UC or CD beyond that captured with response or remission outcomes and their associated health related quality of life. Risk of serious infection for Entyvio versus anti-TNF therapy was assessed in an observational study using US and French claims database,[52] and aligned with the studies we used to inform risk of serious infection in the model. Kirchgesner (2022) did not report relative risks for treatments relative to conventional therapy, thus limiting our ability to use the estimates in our model. We used alternative sources to inform our estimates;[78-81] however, the direction and magnitude of treatment effect for Entyvio versus anti-TNF therapy was similar between studies.

Our model prioritized data from a Medicare population, including population demographics, probability of surgery or colectomy and associated complications, health state costs, colectomy and

surgery costs, and utility estimates. While our intent was to ensure the model was most relevant for a Medicare population, specific data were not available in all cases.

Our threshold price premium results sought to identify a single price for Entyvio that reflected all considerations including the proportion of patients receiving subcutaneous versus IV administration (10% vs. 90%) and proportion of patients using Entyvio to treat UC versus CD (45% vs. 55%). If the Medicare population experiences an increased use of Entyvio in the CD population, or an increased use of the SC form of administration, 30-day threshold price premiums for Entyvio would change. Details regarding the relationship between threshold price premiums and these considerations are presented in Supplement E5.

No publicly available net price for infliximab or ustekinumab from the Medicare population was available for our analysis; therefore, we are unable to compare our results to current Medicare prices for these agents.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Clinical Outcome Measures

Outcomes of clinical trials of UC commonly include clinical response, clinical remission, and endoscopic improvement.

Clinical Response: A reduction of greater than or equal to three points and greater than or equal to 30% from the baseline in total Mayo Score (see definition below) along with a decrease in the rectal bleeding sub-score of greater than or equal to one point or an absolute rectal bleeding subscore of less than or equal to one point.

Clinical Remission: A Mayo Score of less than or equal to two with no individual sub-score greater than one.

Endoscopic Improvement: A Mayo endoscopic sub-score of zero or one.

Corticosteroid-Free Remission: Clinical remission in patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at the end of the study. Delayed response in clinical trials has been defined as clinical response and remission (via partial Mayo Score) achieved by the non-responders to induction therapy.

Mayo Score

The Mayo Score is a disease activity index developed for assessing the severity of UC. It comprises four sub-scores of three points each (stool frequency, rectal bleeding score, mucosal appearance at endoscopy, and physical global assessment). The higher the score (maximum 12 points), the more severe the UC. A Mayo Score between six and 12 classifies the disease as moderate-to-severe.

Crohn's Disease Activity Index

The Crohn's Disease Activity Index (CDAI) is recognized as the standard of measuring Crohn's disease severity. It consists of eight domains, and overall scores range from zero to 600, with a score of 150 defined as the threshold between remission and active disease. Scores ranging from 150 to 219 indicate mild to moderate Crohn's disease, 220 to 450 as moderate to severe Crohn's disease, and scores greater than 450 indicate very severe Crohn's disease. There is no defined MCID for the CDAI, but clinical trials commonly use changes of 50, 60, 70 or 100 points as a clinical response.[75]

Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a 32-item questionnaire the measures the overall health-related quality of life in patients with IBD. Scores range from 32 to 224, with higher scores indicating better health-related quality of life.[82] Although there is no minimal clinically important difference (MCID) established for patients with UC, the MCID for patients living with Crohn's disease is an improvement of at least 16 points. In addition, data have shown that patients with Crohn's in remission generally have an IBDQ score of at least 170 points.[83] Trials in patients with UC have used the thresholds established in patients with Crohn's disease to measure the rates of meaningful improvements in IBDQ score.

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[84] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[85,86] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional evLY shortfalls can be found in ICER's reference case.

A2. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients.

ICER did not receive any feedback on this inquiry.

B. Stakeholder Input: Supplemental Information

B1. Patient Community Insights: Methods

This was fully described in the main report.

B2. Clinical Expert Input: Methods

This was fully described in the main report.

C. Clinical Guidelines

The key recommendations for the use of biologic therapies for induction and maintenance therapy for patients with moderate to severe ulcerative colitis and Crohn's disease are summarized below. The guidelines are more complex and nuanced than the summary below, so careful reading of the most original guidelines is recommended.

American College of Gastroenterology 2025

In patients with moderately to severely active ulcerative colitis, the ACG recommends vedolizumab, ustekinumab, infliximab, adalimumab, golimumab, tofacinitinib, upadacitinib, guselkumab, mirikizumab, or risankizumab for the induction of remission.

In patients with prior moderately to severely active ulcerative colitis, the ACG recommends continuing vedolizumab, ustekinumab, infliximab, adalimumab, golimumab, tofacinitinib, upadacitinib, guselkumab, mirikizumab, or risankizumab for the maintenance of remission.

In patients with moderate to severe Crohn's disease/higher risk for disease progression, the ACG recommends vedolizumab, ustekinumab, infliximab, adalimumab, certolizumab, upadacitinib, guselkumab, mirikizumab, or risankizumab for the induction of remission.

In patients with moderate to severe Crohn's disease/higher risk for disease progression, the ACG recommends continuing vedolizumab, ustekinumab, infliximab, adalimumab, certolizumab, upadacitinib, guselkumab, mirikizumab, or risankizumab for the maintenance of remission.

American Gastroenterological Association 2024 Living Guidelines

In patients with moderate to severe ulcerative colitis, the ACG recommends the use of vedolizumab, ustekinumab, infliximab, golimumab, tofacinitinib, upadacitinib, risankizumab, and guselkumab, and suggests the use of adalimumab, filgotinib, and mirikizumab over no treatment.

In patients with moderate to severe Crohn's disease, the ACG recommends the use of ustekinumab, infliximab, adalimumab, risankizumab, mirikizumab, and guselkumab and suggests the use of vedolizumab and certolizumab over no treatment.

NICE 2019

In patients with moderately to severely active ulcerative colitis, NICE recommends vedolizumab, infliximab, adalimumab, golimumab, tofacinitinib, upadacitinib, etrasimod, or filgotinib for treatment when conventional therapy has failed.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

To inform our review of the clinical evidence, we developed the following research questions:

- What is the net health benefit of Entyvio versus infliximab in the populations described below?
- What is the net health benefit of Entyvio versus adalimumab in the populations described below?
- What is the net health benefit of Entyvio versus ustekinumab in the populations described below?
- What is the net health benefit of Entyvio versus conventional and/or systemic therapy in the populations described below?

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

PICOTS (Ulcerative Colitis)

Population

The population of focus for the review is adults with moderate-to-severe UC, defined as a Mayo score of six to 12 with an endoscopic subscore ≥2, who no longer respond to at least one conventional and/or systemic therapy (i.e., corticosteroids, immunomodulators). Subgroups of interest include those with disabilities, those with end-stage renal disease (ESRD), those with terminal illness, the Medicare-aged population (≥65 years), children (potentially from trials that included both adults and children or adolescents), presence of extraintestinal manifestations (e.g., arthritic symptoms, psychological effects), and treatment experience (TIM naïve vs. TIM experienced).

Interventions

The full list of interventions is as follows:

- Vedolizumab (Entyvio®, Takeda)

Comparators

Data permitting, we intend to compare Entyvio to drugs that are recommended by current guidelines and have Food and Drug Administration (FDA)-approved biosimilar versions available on the market, as well as to conventional systemic therapy.

FDA Approved Biologics	FDA Approved Biosimilars
• **Infliximab (Remicade®, Janssen)**	• Infliximab-abda (Renflexis®, Merck) • Infliximab-axxq (Avsola®, Amgen) • Infliximab-dyyb (Inflectra®, Celltrion) • Infliximab-qbtx (IXIFI®, Pfizer)
• **Adalimumab (Humira®, Abbvie)**	• Adalimumab-aacf (Idacio®, Fresenius Kabi) • Adalimumab-aaty (Yuflyma®, Celltrion) • Adalimumab-adaz (Hyrimoz®, Sandoz/Cordavis) • Adalimumab-adbm (Cyltezo®, Boehringer Ingelheim) • Adalimumab-afzb (Abrilada®, Pfizer) • Adalimumab-atto (Amjevita®, Amgen) • Adalimumab-aqvh (Yusimry®, Meitheal) • Adalimumab-bwwd (Hadlima®, Organon/Samsung Bioepis) • Adalimumab-fkjp (Hulio®, Biocon Biologics) • Adalimumab-ryvk (Simlandi®, Alvotech/Teva)
• **Ustekinumab (Stelara®, Janssen)**	• Ustekinumab-aauz (Otulfi®, Fresenius Kabi) • Ustekinumab-aekn (Selarsdi®, Alvotech) • Ustekinumab-auub (Wezlana, Amgen) • Ustekinumab-hmny (Starjezma®, Bio-Thera Solutions) • Ustekinumab-kfce (Yesintek®, Biocon) • Ustekinumab-srlf (Imuldosa®, Accord BioPharma) • Ustekinumab-stba (Steqeyma®, Celltrion) • Ustekinumab-ttwe (Pyzchiva®, Samsung Bioepis Co.)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Clinical remission
    - Clinical response
    - Corticosteroid-free clinical remission
    - Health-related quality of life (HRQoL)
        - Inflammatory Bowel Disease Questionnaire (IBDQ)
        - SF-36
        - EQ-5D
        - Others as feasible

    - UC-related hospitalization
    - Colectomy
    - Adverse events (AEs) including
        - Serious AEs
        - AEs leading to discontinuation
- Other Outcomes
    - Normalization of C-Reactive Protein (CRP)/ Erythrocyte Sedimentation Rate (ESR)/calprotectin
    - Endoscopic healing
    - Endoscopic improvement
    - Histologic healing
    - Transmural histologic healing
    - Use of rescue medication
    - Functional outcomes
    - Adverse events including
        - Infections
        - Malignancies
        - Thrombotic events
        - Hepatic events

Timing

Evidence on intervention effectiveness will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on all settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size and duration will be included. High-quality comparative and single-arm observational studies (sample size >500) with at least 12 months of study duration will also be included for outcomes related to maintenance therapy.

PICOTS (Crohn's Disease)

Populations

The population of focus for the review is adults with moderate-to-severe CD, defined as a CD Activity Index (CDAI) score of 220 to 450, who no longer respond to at least one conventional and/or systemic therapy (i.e., corticosteroids, immunomodulators).

Subgroups of interest included those with disabilities, those with end-stage renal disease (ESRD), those with terminal illness, the Medicare-aged population (≥65 years), children (potentially from trials that included both adults and children or adolescents), presence of extraintestinal manifestations (e.g., arthritic symptoms, psychological effects), and treatment experience (TIM naïve vs. TIM experienced).

Interventions

The full list of interventions is as follows:

- Vedolizumab (Entyvio®, Takeda)

Comparators

Data permitting, we intend to compare Entyvio to drugs that are recommended by current guidelines and have FDA-approved biosimilar versions available on the market, as well as to conventional systemic therapy.

FDA Approved Biologics	FDA Approved Biosimilars
• **Infliximab (Remicade®, Janssen)**	• Infliximab-abda (Renflexis®, Merck) • Infliximab-axxq (Avsola®, Amgen) • Infliximab-dyyb (Inflectra®, Celltrion) • Infliximab-qbtx (IXIFI®, Pfizer)
• **Adalimumab (Humira®, Abbvie)**	• Adalimumab-aacf (Idacio®, Fresenius Kabi) • Adalimumab-aaty (Yuflyma, Celltrion) • Adalimumab-adaz (Hyrimoz®, Sandoz/Cordavis) • Adalimumab-adbm (Cyltezo®, Boehringer Ingelheim) • Adalimumab-afzb (Abrilada, Pfizer) • Adalimumab-atto (Amjevita®, Amgen) • Adalimumab-aqvh (Yusimry®, Meitheal) • Adalimumab-bwwd (Hadlima®, Organon/Samsung Bioepis) • Adalimumab-fkjp (Hulio®, Biocon Biologics) • Adalimumab-ryvk (Simlandi®, Alvotech/Teva)
• **Ustekinumab (Stelara®, Janssen)**	• Ustekinumab-aauz (Otulfi®, Fresenius Kabi) • Ustekinumab-aekn (Selarsdi®, Alvotech) • Ustekinumab-auub (Wezlana®, Amgen)

FDA Approved Biologics	FDA Approved Biosimilars
	• Ustekinumab-hmny (Starjezma®, Bio-Thera Solutions) • Ustekinumab-kfce (Yesintek®, Biocon) • Ustekinumab-srlf (Imuldosa®, Accord BioPharma) • Ustekinumab-stba (Steqeyma®, Celltrion) • Ustekinumab-ttwe (Pyzchiva®, Samsung Bioepis Co.)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Clinical remission
    - Clinical response
    - Corticosteroid-free clinical remission
    - Health-related quality of life (HRQoL)
        - Inflammatory Bowel Disease Questionnaire (IBDQ)
        - SF-36
        - EQ-5D
        - Others as feasible
    - CD-related hospitalization
    - CD-related surgeries
    - Adverse events including
        - Serious AEs
        - AEs leading to discontinuation
- Other Outcomes
    - Normalization of CRP/ESR/calprotectin
    - Transmural healing
    - Histologic healing
    - Endoscopic healing
    - Endoscopic improvement
    - Mucosal healing
    - Use of rescue medication
    - Functional outcomes
    - Adverse events including
        - Infections
        - Malignancies
        - Thrombotic events
        - Hepatic events

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on all settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size and duration will be included. High-quality comparative and single-arm observational studies (sample size >500) with at least 12 months of study duration will also be included for outcomes related to maintenance therapy.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		

Section and Topic	Item #	Checklist Item
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for ulcerative colitis and Crohn's disease followed established best research methods.[87,88] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[89] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

Table D1.2. Search Strategy of Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for Ulcerative Colitis

#	Search Term	Hits
1	colitis, ulcerative/	47508
2	((ulcera* adj3 colitis) or inflammatory bowel disease* or IBD or UC).mp	151265
3	1 or 2	151265
4	('entyvio' or 'Entyvio' or "'mln 02 monoclonal antibody'" or 'MLN0002' or 'MLN-0002' or 'MLN-02' or 'MLN02').ti,ab.	2965
5	('Humira' or 'Amjevita' or 'Cyltezo' or 'D2E7 Antibody' or 'Antibody, D2E7' or 'Adalimumab-atto' or 'Adalimumab-adbm' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-aaty' or 'yuflyma' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-fkjp' or 'hulio' or 'amjevita' or 'adalimumab-bwwd' or 'hadlima' or 'hulio' or 'hyrimoz' or 'idacio' or 'adalimumab-ryvk' or 'simlandi' or 'adalimumab-afzb' or 'abrilada' or 'adalimumab-aqvh' or 'yusimry').ti,ab.	878
6	('Monoclonal Antibody cA2' or 'Antibody cA2, Monoclonal' or 'cA2, Monoclonal Antibody' or 'MAb cA2' or 'Remicade' or 'Inflectra' or 'Renflexis' or 'Infliximab-dyyb' or 'Infliximab dyyb' or 'Infliximab-abda' or 'Infliximab abda' or 'infliximab' or 'inflectra' or 'renflexis' or 'avsola' or 'infliximab-axxq' or 'zymfentra' or 'IXIFI' or 'infliximab-qbtx').ti,ab.	18573

#	Search Term	Hits
7	('CNTO 1275' or 'CNTO-1275' or 'Stelara' or 'Ustekinumab-aauz' or 'Otulfi' or 'Ustekinumab-aekn' or 'Selarsdi' or 'Ustekinumab-auub' or 'Wezlana' or 'Ustekinumab-kfce' or 'Yesintek' or 'Ustekinumab-srlf' or 'Imuldosa' or 'Ustekinumab-stba' or 'Steqeyma' or 'Ustekinumab-ttwe' or 'Pyzchiva' or 'ustekinumab-hmny').ti,ab.	204
8	4 or 5 or 6 or 7	21672
9	3 and 8	7223
10	9 not (abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.	5620
11	10 not (animals not (humans and animals)).sh.	5581
12	remove duplicates from 11	5350
13	Limit 12 to English language	5189
14	control Groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv" or "controlled clinical trial" or "multicenter study" or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.	3645466
15	exp cohort studies/ or comparative study.pt. or observational study.pt. or exp case-control studies/ or cohort.tw. or (observational adj2 stud*).tw. or prospective.tw. or retrospective.tw. or longitudinal.tw. or compa*.tw. or groups.tw. or case control.tw. or multivariate.tw.	13684486
16	14 or 15	14557625
17	13 and 16	3820
18	limit 17 to yr="2020 - 2025"	1870

Table D1.3. Search Strategy of EMBASE for Ulcerative Colitis

#	Search Term	Hits
1	'ulcerative colitis'/exp	118003
2	((ulcera* NEAR/3 colitis):ab,ti) OR 'inflammatory bowel disease*':ab,ti OR uc:ti,ab OR ibd:ti,ab	215814
3	#1 OR #2	233730
4	'entyvio':ti,ab OR 'Entyvio':ti,ab OR 'mln 02 monoclonal antibody':ti,ab OR 'mln0002':ti,ab OR 'mln-0002':ti,ab OR 'mln-02':ti,ab OR 'mln02':ti,ab	6944
5	'Humira':ti,ab OR 'Amjevita':ti,ab OR 'Cyltezo':ti,ab OR 'D2E7 Antibody':ti,ab OR 'Antibody, D2E7':ti,ab OR 'Adalimumab-atto':ti,ab OR 'Adalimumab-adbm':ti,ab OR 'adalimumab-aacf':ti,ab OR 'idacio':ti,ab OR 'adalimumab-aaty':ti,ab OR 'adalimumab-adaz':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-fkjp':ti,ab OR 'hulio':ti,ab OR 'amjevita':ti,ab OR 'adalimumab-bwwd':ti,ab OR 'hadlima':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-ryvk':ti,ab OR 'simlandi':ti,ab OR 'yuflyma':ti,ab OR 'adalimumab-afzb':ti,ab OR 'abrilada':ti,ab OR 'adalimumab-aqvh':ti,ab OR 'yusimry':ti,ab	1196
6	'Monoclonal Antibody cA2':ti,ab OR 'Antibody cA2, Monoclonal':ti,ab OR 'cA2, Monoclonal Antibody':ti,ab OR 'MAb cA2':ti,ab OR 'Remicade':ti,ab OR 'Inflectra':ti,ab OR 'Renflexis':ti,ab	35907

#	Search Term	Hits
	OR 'Infliximab-dyyb':ti,ab OR 'Infliximab dyyb':ti,ab OR 'Infliximab-abda':ti,ab OR 'Infliximab abda':ti,ab OR 'infliximab':ti,ab OR 'inflectra':ti,ab OR 'renflexis':ti,ab OR 'avsola':ti,ab OR 'infliximab-axxq':ti,ab OR 'zymfentra':ti,ab OR 'IXIFI':ti,ab OR 'infliximab-qbtx':ti,ab	
7	'CNTO 1275':ti,ab OR 'CNTO-1275':ti,ab OR 'Stelara':ti,ab OR 'Ustekinumab-aauz':ti,ab OR 'Otulfi':ti,ab OR 'Ustekinumab-aekn':ti,ab OR 'Selarsdi':ti,ab OR 'Ustekinumab-auub':ti,ab OR 'Wezlana':ti,ab OR 'Ustekinumab-kfce':ti,ab OR 'Yesintek':ti,ab OR 'Ustekinumab-srlf':ti,ab OR 'Imuldosa':ti,ab OR 'Ustekinumab-stba':ti,ab OR 'Steqeyma':ti,ab OR 'Ustekinumab-ttwe':ti,ab OR 'Pyzchiva':ti,ab OR 'ustekinumab-hmny':ti,ab	192
8	#4 OR #5 OR #6 OR #7	41450
9	#3 AND #8	16709
10	#9 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	9905
11	#10 NOT [medline]/lim	7535
12	#11 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)	7523
13	#12 AND [english]/lim	7380
14	#13 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)	7295
15	'clinical':ti,ab AND 'trial':ti,ab OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR control*:ti,ab OR 'control group'/exp OR 'drug therapy':lnk	13229276
16	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'observational study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compa*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR longitudinal:ti,ab OR ((observational NEAR/2 stud*):ti,ab)	23636759
17	#15 OR #16	27856421
18	#14 AND #17	6734
19	#18 AND [2020-2025]/py	2527

Table D1.4. Search Strategy of Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for Crohn's Disease (Clinical Trials Only)

#	Search Term	Hits
1	exp Crohn's Disease/	50148
2	('Crohn* disease' or 'Crohn* Enteritis' or 'Granulomatous Colitis' or 'cleron disease' or 'Inflammatory Bowel Disease 1' or 'Regional Ileiti*' or 'morbus crohn' or 'regional enter*' or 'Granulomatous Enteritis' or 'Ileocolitis').ti,ab.	66860
3	1 or 2	76138
4	('entyvio' or 'Entyvio' or "'mln 02 monoclonal antibody'" or 'MLN0002' or 'MLN-0002' or 'MLN-02' or 'MLN02').ti,ab.	2965
5	('Humira' or 'Amjevita' or 'Cyltezo' or 'D2E7 Antibody' or 'Antibody, D2E7' or 'Adalimumab-atto' or 'Adalimumab-adbm' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-aaty' or 'yuflyma' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-atto' or 'amjevita' or 'adalimumab-bwwd' or 'hadlima' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-ryvk' or	878

#	Search Term	Hits
	'simlandi' or 'adalimumab-aaty' or 'adalimumab-afzb' or 'abrilada' or 'adalimumab-aqvh' or 'yusimry').ti,ab.	
6	('Monoclonal Antibody cA2' or 'Antibody cA2, Monoclonal' or 'cA2, Monoclonal Antibody' or 'MAb cA2' or 'Remicade' or 'Inflectra' or 'Renflexis' or 'Infliximab-dyyb' or 'Infliximab dyyb' or 'Infliximab-abda' or 'Infliximab abda' or 'infliximab' or 'inflectra' or 'infliximab-dyyb' or 'renflexis' or 'infliximab-abda' or 'avsola' or 'infliximab-axxq' or 'zymfentra' or 'infliximab-dyyb' or 'IXIFI' or 'infliximab-qbtx').ti,ab.	18573
7	('CNTO 1275' or 'CNTO-1275' or 'Stelara' or 'Ustekinumab-aauz' or 'Otulfi' or 'Ustekinumab-aekn' or 'Selarsdi' or 'Ustekinumab-auub' or 'Wezlana' or 'Ustekinumab-kfce' or 'Yesintek' or 'Ustekinumab-srlf' or 'Imuldosa' or 'Ustekinumab-stba' or 'Steqeyma' or 'Ustekinumab-ttwe' or 'Pyzchiva' or 'ustekinumab-hmny').ti,ab.	204
8	4 or 5 or 6 or 7	21672
9	3 and 8	6594
10	9 not (abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.	5151
11	10 not (animals not (humans and animals)).sh.	5135
12	remove duplicates from 11	4864
13	Limit 12 to English language	4661
14	control Groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv" or "controlled clinical trial" or "multicenter study" or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.	3645466
15	13 and 14	1357
16	limit 15 to yr="2023 - 2025"	209

Table D1.5. Search Strategy of EMBASE for Crohn's Disease (Clinical Trials Only)

#	Search Term	Hits
1	'crohns disease'/exp	132576
2	'crohn* disease':ti,ab OR 'crohn* enteritis':ti,ab OR 'granulomatous colitis':ti,ab OR 'cleron disease':ti,ab OR 'inflammatory bowel disease 1':ti,ab OR 'regional ileiti*':ti,ab OR 'morbus crohn':ti,ab OR 'regional enter*':ti,ab OR 'granulomatous enteritis':ti,ab OR 'ileocolitis':ti,ab	11788
3	#1 OR #2	233730
4	'entyvio':ti,ab OR 'Entyvio':ti,ab OR 'mln 02 monoclonal antibody':ti,ab OR 'mln0002':ti,ab OR 'mln-0002':ti,ab OR 'mln-02':ti,ab OR 'mln02':ti,ab	6944
5	'Humira':ti,ab OR 'Amjevita':ti,ab OR 'Cyltezo':ti,ab OR 'D2E7 Antibody':ti,ab OR 'Antibody, D2E7':ti,ab OR 'Adalimumab-atto':ti,ab OR 'Adalimumab-adbm':ti,ab OR 'adalimumab-aacf':ti,ab OR 'idacio':ti,ab OR 'adalimumab-aaty':ti,ab OR 'adalimumab-adaz':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-fkjp':ti,ab OR 'hulio':ti,ab OR 'amjevita':ti,ab OR 'adalimumab-bwwd':ti,ab OR 'hadlima':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-ryvk':ti,ab OR 'simlandi':ti,ab OR 'yuflyma':ti,ab OR 'adalimumab-afzb':ti,ab OR 'abrilada':ti,ab OR 'adalimumab-aqvh':ti,ab OR 'yusimry':ti,ab	1196
6	'Monoclonal Antibody cA2':ti,ab OR 'Antibody cA2, Monoclonal':ti,ab OR 'cA2, Monoclonal Antibody':ti,ab OR 'MAb cA2':ti,ab OR 'Remicade':ti,ab OR 'Inflectra':ti,ab OR 'Renflexis':ti,ab OR 'Infliximab-dyyb':ti,ab OR 'Infliximab dyyb':ti,ab OR 'Infliximab-abda':ti,ab OR 'Infliximab abda':ti,ab OR 'infliximab':ti,ab OR 'inflectra':ti,ab OR 'renflexis':ti,ab OR 'avsola':ti,ab OR 'infliximab-axxq':ti,ab OR 'zymfentra':ti,ab OR 'IXIFI':ti,ab OR 'infliximab-qbtx':ti,ab	35907
7	'CNTO 1275':ti,ab OR 'CNTO-1275':ti,ab OR 'Stelara':ti,ab OR 'Ustekinumab-aauz':ti,ab OR 'Otulfi':ti,ab OR 'Ustekinumab-aekn':ti,ab OR 'Selarsdi':ti,ab OR 'Ustekinumab-auub':ti,ab OR 'Wezlana':ti,ab OR 'Ustekinumab-kfce':ti,ab OR 'Yesintek':ti,ab OR 'Ustekinumab-srlf':ti,ab OR 'Imuldosa':ti,ab OR 'Ustekinumab-stba':ti,ab OR 'Steqeyma':ti,ab OR 'Ustekinumab-ttwe':ti,ab OR 'Pyzchiva':ti,ab OR 'ustekinumab-hmny':ti,ab	192
8	#4 OR #5 OR #6 OR #7	41450
9	#3 AND #8	16709
10	#9 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	9905
11	#10 NOT [medline]/lim	7535
12	#11 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)	7523
13	#12 AND [english]/lim	7380
14	#13 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)	6088
15	'clinical':ti,ab AND 'trial':ti,ab OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR control*:ti,ab OR 'control group'/exp OR 'drug therapy':lnk	13229276
16	#14 AND #15	2894
17	#16 AND [2023-2025]/py	493

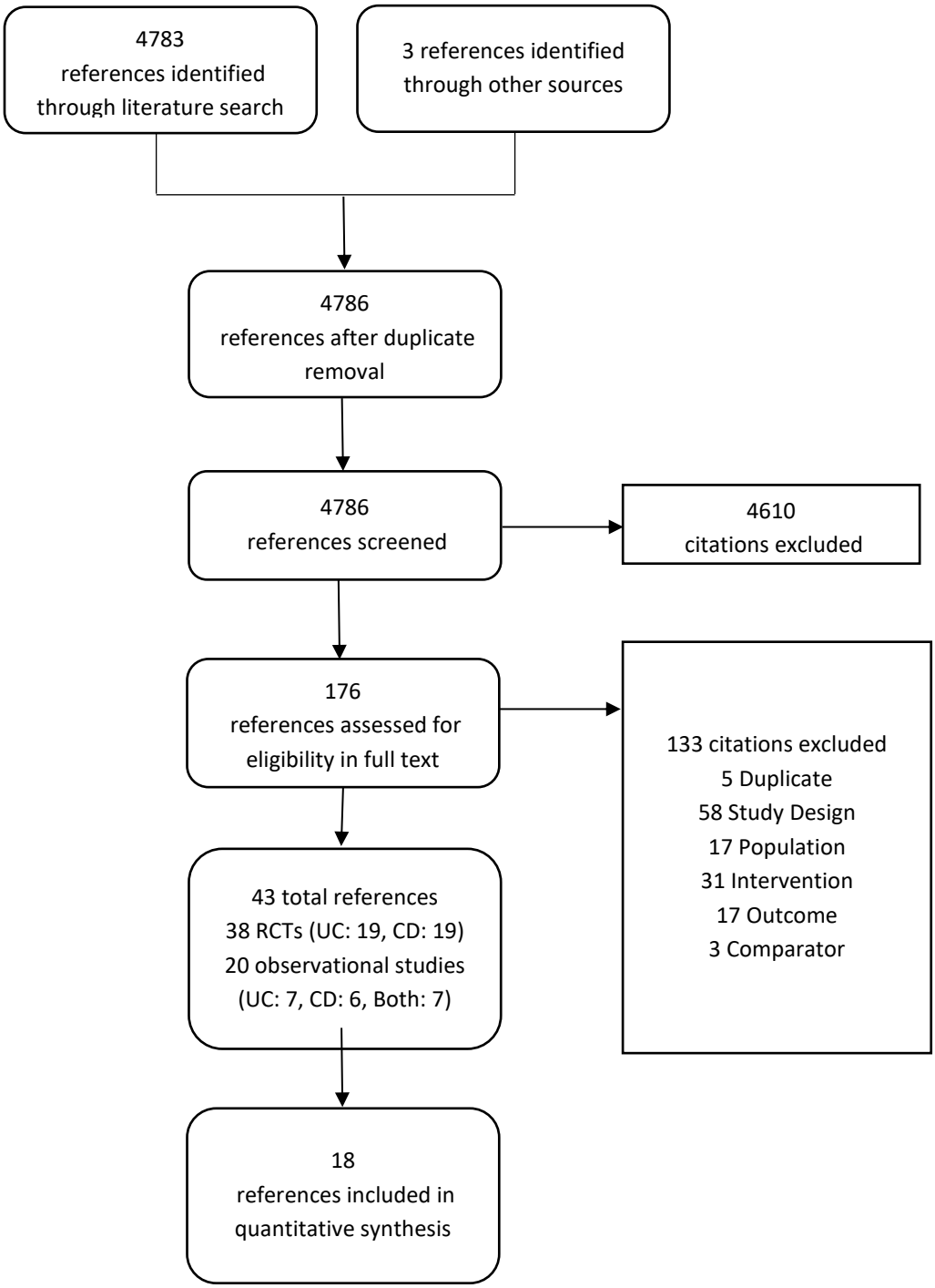
Table D1.6. Search Strategy of Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for Crohn's Disease (Observational Studies Only)

#	Search Term	Hits
1	exp Crohn's Disease/	50148
2	('Crohn* disease' or 'Crohn* Enteritis' or 'Granulomatous Colitis' or 'cleron disease' or 'Inflammatory Bowel Disease 1' or 'Regional Ileiti*' or 'morbus crohn' or 'regional enter*' or 'Granulomatous Enteritis' or 'Ileocolitis').ti,ab.	66860
3	1 or 2	76138
4	('entyvio' or 'Entyvio' or "'mln 02 monoclonal antibody'" or 'MLN0002' or 'MLN-0002' or 'MLN-02' or 'MLN02').ti,ab.	2965
5	('Humira' or 'Amjevita' or 'Cyltezo' or 'D2E7 Antibody' or 'Antibody, D2E7' or 'Adalimumab-atto' or 'Adalimumab-adbm' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-aaty' or 'yuflyma' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-atto' or 'amjevita' or 'adalimumab-bwwd' or 'hadlima' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-ryvk' or 'simlandi' or 'adalimumab-aaty' or 'adalimumab-afzb' or 'abrilada' or 'adalimumab-aqvh' or 'yusimry'').ti,ab.	878
6	('Monoclonal Antibody cA2' or 'Antibody cA2, Monoclonal' or 'cA2, Monoclonal Antibody' or 'MAb cA2' or 'Remicade' or 'Inflectra' or 'Renflexis' or 'Infliximab-dyyb' or 'Infliximab dyyb' or 'Infliximab-abda' or 'Infliximab abda' or 'infliximab' or 'inflectra' or 'infliximab-dyyb' or 'renflexis' or 'infliximab-abda' or 'avsola' or 'infliximab-axxq' or 'zymfentra' or 'infliximab-dyyb' or 'IXIFI' or 'infliximab-qbtx').ti,ab.	18573
7	('CNTO 1275' or 'CNTO-1275' or 'Stelara' or 'Ustekinumab-aauz' or 'Otulfi' or 'Ustekinumab-aekn' or 'Selarsdi' or 'Ustekinumab-auub' or 'Wezlana' or 'Ustekinumab-kfce' or 'Yesintek' or 'Ustekinumab-srlf' or 'Imuldosa' or 'Ustekinumab-stba' or 'Steqeyma' or 'Ustekinumab-ttwe' or 'Pyzchiva' or 'ustekinumab-hmny').ti,ab.	204
8	4 or 5 or 6 or 7	21672
9	3 and 8	6594
10	9 not (abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.	5151
11	10 not (animals not (humans and animals)).sh.	5135
12	remove duplicates from 11	4864
13	Limit 12 to English language	4661
14	exp cohort studies/ or comparative study.pt. or observational study.pt. or exp case-control studies/ or cohort.tw. or (observational adj2 stud*).tw. or prospective.tw. or retrospective.tw. or longitudinal.tw. or compa*.tw. or groups.tw. or case control.tw. or multivariate.tw.	13684486
15	13 and 14	3179
16	limit 15 to yr="2019 - 2025"	1457

Table D1.7. Search Strategy of EMBASE for Crohn's Disease (Observational Studies Only)

#	Search Term	Hits
1	'crohns disease'/exp	132576
2	'crohn* disease':ti,ab OR 'crohn* enteritis':ti,ab OR 'granulomatous colitis':ti,ab OR 'cleron disease':ti,ab OR 'inflammatory bowel disease 1':ti,ab OR 'regional ileiti*':ti,ab OR 'morbus crohn':ti,ab OR 'regional enter*':ti,ab OR 'granulomatous enteritis':ti,ab OR 'ileocolitis':ti,ab	11788
3	#1 OR #2	233730
4	'entyvio':ti,ab OR 'Entyvio':ti,ab OR 'mln 02 monoclonal antibody':ti,ab OR 'mln0002':ti,ab OR 'mln-0002':ti,ab OR 'mln-02':ti,ab OR 'mln02':ti,ab	6944
5	'Humira':ti,ab OR 'Amjevita':ti,ab OR 'Cyltezo':ti,ab OR 'D2E7 Antibody':ti,ab OR 'Antibody, D2E7':ti,ab OR 'Adalimumab-atto':ti,ab OR 'Adalimumab-adbm':ti,ab OR 'adalimumab-aacf':ti,ab OR 'idacio':ti,ab OR 'adalimumab-aaty':ti,ab OR 'adalimumab-adaz':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-fkjp':ti,ab OR 'hulio':ti,ab OR 'amjevita':ti,ab OR 'adalimumab-bwwd':ti,ab OR 'hadlima':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-ryvk':ti,ab OR 'simlandi':ti,ab OR 'yuflyma':ti,ab OR 'adalimumab-afzb':ti,ab OR 'abrilada':ti,ab OR 'adalimumab-aqvh':ti,ab OR 'yusimry':ti,ab	1196
6	'Monoclonal Antibody cA2':ti,ab OR 'Antibody cA2, Monoclonal':ti,ab OR 'cA2, Monoclonal Antibody':ti,ab OR 'MAb cA2':ti,ab OR 'Remicade':ti,ab OR 'Inflectra':ti,ab OR 'Renflexis':ti,ab OR 'Infliximab-dyyb':ti,ab OR 'Infliximab dyyb':ti,ab OR 'Infliximab-abda':ti,ab OR 'Infliximab abda':ti,ab OR 'infliximab':ti,ab OR 'inflectra':ti,ab OR 'renflexis':ti,ab OR 'avsola':ti,ab OR 'infliximab-axxq':ti,ab OR 'zymfentra':ti,ab OR 'IXIFI':ti,ab OR 'infliximab-qbtx':ti,ab	35907
7	'CNTO 1275':ti,ab OR 'CNTO-1275':ti,ab OR 'Stelara':ti,ab OR 'Ustekinumab-aauz':ti,ab OR 'Otulfi':ti,ab OR 'Ustekinumab-aekn':ti,ab OR 'Selarsdi':ti,ab OR 'Ustekinumab-auub':ti,ab OR 'Wezlana':ti,ab OR 'Ustekinumab-kfce':ti,ab OR 'Yesintek':ti,ab OR 'Ustekinumab-srlf':ti,ab OR 'Imuldosa':ti,ab OR 'Ustekinumab-stba':ti,ab OR 'Steqeyma':ti,ab OR 'Ustekinumab-ttwe':ti,ab OR 'Pyzchiva':ti,ab OR 'ustekinumab-hmny':ti,ab	192
8	#4 OR #5 OR #6 OR #7	41450
9	#3 AND #8	16709
10	#9 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	9905
11	#10 NOT [medline]/lim	7535
12	#11 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)	7523
13	#12 AND [english]/lim	7380
14	#13 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)	6088
15	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'observational study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compa*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR longitudinal:ti,ab OR ((observational NEAR/2 stud*):ti,ab)	23636759
16	#14 AND #15	2894
17	#17 AND [2019-2025]/py	2217

Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Entyvio and Listed Comparators



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[88,90] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: clinical response and remission. See Table D1.8 & 9 for UC and Table D1.10 and 11 for CD. We note that a number of trials were rated as having a high risk of bias, primarily due to missing data from a higher study discontinuation rate in the control group. This phenomenon is well-known in IBD trials,[39] so additional levels of caution should be applied when interpreting evidence on treatment effects.

Table D1.8. Risk of Bias Assessment (UC: Response and Remission, Induction Phase)

Studies*	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
ACT 1	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo
ACT 2	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo
GEMINI 1	Low	Low	Low	Low	Low	Low	-
Jiang et al. (2015)	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo
Kobayashi et al. (2015)	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo, due to worsening UC
Motoya et al. (2019)	Low	Low	Low	Low	Low	Low	-
Naganuma et al. (2025)	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
Suzuki et al. (2014)	Low	Low	Low	Low	Low	Low	-
ULTRA 1	Low	Low	Low	Low	Low	Low	-
ULTRA 2	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups. Imputation used but no data on missing data for induction
UNIFI	Low	Low	Low	Low	Low	Low	-
VARSITY	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups

*We did not conduct RoB assessment on EFFICACI study as we only had access to a conference abstract.

Table D1.9. Risk of Bias Assessment (UC: Response and Remission, Maintenance Phase)

Studies*	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
ACT 1	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo
ACT 2	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo
GEMINI 1	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo
Jiang et al. (2015)	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo
Kobayashi et al. (2015)	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo due to worsening UC
LIBERTY UC	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
Motoya et al. (2019)	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo due to lack of efficacy
Suzuki et al. (2014)	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
ULTRA 2	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups. Imputation used but no data on missing data for induction
UNIFI	Low	Low	Low	Low	Low	Low	-
VARSITY	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
VISIBLE	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups

*We did not conduct RoB assessment on EFFICACI study as we only had access to a conference abstract.

Table D1.10. Risk of Bias Assessment (CD: Response and Remission, Induction Phase)

Studies	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
CLASSIC 1	Low	Low	Low	Low	Low	Low	-
CHARM	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
GEMINI II	Low	Low	Low	Low	Low	Low	-
GEMINI III	Low	Low	Low	Low	Low	Low	-
UNITI 1	Low	Low	Low	Low	Low	Low	-
UNITI 2	Low	Low	Low	Low	Low	Low	-
Sandborn et al. (2007c)	Low	Low	Low	Low	Low	Low	-
SEAVUE	Low	Low	Low	Low	Low	Low	-
Watanabe et al. (2012)	Low	Low	Low	Low	Low	Low	-
Watanabe et al. (2020)	Low	Low	Low	Low	Low	Low	-

Table D1.11. Risk of Bias Assessment (CD: Response and Remission, Maintenance Phase)

Studies	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Risk of Bias	Comment
CERTIFI	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
CHARM	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
CLASSIC 2	Low	Low	High risk	Low	High	High risk	Drop-out was higher for placebo and described to be due to withdrawal of consent, and exploratory analyses
GEMINI II	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo due to lack of efficacy
IM UNITI	Low	Low	Low	Low	Low	Low	-
LIBERTY CD	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data due to progressive disease in active treatment arm
VISIBLE 2	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
Watanabe et al. (2012)	Low	Low	Some concerns	Low	Low	Some concerns	Substantial missing data but no clear differences between groups
Watanabe et al. (2020)	Low	Low	High risk	Low	Low	High risk	Greater proportion of missing outcome data in placebo due to lack of efficacy

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[58] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.12. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates,[8] using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between zero to three was assigned based on the PDRR estimate (See Table D1.13 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.14.

Table D1.12. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.13. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.14. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Ulcerative Colitis

Results

Table D1.15. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older adults)
GEMINI I	Fair	Fair	Poor
VISIBLE I	Fair	Fair	NR
Motoya et al. (2019)	NE	Fair	NR
VARSITY	Fair	Good	NR
EFFICACI	NE	Poor	NR
Naganuma et al. (2025)	NE	Fair	NR

NE: Not Estimated, NR: Not Reported.

Table D1.15. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for six trials.

Race and Ethnicity: All trials for which are rating could be assigned were rated as "fair" for racial and ethnic diversity, with Black/African American and Hispanic patients underrepresented. Three studies conducted outside of the US and thus we did not provide a rating for race and ethnicity for these studies. See Table D1.16.

Sex: Four out of the six trials were rated as "fair" reflecting an underrepresentation of females who comprise approximately 52% of UC population in the US.[8] One trial, VARSITY, was rated as "good" and another study, EFFICACI, did not provide any demographic information and thus was rated as "poor". See Table D1.17.

Age: Only one trial reported the proportion of participants aged 65 years or older and we rated this trial as "poor", reflecting an underrepresentation of older adults who comprise approximately 30% of the UC population in the US.[8] See Table D1.17.

Table D1.16. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Prevalence[8]	83%	9.5%	4%	13.8%	-	-	NR	NR
GEMINI I	80.7%	1.5%	16.8%	4.6%	-	-	NR	NR
PDRR	0.97	0.16	4.20	0.33	-	-	NR	NR
Score	3	1	3	1	8	Fair	NC	NC
VISIBLE I	83%	12%	15%	0.6%	-	-	0.6%	NR
PDRR	1.0	1.26	3.75	0.04	-	-	NC	NR
Score	3	3	3	1	10	Fair	NC	NC
Motoya et al. (2019)	NR	NR	NR	NR	-	-	NR	NR
PDRR	NR	NR	NR	NR	-	-	NR	NR
Score	NC	NC	NC	NC	NE	NE	NC	NC
VARSITY	89%	0.7%	8%	1.9%	-	-	1.9%	0.2%
PDRR	1.07	0.07	2.0	0.14	-	-	NC	NC
Score	3	1	3	1	8	Fair	NC	NC
EFFICACI	NR	NR	NR	NR	-	-	NR	NR
PDRR	NR	NR	NR	NR	-	-	NR	NR
Score	NC	NC	NC	NC	NE	NE	NC	NC
Naganuma et al. (2025)	NR	NR	NR	NR	-	-	NR	NR
PDRR	NR	NR	NR	NR	-	-	NR	NR
Score	NC	NC	NC	NC	NE	NE	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.17. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
Prevalence[8]	48.2%	51.8%	-	-	29.5%	-	-
GEMINI I	59.8%	40.2%	-	-	11%	-	-
PDRR	1.24	0.78	-	-	0.37	-	-
Score	3	2	5	Fair	1	1	Poor
VISIBLE I	65.8%	34.2%	-	-	NR	-	-
PDRR	1.37	0.66	-	-	NC	-	-
Score	3	2	5	Fair	NC	NC	NC
Motoya et al. (2019)	61.3%	38.7%	-	-	NR	-	-
PDRR	1.27	0.75	-	-	NC	-	-
Score	3	2	5	Fair	NC	NC	NC
VARSITY	58.4%	41.6%	-	-	NR	-	-
PDRR	1.21	0.80	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
EFFICACI	NR	NR	-	-	NR	-	-
PDRR	0	0	-	-	NC	-	-
Score	0	0	0	Poor	NC	NC	NC
Naganuma et al. (2025)	62.7%	37.3%	-	-	NR	-	-
PDRR	1.30	0.72	-	-	NC	-	-
Score	3	2	5	Fair	NC	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

Crohn's Disease

Results

Table D1.18. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
GEMINI III	Fair	Good	Poor
GEMINI II	Fair	Good	Fair
VISIBLE 2	Fair	Good	NR
Watanabe et al. (2020)	NE	Fair	NR

NE: Not Estimated, NR: Not Reported.

Table D1.18. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for four trials.

Race and Ethnicity: All trials for which are rating could be assigned were rated as "fair" for racial and ethnic diversity, with Black/African American and Hispanic patients underrepresented. The study published by Watanabe et al. was conducted outside of the US and thus we did not provide a rating for race and ethnicity. See Table D1.19.

Sex: Three out of the four trials were rated as "good". One trial, published by Watanabe et al., was rated as "fair" reflecting an underrepresentation of females who comprise approximately 55% of the Crohn's disease population in the US.[8] See Table D1.20.

Age: Half of the trials reported the proportion of participants aged 65 years or older. In one trial, GEMINI II, they were rated as "fair" and in another trial, GEMINI II, they were rated "poor" reflecting an underrepresentation of older adults who comprise approximately 22% of the Crohn's disease population in the US.[8] See Table D1.20.

Table D1.19. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Prevalence[8]	86%	9.5%	3%	10%	-	-	NR	NR
GEMINI III	90%	2%	4%	2%	-	-	NR	NR
PDRR	1.05	0.21	1.33	0.20	-	-	NR	NR
Score	3	1	3	1	8	Fair	NC	NC
GEMINI II	83.3%	2%	14.4%	2.2%	-	-	NR	NR
PDRR	0.97	0.21	4.8	0.22	-	-	NR	NR
Score	3	1	3	1	8	Fair	NC	NC
VISIBLE 2	54.7%	1%	14.3%	0.7%	-	-	0.7%	0.4%
PDRR	0.64	0.11	4.77	0.07	-	-	NE	NE
Score	2	1	3	1	7	Fair	NE	NE
Watanabe et al. (2020)	NR	NR	NR	NR	-	-	NR	NR
PDRR	NR	NR	NR	NR	-	-	NR	NR
Score	NC	NC	NC	NC	NE	NE	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.20. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 Years)	Score	Rating
Prevalence[8]	45.5%	54.5%	-	-	22%	-	-
GEMINI III	43%	57%	-	-	2%	-	-
PDRR	0.95	1.05	-	-	0.09	-	-
Score	3	3	6	Good	1	1	Poor
GEMINI II	47.1%	52.9%	-	-	12.4%	-	-
PDRR	1.04	0.97	-	-	0.56	-	-
Score	3	3	6	Good	2	2	Fair
VISIBLE 2	52.2%	46.8%	-	-	NR	-	-
PDRR	1.15	0.86	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC
Watanabe et al. (2020)	65.6%	34.4%	-	-	NR	-	-
PDRR	1.44	0.63	-	-	NC	-	-
Score	3	2	5	Fair	NC	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[91,92]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: “Ulcerative Colitis”, “Crohn’s Disease”, and “Vedolizumab”. We scanned the site to identify studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Section D3) and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcomes. All data analyses were validated by an independent member of the research team. The validator reviewed and confirmed the data analysis methods, data format, and analysis code. The validator re-ran the analysis, validated the results, and confirmed the appropriateness of reported data.

Feasibility of Conducting Network Meta-Analysis (NMA)

We examined the feasibility of conducting an NMA because direct evidence for the comparative efficacy of Entyvio and listed comparators were limited. We examined whether there were notable differences in study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality of these studies.

For UC, 15 trials were deemed sufficiently similar in terms of population, design, intervention type, outcome definitions or measurement, and analytic methods were included in the NMAs.[36-38,40-43,93-99] See Table D3.1 and D3.2.

For CD, 17 trials were deemed sufficiently similar in terms of population, design, intervention type, outcome definitions or measurement, and analytic methods were included in the NMAs.[38,65,66,100-111] See Table D3.20 and D3.21. Our NMA methods are described below.

NMA Methods

Our NMA methods largely followed the prior ICER report on UC.[30] Clinical response and remission were analyzed as mutually exclusive ordered categorical outcomes ("no response," "response without remission," and "remission") with a multinomial likelihood and a probit link. Endoscopic improvement and harm events (discontinuations due to AEs and serious infections) were analyzed as a dichotomous outcome with a binomial likelihood and log link. Outcomes were analyzed separately for the induction phase (six to 14 weeks) and maintenance phase (44-60 weeks). For induction phase, we included outcomes assessed between six to 14 weeks, as some biologics require more time to reach peak clinical efficacy.[112] For maintenance phase, our primary focus was assessing one-year outcomes (~52 weeks) and thus data from weeks 44 to 60 were included to allow flexibility around this timepoint. Endoscopic improvement was analyzed only for UC due to limited data availability. We were also unable to conduct the NMA of serious infections during the induction phase due to limited data availability.

The evidence base for the maintenance phase included a combination of "treat-through" designs, where patients were randomized only at baseline and followed through until the end of maintenance, and "re-randomized" designs, where responders to induction treatment were re-randomized in the maintenance phase. To analyze all trials in a single network, results from treat-through trials (ACT 1, ULTRA 2, VARSITY, and SEAVUE) were adjusted using the methods described in the prior ICER report to more closely resemble re-randomized trials.[30] In short, the denominator was defined as the number of responders at the end of the induction phase, and the numerators for clinical response and remission were the number of sustained responders and sustained remissions, respectively, at the end of maintenance phase.

Both random- and fixed-effects models were explored. In addition, we explored adjusting for baseline risk given the differences in placebo response rates across trials. We also attempted to adjust for differences in follow-up duration. Given the similarities in model fits, absence of statistical significance for the two adjustments, and broader heterogeneity, we used unadjusted random-effects models for induction and maintenance phases in the UC and CD populations.

For subgroup analyses (bio-naïve and bio-experienced groups), we used fixed-effects unadjusted models due to limited data availability for each network and greater similarity of the trials within the networks. We included both placebo and follow-up duration adjustments for bio-experienced subgroups during the maintenance phase.

All NMAs were conducted in a Bayesian framework in R (version R.5.2). NMAs on clinical response and remission were conducted with JAGS software via R using the R2jags package (version 0.8-9) and we followed codes from the previous ICER report.[30] NMAs on endoscopic improvement and harm events were conducted using the gemtc package (version 1.1.0).

Inputs for the NMAs of response and remission, endoscopic improvement, discontinuations due to AEs, and serious infections in the UC and CD populations are summarized in Tables D1.21-D1.29.

Table D1.21. Inputs Used in NMA of Response and Remission During Induction Phase in UC Population

Trials	Arms	Weeks	No Remission, n	Response without Remission, n	Remission, n	N
ACT 1	**IFX**	8	37	37	47	121
	PBO	8	76	27	18	121
ACT 2	**IFX**	8	43	37	41	121
	PBO	8	87	29	7	123
Jiang et al. (2015)	**IFX**	8	9	10	22	41
	PBO	8	26	6	9	41
Kobayashi et al. (2016)	**IFX**	8	47	36	21	104
	PBO	8	67	26	11	104
ULTRA 1	**ADA**	8	59	47	24	130
	PBO	8	72	46	12	130
ULTRA 2	**ADA**	8	123	84	41	248
	PBO	8	161	62	23	246
Suzuki et al. (2014)	**ADA**	8	45	36	9	90
	PBO	8	62	23	11	96
GEMINI 1	**VEDO**	6	119	68	38	225
	PBO	6	111	30	8	149
Motoya et al. (2019)	**VEDO**	10	99	35	30	164
	PBO	10	55	17	10	82
VARSITY	**VEDO**	14	126	155	102	383
	ADA	14	209	95	82	386
EFFICACI	**VEDO**	14	32	19	27	78
	IFX	14	37	22	14	73
UNIFI	**UST**	8	123	149	50	322
	PBO	8	219	83	17	319
Naganuma et al. (2025)	**VEDO**	12	14	9	11	34
	IFX	12	17	4	12	33
	UST	12	8	9	13	30

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.22. Inputs Used in NMA of Response and Remission During Maintenance Phase in UC Population

Trials	Arms	Weeks	No Remission, n	Response without Remission, n	Remission, n	N
ACT 1	**IFX**	54	37	23	24	84
	PBO	54	28	9	8	45
LIBERTY UC	**IFX**	54	136	31	127	294
	PBO	54	99	15	30	144
ULTRA 2	**ADA**	52	66	38	21	125
	PBO	52	55	20	10	85
GEMINI 1	**VEDO**	52	53	18	51	122

Trials	Arms	Weeks	No Remission, n	Response without Remission, n	Remission, n	N
	PBO	52	96	10	20	126
Motoya et al. (2019)	**VEDO**	60	14	4	23	41
	PBO	60	27	2	13	42
VISIBLE	**VEDO**	52	53	35	72	160
	PBO	52	40	8	8	56
VARSITY	**VEDO**	52	193	NA	70	263
	ADA	52	186	NA	46	232
UNIFI	**UST**	44	51	48	77	176
	PBO	44	97	36	42	175

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.23. Inputs Used in NMA of Endoscopic Improvement in UC Population

Trials	Arms	Induction Phase			Maintenance Phase		
		Weeks	n	N	Weeks	n	N
ACT 1	**IFX**	8	75	121	54	55	121
	PBO	8	41	121	54	22	121
ACT 2	**IFX**	8	73	121	30	56	121
	PBO	8	38	123	30	37	123
Jiang et al. (2015)	**IFX**	8	24	41	30	22	41
	PBO	8	10	41	30	9	41
Kobayashi et al. (2016)	**IFX**	8	48	104	30	43	104
	PBO	8	29	104	30	30	104
ULTRA 1	**ADA**	8	61	130	NR		
	PBO	8	54	130			
ULTRA 2	**ADA**	8	102	248	52	71	248
	PBO	8	78	246	52	38	246
Suzuki et al. (2014)	**ADA**	8	40	90	52	51	177
	PBO	8	29	96	52	15	96
VISIBLE 1	**VEDO**	NR			52	89	160
	PBO				52	12	56
GEMINI 1	**VEDO**	6	92	225	52	63	122
	PBO	6	37	149	52	25	126
Motoya et al. (2019)	**VEDO**	10	60	164	60	26	41
	PBO	10	25	82	60	14	42
VARSITY	**VEDO**	NR			52	152	383
	ADA				52	107	386
UNIFI	**UST**	8	87	322	52	79	176
	PBO	8	44	319	52	41	170
Naganuma et al. (2025)	**VEDO**	12	13	34	NR		
	IFX	12	13	33			
	UST	12	19	30			

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, NR: not reported, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.24. Inputs Used in NMA of Discontinuations due to AEs in UC Population

Trials	Arms	Induction Phase			Maintenance Phase		
		Weeks	n	N	Weeks	n	N
ACT 1	**IFX**	NR			54	10	121
	PBO				54	11	121
Kobayashi et al. (2016)	**IFX**	14	5	104	NR		
	PBO	14	8	104			
LIBERTY UC	**IFX**	NR			54	11	294
	PBO				54	8	144
ULTRA 1	**ADA**	8	4	130	52	12	223
	PBO	8	5	130	52	12	222
ULTRA 2	**ADA**	NR			52	12	248
	PBO				52	25	246
Suzuki et al. (2014)	**ADA**	8	3	90	52	13	177
	PBO	8	2	96	52	7	96
VISIBLE 1	**VEDO**	NR			52	7	160
	PBO				52	5	56
GEMINI 1	**VEDO**	6	0	225	52	7	122
	PBO	6	4	149	52	15	126
Motoya et al. (2019)	**VEDO**	10	8	164	60	1	41
	PBO	10	2	82	60	6	42
VARSITY	**VEDO**	NR			52	17	383
	ADA				52	25	386
UNIFI	**UST**	8	1	322	44	5	176
	PBO	8	3	319	44	20	170

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, NR: not reported, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.25. Inputs Used in NMA of Serious Infections in UC Population

Trials	Arms	Maintenance Phase		
		Weeks	n	N
ACT 1	**IFX**	54	3	121
	PBO	54	5	121
ULTRA 1	**ADA**	52	0	223
	PBO	52	3	223
ULTRA 2	**ADA**	52	4	258
	PBO	52	5	260
Suzuki et al. (2014)	**ADA**	52	8	177
	PBO	52	2	96
VISIBLE 1	**VEDO**	52	2	160
	PBO	52	0	56
GEMINI 1	**VEDO**	52	3	122
	PBO	52	4	126
Motoya et al. (2019)	**VEDO**	60	1	41
	PBO	60	1	42
VARSITY	**VEDO**	52	7	383
	ADA	52	8	386
UNIFI	**UST**	44	3	176

Trials	Arms	Maintenance Phase		
		Weeks	n	N
	PBO	44	4	170

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.26. Inputs Used in NMA of Response and Remission During Induction Phase in CD Population

Trials	Arms	Weeks	No Remission, n	Response without Remission, n	Remission, n	N
CLASSIC 1	ADA	4	38	11	27	76
	PBO	4	55	10	9	74
Watanabe et al. (2012)	ADA	4	18	4	11	33
	PBO	4	19	1	3	23
Sandborn et al. (2007)	ADA	4	98	27	34	159
	PBO	4	125	29	12	166
GEMINI 2	VEDO	6	151	37	32	220
	PBO	6	110	28	10	148
GEMINI 3	VEDO	6	127	42	40	209
	PBO	6	160	22	25	207
Watanabe et al. (2020)	VEDO	6	60	8	11	79
	PBO	6	68	0	10	78
CERTIFI	UST	6	79	36	16	131
	PBO	6	101	17	14	132
UNITI 1	UST	6	165	38	46	249
	PBO	6	194	31	22	247
UNITI 2	UST	6	93	43	73	209
	PBO	6	149	23	37	209
SEAVUE	UST	8	61	34	96	191
	ADA	8	66	35	94	195

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.27. Inputs Used in NMA of Response and Remission During Maintenance Phase in CD Population

Trials	Arms	Weeks	No Remission, n	Response without Remission, n	Remission, n	N
LIBERTY CD	IFX	54	79	8	144	231
	PBO	54	69	7	36	112
CLASSIC 2	ADA	56	4	0	15	19
	PBO	56	8	2	8	18
Watanabe et al. (2012)	ADA	52	15	0	10	25
	PBO	52	22	0	3	25
CHARM	ADA	56	101	9	62	172
	PBO	56	142	8	20	170
GEMINI 2	VEDO	52	87	7	60	154

Trials	Arms	Weeks	No Remission, n	Response without Remission, n	Remission, n	N
	PBO	52	107	13	33	153
VISIBLE 2	VEDO	52	132	11	132	275
	PBO	52	74	14	46	134
Watanabe et al. (2020)	VEDO	60	5	2	5	12
	PBO	60	10	0	2	12
IM UNITI	UST	44	52	8	68	128
	PBO	44	73	11	47	131
SEAVUE	UST	52	6	27	97	130
	ADA	52	10	18	101	129

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.28. Inputs Used in NMA of Discontinuations due to AEs in CD Population

Trials	Arms	Induction Phase			Maintenance Phase		
		Weeks	n	N	Weeks	n	N
ACCENT 1	IFX	NR			54	29	193
	PBO				54	5	188
LIBERTY CD	IFX				54	8	231
	PBO				54	6	112
CLASSIC 1	ADA	4	0	76	NR		
	PBO	4	2	74			
CLASSIC 2	ADA	NR			56	1	19
	PBO				56	1	18
Chen et al. (2020)	ADA	4	2	102	NR		
	PBO	4	4	103			
Watanabe et al. (2012)	ADA	4	1	33	52	1	25
	PBO	4	1	23	52	6	25
Sandborn et al. (2007)	ADA	4	2	159	NR		
	PBO	4	4	166			
CHARM	ADA	NR			56	18	260
	PBO				56	35	261
CERTIFI	UST	8	1	131	NR		
	PBO	8	5	132			
GEMINI 2	VEDO	6	9	220	52	12	154
	PBO	6	7	148	52	15	153
GEMINI 3	VEDO	10	4	209	NR		
	PBO	10	8	207			
VISIBLE 2	VEDO	NR			52	11	275
	PBO				52	12	135
Watanabe et al. (2020)	VEDO	10	3	79	60	2	12
	PBO	10	12	78	60	4	12
SEAVUE	UST	NR			52	11	191
	ADA				52	21	195

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table D1.29. Inputs Used in NMA of Serious Infections in CD Population

Trials	Arms	Induction Phase			Maintenance Phase		
		Weeks	n	N	Weeks	n	N
ACCENT 1	**IFX**	NR			54	8	193
	PBO				54	8	188
CLASSIC 1	**ADA**	4	2	76	NR		
	PBO	4	0	74			
CLASSIC 2	**ADA**	NR			56	0	19
	PBO				56	0	18
Chen 2020	**ADA**	4	0	102	NR		
	PBO	4	0	103			
Watanabe et al. (2012)	**ADA**	4	0	33	52	1	25
	PBO	4	0	23	52	2	25
Sandborn et al. (2007)	**ADA**	4	0	159	NR		
	PBO	4	4	166			
CHARM	**ADA**	NR			56	7	260
	PBO				56	9	261
CERTIFI	**UST**	8	5	131	NR		
	PBO	8	1	132			
IM UNITI	**UST**	NR			44	3	131
	PBO				44	3	133
GEMINI 2	**VEDO**	6	1	220	52	6	154
	PBO	6	2	148	52	5	153
GEMINI 3	**VEDO**	10	2	209	NR		
	PBO	10	0	207			
VISIBLE 2	**VEDO**	NR			52	4	275
	PBO				52	6	135
SEAVUE	**UST**	NR			52	4	191
	ADA				52	5	195

ADA: adalimumab, IFX: infliximab, n: number, N: sample size, NR: not reported, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

NMA Limitations

There were limitations to our NMAs. While we used random-effects models to account for some of the heterogeneity, there were differences in trial populations in terms of prior conventional therapies used, demographic or clinical risk factors, and timing of trial assessments that should be acknowledged.

Both UC and CD NMAs included studies rated as having "high" risk of bias. The majority of included trials, particularly during the maintenance phase, were rated as having "high" risk of bias or "some concerns", due to the differential attrition in the missing outcome domain. This pattern is common in trials of chronic inflammatory diseases as patients may be more likely to discontinue placebo and remain in the intervention arm when the intervention is effective.[39]

For CD NMA, one major limitation was the absence of infliximab trials from the NMA of response and remission during the induction phase. After review of identified clinical trials, we excluded some trials for study design or data issues. For example, Targan et al. (1997) was excluded due to data inconsistency. Placebo response and remission rates from this trial were considerably lower (17% and 4%) than those identified in a previous systematic review (28% and 18%).[113] Additionally, we excluded ACCENT 1 trial comparing infliximab versus placebo due to a study design issue.[111] A total of 92 (49%) patients crossed over to episodic retreatment in this trial and received two or more infliximab infusions. Although FDA label allows an increase from 5 mg/kg to 10 mg/kg if response is lost, almost half of the patients moving to placebo group suggest that placebo group does not accurately represent no treatment. However, we did include ACCENT 1 in the NMAs of harms data as the impact of placebo crossovers is expected to be greater for response and remission than for long-term harms.

D2. Additional Comparative Clinical Evidence

Additional Evidence Base

Ulcerative Colitis

Clinical Trial Evidence

In addition to the six trials evaluating Entyvio mentioned in the main section of the report, we included another placebo-controlled trial to support the clinical evidence section. EARNEST was a treat-through, Phase IV trial comparing Entyvio with placebo during both induction and maintenance period. Participants enrolled in this trial had undergone proctocolectomy with ileal-pouch anal anastomosis at least a year before screening and had active chronic pouchitis. Because this trial included a specific subset of the UC population assessed in this report, we presented results from this trial separately here.[114] Baseline characteristics are available in Supplement Tables D2.1 and D3.2.

Table D2.1. Overview of Key Entyvio Trials in UC Population

Trial (RR or TT)	Randomized Treatment Arms		IND/ MAINT Timepoints	Prior Anti-TNF	Mean Age	Female, %	Disease Duration, Years	Mayo Score
	Induction	Maintenance						
Placebo-Controlled Trials								
GEMINI 1 (RR)[41]	1) VEDO 300 mg (n=225) 2) Placebo (n=149)	1) VEDO 300 mg q8w (n=122) 2) VEDO 300 mg q4w (n=125) 3) Placebo (n=126)	6 weeks/ 52 weeks	Naïve (52%) Exp (48%)	41	40%	6.5	8.6
NCT02039505 (RR)[42]	1) VEDO 300 mg (n=164) 2) Placebo (n=82)	1) VEDO 300 mg q8w (n=41) 2) Placebo (n=42)	6 weeks/ 52 weeks	Naïve (49%) Exp (51%)	43	37%	7.7	8.2
VISIBLE 1 (RR)[43]	1) VEDO 300 mg (n=160) 2) Placebo (n=56)	1) VEDO 300 mg q8w (n=54) 2) Placebo (n=56)	6 weeks/ 52 weeks	Naïve (61%) Exp (39%)	39	40%	7.9	9.0*
EARNEST (TT)[114]	1) VEDO 300 mg IV (n=51) 2) Placebo (n=51)	1) VEDO 300 mg IV (n=51) 2) Placebo (n=51)	14 weeks/ 34 weeks	Naïve (73%) Exp (27%)	44	31%	NR	NR
Head-to-Head Trials								
VARSITY (TT)[40]	1) VEDO 300 mg (n=383) 2) ADA 160/80 mg (n=386)	1) VEDO 300 mg (n=383) 2) ADA 40 mg (n=386)	6 weeks/ 52 weeks	Naïve (79%) Exp (21%)	41	42%	6.8	8.7
EFFICACI[36]	1) VEDO 300 mg (n=78) 2) IFX 5 mg/kg (n=73)	NA	Up to 14 weeks	Exp (100%)	NR	NR	NR	NR
Naganuma et al. (2025)[37]	1) VEDO 300 mg (n=34) 2) IFX 5 mg/kg (n=33) 3) UST (n=30)	NA	Up to 12 weeks	Naive (100%)	44	37%	NR	9

ADA: adalimumab, EXP: experienced, IFX: infliximab, IND: induction, MAINT: maintenance, n: number, N: sample size, NA: not available, NR: not reported, PBO: placebo, RR: re-randomization, TT: trial-through, UST: ustekinumab, VEDO: vedolizumab
*Median across all study arms.

Observational Study Evidence

Dubinsky et al. (2018) was a retrospective cohort study using data collected over a period of more than four years from Truven Health MarketScan Commercial and Medicare Supplemental databases. A total of 544 and 8,574 participants were included in the Entyvio and anti-TNF cohorts, respectively, to compare the real-world incidence of extraintestinal manifestations. The mean age of UC cohort was 43 years and 48% of them were female. Around three-quarters of the UC cohort were using corticosteroids (73%) and more than a third were using immunomodulators (35%).[46]

Bressler et al. (2021) was another retrospective cohort study that compared real-world clinical effectiveness and safety of Entyvio (N=380) and anti-TNF (N=224) using data from three different countries including US. Adult participants were eligible if they had a diagnosis of UC or CD, were biologic-naïve, and initiated either Entyvio or an anti-TNF. Participants treated with Entyvio were slightly older, had longer disease duration, but less severe than those treated with anti-TNFs. The most common non-biologic therapies were mesalamine (82%) and prednisone (61%).[47]

Lukin et al. (2022) used a North American-based consortium registry to compare the risk of developing serious infections and serious adverse events between Entyvio (N=454) and anti-TNFs (N=268). The median follow-up period was almost a year. Half of the participants were female and around 58% had prior experience with anti-TNFs. The commonly used concomitant medications were corticosteroids (54%), mesalamine (51%), and immunosuppressants (36%).[50]

Singh et al. (2022) used OptumLabs Data Warehouse and included 2,356 individuals treated with either Entyvio (N=443) or anti-TNFs (N=1913) for the management of UC. The study endpoint was risk of malignancy based on claims data collected over five years. Baseline characteristics were only available for the overall IBD population evaluated in the study.[49]

Singh et al. (2022) also used OptumLabs Data Warehouse and included 2,584 individuals treated with either Entyvio (N=671) or anti-TNFs (N=1952) for the management of UC. The study endpoint was risk of serious infections based on similar claims data collected over five years. The mean age of the UC cohort was 43, with 45% of them being female and 72% were Whites. More than 8% of them used oral corticosteroids in the last 12 months.[48]

Kirchgesner et al. (2022) was the largest observational study focusing on US and French claims databases to assess the risk of serious infections among UC population treated with Entyvio (N=2,624) and anti-TNF (N=5,243). Around 54% of the UC cohort had experience with anti-TNFs.

Other baseline characteristics were only available for the overall IBD population evaluated in the study. [52]

Karlqvist et al. (2024) was a propensity score matched Swedish cohort study. A total of 1,294 patients with UC were included 1:1 to assess the comparative risk of serious infections between Entyvio and anti-TNF therapies. Overall, the baseline characteristics were similar across both arms. Around 76% patients had prior experience with anti-TNFs. The most common concomitant medications were corticosteroids (65%) and immunosuppressants (33%).[53]

Long et al. (2019) used IBM MarketScan Research Database to identify UC patients initiating Entyvio (N=103), infliximab (N=810), and adalimumab (N=1,291). The mean age of all three cohorts was 45 years and almost half of them were female. The study also included patients initiating golimumab and immunosuppressants.[45]

Dalal et al. (2023) published two studies using data from two large academic medical centers affiliated with several hospitals in the US. A total of 195 patients initiated Entyvio and 610 patients initiated anti-TNFs. Patients in the Entyvio group differed from those in the anti-TNFs group in several aspects: they were older (48 years vs. 35 years), had longer disease duration (seven years vs. three years), less commonly used concomitant corticosteroids (43% vs. 71%), and were more likely to have a history of malignancy (31% vs. 10%).[55]

Kochhar et al. (2023) was a retrospective cohort study that included 1,132 patients diagnosed with UC after 1:1 propensity score matching from TriNetX multi-institutional database to assess Entyvio and ustekinumab as second line therapy. The majority of the participants were Whites (80%) and female (56%), with a mean age of 40 years.[51]

Farkas et al. (2025) compared persistence and colectomy-free survival rates between Entyvio (N=492) and ustekinumab (N=94) using data from multiple countries. The mean age at diagnosis was 31 years old and the mean disease duration was around seven years. All cohort patients had experience with prior anti-TNFs and a quarter of them were using concomitant immunosuppressants.[54]

Koliani-Pace et al. (2019) used two data sets, VICTORY consortium and Truven MarketScan, to compare treatment patterns and outcomes of Entyvio in two different time frames. A total of 1,566 patients diagnosed with UC were included in this study, with majority coming from the Truven MarketScan database (72%). More than half of them were female (51%) and almost two-thirds of them (65%) had experience with prior anti-TNFs.[57]

Cohen et al. (2020) evaluated the safety profile of Entyvio using four years of post-marketing data from Vedolizumab Global Safety Database. The study had a total of 14,042 patients diagnosed with UC. Half of them were female and the majority of them (82%) were below 70 years old. Around 48% of them had experience with anti-TNFs and 42% of the total UC patients were using concomitant corticosteroids.[56]

Table D2.2. Summary of Included UC Observational Studies

Author, Year	Comparators (Sample Size, N)	Database & Country	Outcomes Assessed & Follow-up	Baseline Characteristics
Dubinsky et al. (2018)[46]	Entyvio (N=544) Anti-TNF (N=8,574)	Truven Health MarketScan Commercial and Medicare Supplemental Databases from US	Extraintestinal Manifestations	Age: 43 Female: 48% White: NR Prior Anti-TNF: NR
Bressler et al. (2021)[47]	Entyvio (N=380) Anti-TNF (N=224)	Chart Review from US, Canada, and Greece	Efficacy and Safety Outcomes	Age: 43 Female: 45% White: NR Prior Anti-TNF: 0%
Lukin et al. (2022)[50]	Entyvio (N=454) Anti-TNF (N=103) IFX (N=165)	VICTORY Consortium Registry Dataset from US	Efficacy and Safety Outcomes	Age: 41 Female: 50% White: NR Prior Anti-TNF: 58%
Singh et al. (2022)[49]	Entyvio (N=443) Anti-TNF (N=1,913)	OptumLabs (commercially insured and Medicare Advantage) from US	Malignancy Rates	Age: NR Female: NR White: NR Prior Anti-TNF: NR
Singh et al. (2022)[48]	Entyvio (N=671) Anti-TNF (N=1,950)	OptumLabs from US	Serious Infections	Age: 43 Female: 45% White: 72% Prior Anti-TNF: 34%*
Kirchgesner et al. (2022)[52]	Entyvio (N=4,042) Anti-TNF (N=10,612)	IBM MarketScan and Optum Clinformatics from US, Database from France	Serious Infections	Age:NR Female: NR White: NR Prior Anti-TNF: 53%
Karlqvist et al. (2024)[53]	Entyvio (N=647) Anti-TNF (N=647)	Healthcare Registry from Sweden	Serious Infections	Age: NR Female: 45% White: NR Prior Anti-TNF: 76%
Long et al. (2019)[45]	Entyvio (N=103) IFX (N=810) ADA (N=1,291)	IBM MarketScan from US	Hospitalizations	Age: 45 Female: 49% White: NR Prior Anti-TNF: NR
Dalal et al. (2023)[55]	Entyvio (N=195) IFX (N=332) ADA (N=278)	Data from large academic medical center in US	Remission and Discontinuations	Age: 38* Female: 55% White: 88% Prior Anti-TNF: 0%

Author, Year	Comparators (Sample Size, N)	Database & Country	Outcomes Assessed & Follow-up	Baseline Characteristics
Kochhar et al. (2023)[51]	Entyvio (N=566) UST (N=566)	TriNetX from US	Safety Outcomes (Malignancy and Colectomy)	Age: 40 Female: 56% White: 80% Prior Anti-TNF: 100%
Farkas et al. (2025)[54]	Entyvio (N=492) UST (N=94)	Medical records from outside of US	Colectomy free survival	Age: NR Female: 47% White: NR Prior Anti-TNF: 100%
Koliani-Pace et al. (2019)[57]	Entyvio (N=1,566)	VICTORY Consortium Registry and Truven Health Analytics MarketScan Data from US	Remission, Mucosal healing, Hospitalizations, Surgery	Age: NR Female: 51% White: NR Prior Anti-TNF: 65%
Cohen et al. (2020)[56]	Entyvio (N=14,042)	Vedolizumab Global Safety Database by Takeda	Safety Outcomes	Age: NR Female: 50% White: NR Prior Anti-TNF: 48%

ADA: adalimumab, EXP: experienced, IFX: infliximab, n: number, N: sample size, NR: not reported, US: United States, UST: ustekinumab

*Reported in the Entyvio arm.

†Reported median age.

Crohn's Disease

NMA Evidence

LIBERTY CD was the only new Phase III study included in our updated NMA. This trial incorporated an open-label induction phase with all patients receiving infliximab IV and those who responded at week 10 were then randomized to infliximab SC (N=231) and placebo (N=112).[38] Baseline characteristics are available in Supplement Table D3.21. Additional details regarding NMA inclusion and exclusion criteria and methods can be found in the Supplement Section D1 above.

Clinical Trial Evidence

In addition to the four trials evaluating Entyvio mentioned in the main section of the report, we included another single-arm, Phase III trial to support the clinical evidence section.[73] NCT02425111 was a treat-through trial in which 101 patients received Entyvio IV 300 mg during the 26-week primary study and 56 patients were included in the 52-week substudy after protocol amendment. Participants enrolled in this trial had moderate to severe active CD during the last three months. Active CD was defined as a CDAI score of 220-450 and SES-CD score ≥7 with evidence of any ulcer. Data on endoscopic improvement outcome for CD population was only available from this trial and GEMINI LTS. Baseline characteristics are available in Supplement Table D2.3 and D3.21.

Table D2.3. Overview of Key Entyvio Trials in CD Population

Trial (RR or TT)	Randomized Treatment Arms		IND/ MAINT Timepoints	Prior Anti-TNF and Surgery	Age, Years	Female, %	Disease Duration, Years	Ileum (%) Colon (%) Both (%)
	Induction	Maintenance						
Placebo-Controlled Trials								
GEMINI 2 (RR)[106]	1) VEDO 300 mg (n=220) 2) Placebo (n=148)	1) VEDO 300 mg q8w (n=154) 2) VEDO 300 mg q4w (n=154) 3) Placebo (n=153)	6 weeks/ 52 weeks	Naïve (48%) Exp (62%) Surgery (42%)	37	53%	9	16%, 28%, 56%
GEMINI 3 (RR)[107]	1) VEDO 300 mg (n=209) 2) Placebo (n=207)	NR	10 weeks/ NR	Naïve (24%) Exp (76%) Surgery (44%)	NR	57%	8	15%, 24%, 61%
VISIBLE 2 (RR)[65]	1) VEDO 300 mg IV (N=644)	1) VEDO 108 mg SC (n=275) 2) Placebo (n=134)	6 weeks/ 52 weeks	Naïve (43%) Exp (57%) Surgery (27%)	38	45%	9	21%, 20%, 48%
Watanabe et al. (2020) (TT)[66]	1) VEDO 300 mg IV (n=79) 2) Placebo (n=78)	1) VEDO 300 mg IV (n=12) 2) Placebo (n=12)	14 weeks/ 54 weeks	Naïve (22%) Exp (78%) Surgery (34%)	33	34%	9	14%, 19%, 67%
Single-Arm Trial								
NCT02425111 (2019) (TT)[73]	NA	1) 26-week Primary Study (n=101) 2) 52-week Substudy (n=56)	26 weeks/ 52 weeks	Naïve (45%) Exp (55%)	38	49%	12	62%, NR, NR

EXP: experienced, IND: induction, MAINT: maintenance, n: number, N: sample size, NR: not reported, PBO: placebo, RR: re-randomization, TT: trial-through, VEDO: vedolizumab

Observational Study Evidence

Dubinsky et al. (2018) was a retrospective cohort study using data collected over a period of more than four years from Truven Health MarketScan Commercial and Medicare Supplemental databases. A total of 756 and 19,584 CD participants were included in the Entyvio and anti-TNF cohorts, respectively, to compare the real-world incidence of extraintestinal manifestations. The mean age of CD cohort was 41 years and 54% of them were female. Around 57% of the CD cohort were using corticosteroids and less than a third were using immunomodulators (32%).[46]

Bohm et al. (2020) was another retrospective cohort study that compared real-world clinical outcomes of Entyvio (N=659), infliximab (N=305), and subcutaneous anti-TNF (N=302) using data from US VICTORY Consortium. The mean age at diagnosis ranges from 36-40 years old across three CD cohorts. Participants treated with Entyvio had longer disease duration (12 years) compared to infliximab (three years) and subcutaneous anti-TNFs (6 years). More people in the Entyvio group (46%) were using concomitant corticosteroids than in the infliximab (27%) and subcutaneous anti-TNF (27%) groups. The majority of patients treated with Entyvio (91%) had experience with prior anti-TNFs compared to only 47% of patients treated with infliximab and 57% of patients treated with subcutaneous anti-TNFs.[68]

Macaluso et al. (2021) used the Sicilian Network for Inflammatory Bowel Disease from Italy to compare the effectiveness of Entyvio (N=277) and anti-TNFs (N=308). The mean age of the cohort was 46 years. Around 42% of the participants were female and around 57% were biologic-naive. The concomitant medications were corticosteroids (41%) and immunosuppressants (10%).[69]

Singh et al. (2022) used OptumLabs Data Warehouse and included 3,215 individuals treated with either Entyvio (N=316) or anti-TNFs (N=2,899) for the management of CD. The study endpoint was risk of malignancy based on claims data collected over five years. Baseline characteristics were only available for the overall IBD population evaluated in the study.[49]

Singh et al. (2022) also used OptumLabs Data Warehouse and included 3,366 individuals treated with either Entyvio (N=435) or anti-TNFs (N=2,931) for the management of CD. The study endpoint was risk of serious infections based on similar claims data collected over five years. The mean age of the CD cohort was 41, with 55% of them being female and 73% were Whites. More than two-thirds of them used oral corticosteroids in the last 12 months.[48]

Kirchgesner et al. (2022) was the largest observational study focusing on US and French claims databases to assess the risk of serious infections among CD population treated with Entyvio (N=3210) and anti-TNF (N=10157). Around 66% of the CD cohort had experience with anti-TNFs. Other baseline characteristics were only available for the overall IBD population evaluated in the study.[52]

Singh et al. (2023) primarily compared risk of serious infections between Entyvio (N=221) and ustekinumab (N=221) after 1:1 propensity score matching using data from five health systems in California, US. The mean age at diagnosis was 41 years old and 54% of them were female. The majority of the cohort were Whites (84%). Around 39% had experience with prior anti-TNFs while 44% and 27% were using concomitant corticosteroids and immunosuppressants at the cohort entry.[70]

Karlqvist et al. (2024) was a propensity score matched Swedish cohort study. A total of 1,376 patients with CD were included 1:1 to assess the comparative risk of serious infections between Entyvio and anti-TNF therapies. Overall, the baseline characteristics were similar across both arms. Around 84% patients had prior experience with anti-TNFs. The most common concomitant medications were corticosteroids (56%) and immunosuppressants (28%).[53]

Supovec et al. (2025) used data from a medical center in Slovenia to identify CD patients initiating Entyvio (N=59), ustekinumab (N=55), and anti-TNFs (N=473). Overall, around 45% of them were female. Those treated with Entyvio and those with ustekinumab were older (56 years) compared to those in the anti-TNF group (38 years). The median disease durations were also longer with Entyvio (12 years) and ustekinumab (10 years) than with anti-TNFs (seven years).[71]

Vu et al. (2023) compared surgery rates between Entyvio (N=578) and ustekinumab (N=544) among biologic-naïve CD patients using data from Optum Research. The mean age of CD patients included in this study was 48 years. Around 55% of them were female and the majority of them (79%) were Whites.[72]

Garcia et al. (2024) used the ENEIDA registry from Spain to compare the real-world outcomes between Entyvio (N=207) and ustekinumab (N=628) after anti-TNF failure. Overall, the baseline characteristics were similar across both groups, with a mean age at diagnosis of 33 years and half of them were female. The disease duration was around 12 years for both groups. The most common concomitant medications were corticosteroids (26%) and immunosuppressants (33%).[67]

Koliani-Pace et al. (2019) used two data sets, VICTORY consortium and Truven MarketScan, to compare treatment patterns and outcomes of Entyvio in two different time frames. A total of 2,095 patients diagnosed with CD were included in this study, with majority coming from the Truven MarketScan database (69%). Around 58% of them were female and 78% of them had experience with prior anti-TNFs.[57]

Cohen et al. (2020) evaluated the safety profile of Entyvio using four years of post-marketing data from Vedolizumab Global Safety Database. The study had a total of 14,191 patients diagnosed with CD. Around 60% of them were female and the majority of them (80%) were below 70 years old. Around 51% of them had experience with anti-TNFs and 28% of the total CD patients were using concomitant corticosteroids.[56]

Table D2.4. Summary of Included CD Observational Studies

Author, Year	Comparators (Sample Size, N)	Database & Country	Outcomes Assessed & Follow-up	Baseline Characteristics
Dubinsky et al. (2018)[46]	Entyvio (N=756) Anti-TNF (N=19,584)	Truven Health MarketScan Commercial and Medicare Supplemental Databases	Extraintestinal Manifestations	Age: 41 Female: 54% White: NR Prior Anti-TNF: NR
Bohm et al. (2020)[68]	Entyvio (N=659) IFX (N=305) ADA (N=302)	VICTORY Consortium Registry Dataset from US	Efficacy and Safety Outcomes	Age: NR Female: 54% White: NR Prior Anti-TNF: 72%
Macaluso et al. (2021)[69]	Entyvio (N=277) ADA (N=308)	Sicilian Network Data from Italy	Efficacy and Safety Outcomes	Age: 46 Female: 42% White: NR Prior Biologics: 43%
Singh et al. (2022)[49]	Entyvio (N=316) Anti-TNF (N=2,899)	OptumLabs (commercially insured and Medicare Advantage) from US	Malignancy Rates	Age: NR Female: NR White: NR Prior Anti-TNF: NR
Singh et al. (2022)[48]	Entyvio (N=435) Anti-TNF (N=2,931)	OptumLabs	Serious Infections	Age: 41 Female: 45% White: 73% Prior Anti-TNF: NR
Kirchgesner et al. (2022)[52]	Entyvio (N=3,210) Anti-TNF (N=10,157)	IBM MarketScan and Optum Clinformatics from US, Database from France	Serious Infections	Age: NR Female: NR White: NR Prior Anti-TNF: 66%
Singh et al. (2023)[70]	Entyvio (N=221) UST (N=221) ADA (N=442)	EHR data from 5 health systems in California, US	Efficacy and Safety Outcomes	Age: 41 Female: 54% White: 84% Prior Biologics: 39%
Karlqvist et al. (2024)[53]	Entyvio (N=688) Anti-TNF (N=688)	Healthcare Registry from Sweden	Serious Infections	Age: NR Female: 53% White: NR Prior Anti-TNF: 84%
Supovec et al. (2025)[71]	Entyvio (N=55) UST (N=59) Anti-TNF (N=473)	Data from academic medical center from Slovenia	Survival and Efficacy Outcomes	Age: 41* Female: 45 White: NR Prior Anti-TNF: NR
Vu et al. (2023)[72]	Entyvio (N=578) UST (N=544)	Optum Research Database from US	Surgery Rates	Age: 48 Female: 55% White: 79% Prior Anti-TNF: 0%
Garcia et al. (2024)[67]	Entyvio (N=207) UST (N=628)	ENEIDA registry from Spain	Efficacy and Safety Outcomes	Age: 33 Female: 50%

Author, Year	Comparators (Sample Size, N)	Database & Country	Outcomes Assessed & Follow-up	Baseline Characteristics
				White: NR Prior Anti-TNF: 100%
Koliani-Pace et al. (2019)[57]	Entyvio (N=2,095)	VICTORY Consortium Registry and Truven Health Analytics MarketScan Data from US	Remission, Mucosal healing, Hospitalizations, Surgery	Age: NR Female: 58% White: NR Prior Anti-TNF: 78%
Cohen et al. (2020)[56]	Entyvio (N=14,191)	Vedolizumab Global Safety Database by Takeda	Safety Outcomes	Age: NR Female: 60% White: NR Prior Anti-TNF: 51%

ADA: adalimumab, EXP: experienced, IFX: infliximab, n: number, N: sample size, NR: not reported, US: United States, UST: ustekinumab.

*reported median age

Additional Clinical Benefits

Ulcerative Colitis

Direct Evidence of Health-Related Quality of Life (HRQoL)

In another single-arm trial, Entyvio showed clinically meaningful improvements in IBDQ total score (+43 points from baseline) and EQ-5D VAS score (+19 points from baseline) at week 52.[73] The EARNEST trial only reported data related to IBDQ score and showed no statistical differences between Entyvio and placebo in IBDQ score, IBDQ-defined response, and IBDQ-defined remission at weeks 14 and 34.[114]

Additional Outcomes

Entyvio demonstrated superiority over placebo on additional secondary endpoints including partial Mayo scores and change in CRP concentrations during both induction and maintenance phases.[40,41,43] Although a greater proportion of UC patients treated with Entyvio achieved corticosteroid-free remission during the maintenance period, none of the trials reporting this outcome showed statistical significance.[37,40-43] See Supplement Tables D3.9-D3.10.

Crohn's Disease

Additional Outcomes

In a post-hoc analysis of GEMINI 2 and GEMINI 3 trials, a greater percentage of participants treated with Entyvio achieved the average daily composite score of abdominal pain score (APS) of at least one and loose stool frequency subscore (LSFS) of at least three compared to those treated with placebo; however, the difference reached the statistical significance at week four (15% vs. 9%) only but not at week six (18% vs. 14%).[115] No Entyvio trials reported data on changes in CRP concentrations during any of the phases.

Additional Harms

Ulcerative Colitis

NMA Evidence for Discontinuations due to AEs

During the induction phase, the NMA showed no significant differences in discontinuation due to AEs between Entyvio and any of its therapeutic alternatives (Supplement Table D2.5).

Table D2.5. Risk Ratios for Discontinuations due to AEs at the End of Induction Phase

Ustekinumab				
0.42 (0.01, 5.36)	**Infliximab**			
0.34 (0.01, 4.08)	0.80 (0.16, 3.70)	**Entyvio**		
0.26 (0.01, 2.39)	0.61 (0.18, 1.80)	0.75 (0.26, 2.32)	**Adalimumab**	
0.25 (0.01, 3.01)	0.59 (0.12, 2.74)	0.74 (0.16, 3.46)	0.98 (0.33, 2.84)	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence for Serious Infections

During the maintenance phase, there were no statistically significant differences between Entyvio and any of its therapeutic alternatives as well as in comparisons of any of these to placebo. (Supplement Table D2.6).

Table D2.6. Risk Ratios for Serious Infections at the End of Maintenance Phase

Infliximab				
0.79 (0.08, 7.00)	**Ustekinumab**			
0.61 (0.10, 3.30)	0.78 (0.12, 4.62)	**Entyvio**		
0.58 (0.10, 2.91)	0.74 (0.12, 4.08)	0.95 (0.41, 2.21)	**Adalimumab**	
0.57 (0.11, 2.37)	0.73 (0.14, 3.39)	0.93 (0.38, 2.30)	0.98 (0.47, 2.10)	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Direct Evidence from Clinical Trials on Additional Harms

GEMINI 1 and Motoya et al. (2019) presented data on harms during induction phase at weeks six and 10, respectively.[41,42] Adverse events were comparable across Entyvio (40-50%) and placebo (46-52%). Although GEMINI 1 reported marginally higher serious adverse events in the placebo arm (7%) than in the Entyvio arm (2%), Motoya et al 2019 reported similar rates across the two arms. The rates of malignancies were generally low (0-1%) and comparable during this phase. There was one death in the Entyvio arm of the GEMINI trial, and it was deemed related to a cardiac event.

Four placebo-controlled trials and two head-to-head trials presented data on harms during maintenance phase (44-60 weeks).[37,40-43,114] Discontinuations due to adverse events were generally higher in the placebo arm (9-14%) compared to the Entyvio arm (2-6%). The rates of malignancies were low (<1%) and comparable across all arms and trials. One patient had experienced deep vein thrombosis int the NCT02039505 trial.[42] Two patients, one in each treatment arm, had experienced thrombophlebitis superficial in the VARSITY trial. There was one death in the Entyvio arm of VARSITY trial but was considered as unrelated to the study treatment.[40] See Table D2.7.

Table D2.7. Key Harms Table During Maintenance Phase (44-60 Weeks)

Trials (Weeks)	Arms	N	Any AEs, n (%)	Serious AEs, n (%)	AEs Leading to Discontinuations, n (%)	Serious Infections, n (%)	Malignancy, n (%)
GEMINI 1 (52 Weeks)	VED	122	100 (82)	10 (8)	7 (6)	3 (2)	1 (<1)
	PBO	126	106 (84)	20 (16)	15 (12)	4 (3)	1 (<1)
Motoya et al. (2019) NCT02039505 (60 Weeks)	VED	41	36 (88)	4 (10)	1 (2)	1 (2)	1 (2)
	PBO	42	33 (79)	3 (7)	6 (14)	1 (2)	0
VISIBLE 1 (52 Weeks)	VED	160	110 (69)	17 (11)	7 (4)	2 (1)	0
	PBO	56	41 (73)	6 (11)	5 (9)	0	0
EARNEST (34 Weeks)	VED	51	47 (92)	3 (6)	2 (4)	1 (2)	0
	PBO	51	44 (86)	5 (10)	5 (10)	0	2 (4)
VARSITY (52 Weeks)	VED	383	240 (63)	42 (11)	17 (4)	7 (2)	1 (<1)
	ADA	386	267 (69)	53 (14)	25 (6)	8 (2)	0
Naganuma et al. (2025) (26 Weeks)	VED	36	13 (36)	2 (6)	2 (6)	0	NR
	UST	34	3 (9)	0	0	0	NR
	IFX	34	11 (32)	1 (3)	1 (3)	0	NR

Data are presented as number (%). ADA: adalimumab, AEs: adverse events, IFX: infliximab, n: number, N: sample size, NR: not reported, UST: ustekinumab

Crohn's Disease

NMA Evidence for Discontinuation Due to Adverse Events

For the induction and maintenance phases, the NMA showed no significant differences in discontinuation due to AEs between Entyvio and any of its therapeutic alternatives as well as in comparisons of any of these to placebo (Supplement Table D2.8 and D2.9).

Table D2.8. Risk Ratios for Discontinuations due to Adverse Events at the End of Induction Phase

Ustekinumab			
0.37 (0.01, 6.62)	**Adalimumab**		
0.31 (0, 4.53)	0.84 (0.14, 4.31)	**Entyvio**	
0.15 (0, 1.74)	0.40 (0.09, 1.42)	0.48 (0.16, 1.34)	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.9. Risk Ratios for Discontinuations due to Adverse Events at the End of Maintenance Phase

Ustekinumab				
0.52 (0.12, 2.13)	**Adalimumab**			
0.39 (0.05, 2.62)	0.75 (0.18, 2.75)	**Entyvio**		
0.35 (0.03, 3.37)	0.66 (0.09, 4.07)	0.88 (0.13, 5.33)	**Infliximab**	
0.23 (0.04, 1.20)	0.44 (0.14, 1.11)	0.58 (0.23, 1.37)	0.66 (0.13, 3.36)	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence for Serious Infections

For the induction and maintenance phases, there were no statistically significant differences between Entyvio and any of its therapeutic alternatives as well as in comparisons of any of these to placebo. (Supplement Table D2.9 and D2.10).

Table D2.10. Risk Ratios for Serious Infections at the End of Induction Phase

Adalimumab			
0.48 (0.06, 2.60)	**Placebo**		
0.37 (0.02, 4.83)	0.79 (0.09, 5.23)	**Entyvio**	
0.25 (0.03, 1.72)	0.53 (0.20, 1.29)	0.66 (0.08, 6.81)	**Ustekinumab**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.11. Risk Ratios for Serious Infections at the End of Maintenance Phase

Entyvio			
0.82 (0.12, 5.47)	Ustekinumab		
0.81 (0.15, 4.35)	0.99 (0.24, 4.16)	Adalimumab	
0.64 (0.19, 2.07)	0.78 (0.17, 3.38)	0.79 (0.24, 2.48)	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Direct Evidence from Clinical Trials on Additional Harms

For CD, three placebo-controlled trials presented data on harms during both induction and maintenance phases.[65,66,106] During the induction phase, all trials reported largely similar proportions of any adverse events across the arms (54-62%). Any adverse events during the maintenance were numerically higher (74-88%) than the induction phase. Discontinuations due to adverse events were generally higher in the placebo arm (4-17%) compared to the Entyvio arm (8-33%). Serious infections were comparable across arms during both phases. The rates of malignancies were generally low across arms (0-1% in the Entyvio arm and 0-2% in the placebo arm). See table D2.10.

Table. D2.12. Key Harms Table During Maintenance Phase (44-60 Weeks)

Trials (Weeks)	Arms	N	Any AEs, n (%)	Serious AEs, n (%)	AEs Leading to Discontinuations, n (%)	Serious Infections, n (%)	Malignancy, n (%)
GEMINI 2	**VEDO**	154	135 (88)	28 (18)	12 (8)	6 (4)	1 (<1)
	PBO	153	128 (84)	23 (15)	15 (10)	5 (3)	0
VISIBLE 2	**VEDO**	275	202 (74)	23 (8)	11 (4)	4 (2)	2 (1)
	PBO	135	102 (76)	14 (10)	11 (8)	6 (5)	3 (2)
Watanabe et al. (2020)	**VEDO**	12	9 (75)	2 (17)	2 (17)	NR	NR
	PBO	12	10 (83)	4 (33)	4 (33)	NR	NR

Data are presented as number (%). AEs: adverse events, n: number, N: sample size, NR: not reported, VEDO: vedolizumab

Additional Evidence from Observational Studies

Observational studies were primarily used to assess long-term safety outcomes, with the emphasis on serious infections, malignancies, and colectomy. We presented most data on these outcomes from observational studies in the main section of the report.

Ulcerative Colitis

Findings from two observational studies showed no statistical difference in proportions of UC patients achieving clinical response and remission between Entyvio and anti-TNFs.[50,116] Data on endoscopic improvement was sparse, with one study reporting comparable proportions of patients treated with Entyvio (87%) and anti-TNFs (81%) achieving this outcome at two years.[116] There were no differences between Entyvio and anti-TNFs in achieving corticosteroid-free remission at 12 months.[45,50] However, longer term data showed that Entyvio had a greater odds of achieving corticosteroid-free remission compared to adalimumab (odds ratio [OR] 1.99; 95% CI: 1.11 to 3.54) at 24 months.[55]

Lukin et al. (2022) reported that fewer patients treated with Entyvio (4.6%) had experienced serious infections compared to those treated with anti-TNFs (10.2%) at 12 months.[50] However, another study reported no statistical difference between Entyvio and anti-TNFs in the rates of serious infections or malignancies at 24 months.[116]

In the Entyvio Global Safety Database, a total of 117 malignancies (<1%) were reported with Entyvio among 14,042 UC patients over four years of follow-up period. Around 3% (N=90) UC patients receiving Entyvio experienced colectomy and 1% (N=41) were hospitalized.[56]

Treatment persistence, defined as patients who did not discontinue index treatment during follow-up, was better with Entyvio (76%) than anti-TNF (52%),[116] but worse when compared with ustekinumab (38% vs. 55%).[54] See Supplement Table D3.17-D3.19.

Crohn's Disease

Data from two observational studies suggest no statistical differences between Entyvio and listed comparators in achieving clinical response and remission.[67,68] Data on endoscopic improvement, corticosteroid-free remission, and treatment persistence were limited, with no statistical difference between treatments. Vu et al. (2023) reported that CD-related surgeries were comparable between Entyvio (7%) and ustekinumab (10%) at 12 months.[72] Singh et al. (2023) reported that there were no differences in 1-year risks of hospitalizations and surgery rates between vedolizumab and ustekinumab.[70] See Supplement Table D3.31-D3.33.

Additional Evidence on Subgroup Analyses and Heterogeneity

Here, we present the subgroup analysis of the primary outcomes, clinical response and remission, for both UC and CD, subsequently. We conducted separate NMAs for biologic-naïve and biologic-experienced subgroups to address any potential subgroup difference. Unlike the main analyses, we choose fixed-effects unadjusted models in most cases, due to sparse data. Model fit supported the use of fixed-effects placebo and time adjusted model for response and remission at the end of maintenance phase among biologic-experienced CD patients.

Ulcerative Colitis

NMA Evidence of Clinical Response and Remission for Biologic-Naïve Subgroups During Induction Period

A total of 12 RCTs were available for Entyvio and listed comparators with data on induction phase (six-14 weeks) for the biologic-naive subgroup.[37,40-42,93-99] All included treatments were 1.4 to 1.8 times more likely to achieve clinical response and 1.7 to 3.1 times more likely to achieve clinical remission compared to placebo (See Tables D2.13 and D2.14). Entyvio was statistically superior to adalimumab for both outcomes. Pairwise comparisons among infliximab, ustekinumab, and Entyvio did not demonstrate any statistically significant differences.

Table D2.13. Risk Ratios for Response at the End of Induction Phase in Biologic-Naïve Patients

Infliximab				
1.02 (0.88, 1.2)	**Ustekinumab**			
1.06 (0.93, 1.22)	1.04 (0.87, 1.22)	**Entyvio**		
1.35 (1.17, 1.58)	**1.32 (1.1, 1.58)**	**1.27 (1.14, 1.43)**	**Adalimumab**	
1.85 (1.64, 2.1)	**1.81 (1.54, 2.11)**	**1.73 (1.52, 1.99)**	**1.37 (1.2, 1.55)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.14. Risk Ratios for Remission at the End of Induction Phase in Biologic-Naïve Patients

Infliximab				
1.04 (0.78, 1.45)	**Ustekinumab**			
1.13 (0.87, 1.48)	1.08 (0.76, 1.5)	**Entyvio**		
1.78 (1.35, 2.38)	**1.7 (1.2, 2.38)**	**1.57 (1.28, 1.96)**	**Adalimumab**	
3.06 (2.48, 3.79)	**2.93 (2.16, 3.89)**	**2.7 (2.14, 3.45)**	**1.72 (1.37, 2.15)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Clinical Response and Remission for Biologic-Experienced Subgroups During Induction Period

Six RCTs contributed induction phase (six-14 weeks) data for the biologic-experienced subgroup.[36,40-42,97,99] Ustekinumab and Entyvio were the only treatments that were statistically significantly more likely to achieve clinical response and remission compared to placebo, with relative effect estimates ranging from 1.6 to 2.1 for clinical response and 2.2 to 3.6 for clinical remission. Both these drugs were also statistically significantly more likely to achieve clinical response and remission compared to both anti-TNFs. There was no statistical difference between ustekinumab and Entyvio for these outcomes. See Tables D2.15 and D2.16.

Table D2.15. Risk Ratios for Response at the End of Induction Phase in Biologic-Experienced Patients

Ustekinumab				
1.32 (0.96, 1.83)	Entyvio			
1.94 (1.15, 3.64)	1.48 (1, 2.42)	Infliximab		
1.96 (1.34, 2.99)	**1.49 (1.08, 2.11)**	1.01 (0.55, 1.7)	Adalimumab	
2.06 (1.65, 2.51)	**1.57 (1.18, 2)**	1.05 (0.58, 1.71)	1.05 (0.73, 1.44)	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.16. Risk Ratios for Remission at the End of Induction Phase in Biologic-Experienced Patients

Ustekinumab				
1.67 (0.93, 3.03)	Entyvio			
3.26 (1.29, 9.34)	1.97 (1, 4.26)	Infliximab		
3.3 (1.7, 6.59)	**1.98 (1.15, 3.53)**	1.01 (0.38, 2.44)	Adalimumab	
3.58 (2.39, 5.28)	**2.17 (1.33, 3.34)**	1.08 (0.42, 2.5)	1.08 (0.60, 1.86)	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Clinical Response and Remission for Biologic-Naïve Subgroups During Maintenance Period

Eight RCTs were available on maintenance phase (52-60 weeks) for the biologic-naive subgroup.[38,40-42,93,97,99] All treatments except adalimumab were 1.6 to 2 times more likely to achieve clinical response and 1.9 to 2.5 times more likely to achieve clinical remission compared to placebo (Table D2.17 and D2.18). Entyvio was superior to adalimumab for both outcomes, but showed similar efficacy when compared with infliximab and ustekinumab.

Table D2.17. Risk Ratios for Response at the End of Maintenance Phase in Biologic-Naïve Patients

Entyvio				
1.19 (0.98, 1.47)	Infliximab			
1.22 (0.95, 1.66)	1.02 (0.78, 1.39)	Ustekinumab		
1.71 (1.2, 2.73)	1.42 (1, 2.25)	1.4 (0.92, 2.25)	Adalimumab	
1.95 (1.66, 2.3)	**1.63 (1.38, 1.91)**	**1.6 (1.22, 2.02)**	1.14 (0.74, 1.58)	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.18. Risk Ratios for Remission at the End of Maintenance Phase in Biologic-Naïve Patients

Entyvio				
1.3 (0.97, 1.74)	Infliximab			
1.34 (0.93, 2.06)	1.03 (0.7, 1.58)	Ustekinumab		
2.14 (1.3, 3.96)	1.63 (1, 3.02)	1.6 (0.89, 3.06)	Adalimumab	
2.54 (2.02, 3.2)	**1.95 (1.54, 2.44)**	**1.9 (1.3, 2.66)**	1.19 (0.68, 1.87)	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Clinical Response and Remission for Biologic-Experienced Subgroups During Maintenance Period

A total of seven trials informed the maintenance phase (52-60 weeks) data for the biologic-experienced subgroup.[38,40-42,97,99] Only ustekinumab and Entyvio were 2.1 to 2.7 times more likely to achieve clinical response and 2.7 to 4 times more likely to achieve clinical remission compared to placebo. Pairwise comparisons within the network did not show statistically significant differences between the active treatments. See Table D2.19 and D2.20.

Table D2.19. Risk Ratios for Response at the End of Maintenance Phase in Biologic-Experienced Patients

Entyvio				
1.18 (0.67, 3.08)	Infliximab			
1.32 (0.89, 2.04)	1.11 (0.43, 2.06)	Ustekinumab		
1.41 (0.81, 3.13)	1.19 (0.45, 2.89)	1.07 (0.6, 2.32)	Adalimumab	
2.72 (1.98, 3.58)	2.29 (0.92, 3.86)	**2.07 (1.46, 2.72)**	1.93 (0.93, 3.12)	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.20. Risk Ratios for Remission at the End of Maintenance Phase in Biologic-Experienced Patients

Entyvio				
1.28 (0.54, 4.76)	Infliximab			
1.5 (0.84, 2.81)	1.16 (0.31, 2.92)	Ustekinumab		
1.66 (0.73, 4.9)	1.29 (0.33, 4.43)	1.1 (0.48, 3.17)	Adalimumab	
3.99 (2.53, 6.11)	3.1 (0.9, 6.84)	**2.66 (1.66, 3.97)**	2.42 (0.91, 4.95)	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Crohn's Disease

NMA Evidence of Clinical Response and Remission for Biologic-Naïve Subgroups During Induction Period

A total of six RCTs were available for Entyvio and listed comparators with data on induction phase (6-14 weeks) for the biologic-naive subgroup.[66,100,103,106,107,110] All included treatments were 1.6 to 2.2 times more likely to achieve clinical response and 1.8 to 2.8 times more likely to achieve clinical remission compared to placebo. (See Tables D2.21 and D2.22) Pairwise comparisons among ustekinumab, adalimumab, and Entyvio did not demonstrate any statistically significant differences.

Table D2.21. Risk Ratios for Response at the End of Induction Phase in Biologic-Naïve Patients

Ustekinumab			
1.04 (0.86, 1.23)	Adalimumab		
1.38 (0.89, 2.07)	1.32 (0.89, 1.97)	Entyvio	
2.16 (1.49, 2.92)	**2.07 (1.51, 2.72)**	**1.57 (1.17, 2.05)**	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.22. Risk Ratios for Remission at the End of Induction Phase in Biologic-Naïve Patients

Ustekinumab			
1.06 (0.81, 1.34)	Adalimumab		
1.56 (0.85, 2.74)	1.46 (0.85, 2.53)	Entyvio	
2.84 (1.7, 4.33)	**2.67 (1.71, 3.92)**	**1.82 (1.22, 2.61)**	Placebo

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Clinical Response and Remission for Biologic-Experienced Subgroups During Induction Period

Seven RCTs contributed induction phase (six-14 weeks) data for the biologic-experienced subgroup.[66,101,103,106-109] All included treatments were statistically significantly more likely to achieve clinical response and remission compared to placebo, with relative effect estimates ranging from 1.4 to 1.8 for clinical response and 1.7 to 2.3 for clinical remission. There were no statistical differences between adalimumab, ustekinumab, and Entyvio for these outcomes. See Table D2.23 and D2.24.

Table D2.23. Risk Ratios for Response at the End of Induction Phase in Biologic-Experienced Patients

Adalimumab			
1.12 (0.79, 1.56)	**Ustekinumab**		
1.25 (0.86, 1.81)	1.12 (0.82, 1.56)	**Entyvio**	
1.81 (1.35, 2.36)	**1.61 (1.3, 1.97)**	**1.44 (1.11, 1.84)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.24. Risk Ratios for Remission at the End of Induction Phase in Biologic-Experienced Patients

Adalimumab			
1.18 (0.72, 1.89)	**Ustekinumab**		
1.37 (0.81, 2.3)	1.17 (0.76, 1.85)	**Entyvio**	
2.26 (1.49, 3.32)	**1.92 (1.43, 2.54)**	**1.65 (1.15, 2.31)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Clinical Response and Remission for Biologic-Naïve Subgroups During Maintenance Period

Seven RCTs were available on maintenance phase (52-60 weeks) for the biologic-naive subgroup.[38,65,66,101,105,107,110] All treatments were 1.4 to 1.9 times more likely to achieve clinical response and 1.5 to 2.2 times more likely to achieve clinical remission compared to placebo (Tables D2.25 and D2.26). Participants treated with adalimumab also statistically significantly more likely to achieve clinical response and remission compared to those treated with Entyvio.

Table D2.25. Risk Ratios for Response at the End of Maintenance Phase in Biologic-Naïve Patients

Adalimumab				
1.02 (0.89, 1.25)	**Ustekinumab**			
1.09 (0.85, 1.37)	1.06 (0.77, 1.38)	**Infliximab**		
1.34 (1.03, 1.77)	1.31 (0.94, 1.76)	1.25 (0.96, 1.63)	**Entyvio**	
1.86 (1.5, 2.22)	**1.81 (1.34, 2.25)**	**1.71 (1.41, 2.03)**	**1.38 (1.1, 1.67)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.26. Risk Ratios for Remission at the End of Maintenance Phase in Biologic-Naïve Patients

Adalimumab				
1.03 (0.85, 1.33)	**Ustekinumab**			
1.11 (0.81, 1.5)	1.07 (0.71, 1.52)	**Infliximab**		
1.46 (1.04, 2.07)	1.41 (0.93, 2.05)	1.32 (0.95, 1.85)	**Entyvio**	
2.16 (1.65, 2.73)	**2.1 (1.42, 2.79)**	**1.94 (1.53, 2.43)**	**1.48 (1.12, 1.89)**	**Placebo**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Evidence of Clinical Response and Remission for Biologic-Experienced Subgroups During Maintenance Period

A total of six trials informed the maintenance phase (52-60 weeks) data for the biologic-experienced subgroup.[38,65,66,105,107,109] Entyvio was 1.5 times more likely to achieve clinical response and 1.6 times more likely to achieve clinical remission compared to placebo. Ustekinumab demonstrated superiority over Entyvio and adalimumab for both outcomes. See Tables D2.27 and D2.28.

Table D2.27. Risk Ratios for Response at the End of Maintenance Phase in Biologic-Experienced Patients

Ustekinumab				
1.86 (0.68, 7.43)	**Infliximab**			
2.44 (1.25, 3.59)	1.32 (0.34, 2.49)	**Entyvio**		
3.68 (1.97, 4.72)	1.97 (0.52, 3.58)	**1.49 (1.13, 1.94)**	**Placebo**	
8.35 (1.02, 107.59)	**4.08 (1.02, 38.19)**	3.29 (0.72, 37.67)	2.2 (0.48, 26)	**Adalimumab**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.28. Risk Ratios for Remission at the End of Maintenance Phase in Biologic-Experienced Patients

Ustekinumab				
2.1 (0.64, 9.99)	**Infliximab**			
2.89 (1.29, 4.43)	1.38 (0.3, 2.86)	**Entyvio**		
4.55 (2.13, 6.11)	2.15 (0.49, 4.3)	**1.57 (1.15, 2.09)**	**Placebo**	
11.16 (1.03, 171.69)	**4.77 (1.02, 51.71)**	3.7 (0.7, 49.12)	2.35 (0.43, 33.32)	**Adalimumab**

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

D3. Evidence Tables

Ulcerative Colitis – RCTs

Table D3.1. Study Design of Included RCTs

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
Infliximab					
ACT 1[93] **IND + MAINT (8/54 weeks)**	Naïve (100%)	- IFX 5 mg/kg (n=121) - Placebo at weeks 0, 2, and 6 (n=121)	- IFX 5 mg/kg (n=121) - Placebo q8w through week 46 (n=121)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Inadequate response or intolerance to ≥1 conventional therapy	- Prior treatment with IFX or any anti-TNF
ACT 2[93] **IND + MAINT (8/30 weeks)**	Naïve (100%)	- IFX 5 mg/kg (n=121) - Placebo at weeks 0, 2, and 6 (n=123)	- IFX 5 mg/kg (n=121) - Placebo q8w through week 22 (n=123)		
Kobayashi et al. (2016)[95] **IND + MAINT (8/30 weeks)**	Naïve (100%)	- IFX 5 mg/kg (n=104) - Placebo at weeks 0, 2, and 6 (n=104)	- IFX 5 mg/kg (n=73) - Placebo q8w through week 22 (n=72)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Inadequate response or intolerance to ≥1 conventional therapy	- Recent bowel surgery or complications such as stricture, fistula, or dysplasia - Treatment with other biologics, MTX, calcineurin inhibitors, or cytapheresis within the previous 18 months - Serious medical conditions e.g., chronic heart failure or latent infectious diseases
Jiang et al. (2015)[94] **IND + MAINT (8/30 weeks)**	Naïve (100%)	- IFX 5mg/kg (n=41) - Placebo at weeks 0, 2, and 6 (n=41)	- IFX 5mg/kg (n=41) - Placebo q8w through week 22 (n=41)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Inadequate response or intolerance to ≥1 conventional therapy	- Received CS or drugs containing 5-AMAs within 2 weeks of screening - Prior treatment with IFX or any anti-TNF

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
NCT01551290[117] **IND + MAINT (8 / 26 weeks)**	Naïve (100%)	- IFX 5 mg/kg (n=50) - Placebo at weeks 0, 2 and 6 (n=49)	- IFX 5 mg/kg (n=50) -Placebo at weeks 14 and 22 (n=49)	- Active UC of ≥3 months - Endoscopic subscore of ≥2 - Mayo score of 6–12 -Concomitant medications: either have concurrent treatment with ≥1 of therapies (e.g., oral CSs and 6-MPs)	- Has severe extensive colitis or UC limited to the rectum or <20 cm of the colon - Requires/required within 2 months any surgery for active GI bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess
LIBERTY-UC[38] **MAINT (54 weeks)**	Naïve (91%) Experienced (9%)	--	- IFX 120mg SC (n=294) - Placebo SC (n=144)	- Modified Mayo score of 5–9 - Endoscopic subscore of ≥2 points	- Prior treatment with ≥2 biologic agents and/or JAK inhibitors - Previous inadequate response or intolerance to anti-TNFs
LIBERTY-UC EXTENSION[118] **(102 weeks)**	Naïve (91%) Experienced (9%)	--	- IFX 120mg SC (n=237) - Placebo SC (n=111)		
Adalimumab					
ULTRA 1[96] **IND (8 weeks)**	Naive (100%)	- ADA 160/80 mg (n=130). 160 mg at week 0, 80 mg at week 2, then 40 mg at weeks 4 and 6 - ADA 80/40 mg (n=130). 80 mg at week 0, then 40 mg at weeks 2, 4 and 6 - Placebo (n=130)	--	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Inadequate response, loss of response, or intolerance to ≥ 1 (oral CSs and/or IMMs)	- Prior treatment with anti-TNFs or biologics
ULTRA 2[97] **IND + MAINT (8 / 52 weeks)**	Naive (60%) Experienced (40%)	- ADA 160/80 mg (n=248). 160 mg at week 0, 80 mg at week 2, then 40 mg EOW	- ADA 40 mg EOW (n=248) - Placebo through week 52 (n=246)	- Mayo score 6–12 - Endoscopic subscore of ≥2 -Inadequate response or intolerance to ≥1 conventional therapy	- History of subtotal colectomy, koch pouch, or planned bowel surgery - Receipt of IV CS within 2 weeks - Receipt of therapeutic enema or

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
		- Placebo (n=246)			suppository, other than required for endoscopy, within 2 weeks
Suzuki et al. (2014)[98] IND + MAINT (8 / 52 weeks)	Naive (60%) Experienced (40%)	- ADA 160/80 mg (n=87). 160 mg at week 0, 80 mg at week 2, then 40mg EOW - Placebo (n=96)	- ADA 40 mg EOW (n=177) - Placebo through week 52 (n=96)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Inadequate response or intolerance to ≥1 conventional therapy	- Prior treatment with anti-TNFs or other biologics
Vedolizumab					
GEMINI 1[41] IND + MAINT (6 / 52 weeks)	Naïve (52%) Experienced (48%)	Cohort 1 - VEDO 300 mg (n=225) - Placebo (n=149) Cohort 2 - OL VEDO 300 mg at weeks 0 and 2 (n=521)	- VEDO q8w (n=122) - VEDO q4w (n=125) - Placebo through week 52 (n=126)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Disease extended ≥15 cm from anal verge - Inadequate response to or intolerance to ≥1 conventional therapy	- Received anti-TNFs within 60 days - Previous treatment with VEDO, natalizumab, efalizumab, or rituximab
GEMINI LTS[44,119,120] MAINT (104 weeks)	Naïve (46%) Experienced (54%)	--	- OL VEDO q4w	- Recruited from GEMINI 1, GEMINI 2, GEMINI 3, and an OL phase II trial (NCT00619489)	- Prior history of malignancy
VISIBLE 1[43] MAINT (52 weeks)	Naïve (61%) Experienced (39%)	- OL VEDO 300 mg (n=383) at weeks 0 and 2	- VEDO 108 mg SC q2w (n=106) - VEDO 300 mg IV q8w (n=154) - Placebo through week 52 (n=56)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Inadequate response to or intolerance to ≥1 conventional therapy	- Received anti-TNFs within 60 days - Previous treatment with VEDO, natalizumab, efalizumab, or rituximab
Motoya et al. (2019)[42] IND + MAINT (10 / 60 weeks)	Naïve (49%) Experienced (51%)	Cohort 1 - VEDO 300 mg (n=164) - Placebo (n=82) Cohort 2 - OL VEDO 300	- VEDO 300 mg q8w (n=41) - Placebo through week 52 (n=42)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Total or left-side diagnosis with treatment failure with CSs, IMMs, or anti-TNFs	- Patients with ≥3 point decrease in partial mayo score between screening and start of study - History of colectomy or recent enterectomy

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
		mg (n=46) at weeks 0, 2, and 6			- Previous treatment with VEDO, natalizumab, efalizumab, or rituximab
EARNEST[114] **NA*** **(34 weeks)**	Naïve (72%) Experienced (28%)	- VEDO 300 mg (n=51) - Placebo (n=51)	--	- mPDAI score ≥5 - Endoscopic subscore of ≥2 with either... - ≥3 recurrent episodes within 1 year with ≥2 weeks of antibiotic/ prescription therapy OR - requiring maintenance antibiotic therapy continuously for ≥4 weeks prior to baseline	- Has CD, or CD of the pouch
Ustekinumab					
UNIFI[99] **IND + MAINT** **(8 / 52 weeks)**	Naïve (49%) Experienced (51%)	-UST 6mg/kg (n=322) - Placebo single dose (n=319)	- UST 90mg SC q8w (N=176)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Failed biologic therapy with ≥1 anti-TNFs or VEDO - Biologic naïve	- Severe extensive colitis - UC limited to the rectum, presence of a stoma or history of a fistula
Head-to-Head					
VARSITY[40] **IND + MAINT** **(6 / 52 weeks)**	Naïve (79%) Experienced (21%)	- VEDO 300 mg (n=383) at week 0, 2, and 6 - ADA 160/80 mg (n=386). 160 mg at week 0, 80 mg at week 2, and 40 mg at week 4 and 6.	-VEDO 300 mg q8w (n=383) -ADA 40 mg EOW through week 50 (n=386)	- Mayo score 6–12 - Endoscopic subscore of ≥2 - Disease extended with colonic involvement of ≥15 cm - No response or loss of response to conventional treatments or discontinued treatment with anti-TNFs, or TNF-naïve	--
EFFICACI[36] **IND** **(14 weeks)**	Experienced (100%)	- VEDO 300 mg (n=78) - IFX 5 mg/kg (n=73)	--	- Mayo score ≥6 - ≥12 weeks of treatment with ADA or golimumab as first-line therapy	--

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
Naganuma et al. (2025)[37] IND (14 weeks)	Naïve (100%)	- IFX 5mg/kg (n=33) - VEDO 300 mg (n=34) - UST 6 mg/kg (n=30)	--	- Aged ≥16 - Mayo score ≥6 - Colonoscopy sub-score of ≥2	- History of steroid resistance/dependence or previous systemic steroid administration

ADA: adalimumab, CD: Crohn's disease, cm: centimeter, CSs: corticosteroids, EOW: every other week, GI: gastrointestinal, IFX: infliximab, IMMs: immunomodulators, IND: induction, IV: intravenous, JAK: Janus kinase, MAINT: maintenance, mg: milligrams, mg/kg: milligram per kilogram, n: number, mPDAI: Modified Pediatric Disease Activity Index, MTX: Methotrexate, OL: open-label, q2w: every 2 weeks, q4w: every 4 weeks, q8w: every 8 weeks, SC: subcutaneous, TNF: tumor necrosis factor, UC: ulcerative colitis, UST: ustekinumab, VEDO: vedolizumab, 5-AMAs: 5-aminosalicylic acids

Table D3.2. Baseline Characteristics

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MER-C
ACT 1 IFX	IFX 5 mg	121	42.4 (14.3)	43 (35.5)	5.9 (5.4)	NA	8.5 (1.7)	Left Side: 63 (52.9) Extensive: 56 (47.1)	1.4 (1.9)	70 (57.9)	66 (54.5)	NR	45 (37.2)	21 (17.4)
	Placebo	121	41.4 (13.7)	49 (40.5)	6.2 (5.9)	NA	8.4 (1.8)	Left Side: 66 (55) Extensive: 54 (45)	1.7 (2.7)	79 (65.3)	53 (43.8)	NR	36 (29.8)	17 (14.0)
ACT 2 IFX	IFX 5 mg	121	40.5 (13.1)	45 (37.2)	6.7 (5.3)	NA	8.3 (1.5)	Left Side: 70 (59.3) Extensive: 48 (40.7)	1.3 (2.3)	60 (49.6)	52 (43)	NR	41 (33.9)	11 (9.1)
	Placebo	123	39.3 (13.5)	52 (42.3)	6.5 (6.7)	NA	8.5 (1.5)	Left Side: 70 (58.3) Extensive: 50 (41.7)	1.6 (2.9)	60 (48.8)	54 (43.9)	NR	35 (28.5)	19 (15.4)
	IFX 5 mg	104	40 (12.7)	38 (36.5)	8.1 (7.2)	NA	8.6 (1.4)	Left Side: 21 (20.2)	1.0 (1.5)	68 (65.4)	50 (48.1)	NR	38 (36.5)	12 (11.5)

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MER-C
Kobayashi et al. (2016) IFX								Extensive: 83 (79.8)						
	Placebo	104	37.8 (12.9)	37 (35.6)	7.1 (6.6)	NA	8.5 (1.4)	Left Side: 20 (19.2) Extensive: 84 (80.8)	0.7 (1.1)	69 (66.3)	49 (47.1)	NR	34 (32.7)	15 (14.4)
Jiang et al. (2015) IFX	IFX 5 mg	41	34.3 (14.3)	15 (36.6)	4.4 (2.8)	NA	NR	Left side: 16 (39.1) Pancolitis: 25 (60.9)	35.8 (22.6)	22 (53.7)	NR	NR	12 (29.3)	NR
	Placebo	41	34.5 (14.9)	16 (39.1)	4.4 (2.6)	NA	NR	Left Side: 17 (41.5) Pancolitis: 24 (58.5)	35.1 (17.8)	21 (51.2)	NR	NR	13 (31.7)	NR
NCT01551290 IFX	IFX 5 mg	50	37†	NR	3.7†	NA	8.0†	NR	NR	30 (60)	NR	NR	NR	NR
	Placebo	49		NR		NA		NR	NR	39 (80)	NR	NR	NR	NR
LIBERTY-UC IFX	IFX 120 mg SC	294	37†	131 (44.6)	6.09 (6.01)	29 (9.9)	8.8 (1.30)	NR	8.62 (17.72)	NR	NR	NR	63 (21.4)	2 (0.7)
	Placebo	144	39†	61 (42.4)	6.80 (6.81)	13 (9.0)	8.8 (1.42)	NR	8.32 (18.74)	NR	NR	NR	30 (20.8)	2 (1.4)
LIBERTY-UC Extension IFX	IFX 120 mg SC	237	37†	101 (42.6)	5.87 (5.629)	24 (10.1)	6.6 (1.10)	NR	NR	NR	NR	NR	55 (23.2)	2 (0.8)
	Placebo	111	40†	49 (44.1)	7.26 (7.214)	7 (6.3)	6.6 (1.17)	NR	NR	NR	NR	NR	22 (19.8)	2 (1.8)
GEMINI I‡ VEDO	VEDO (Cohort 1)	225	40.1 (13.1)	93 (41.3)	6.1 (5.1)	95 (42.2)	8.5 (1.8)	Rectum & Sigmoid Colon: 25 (11.1) Left Side: 92 (40.9)	NR	79 (35.1)	28 (12.4)	47 (20.9)	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MER-C
								Proximal to splenic flexure: 25 (11.1) All: 83 (36.9)						
	VEDO (Cohort 2)	521	40.1 (13.3)	220 (42.2)	7.2 (6.6)	263 (50.5)	8.6 (1.8)	Rectum & Sigmoid Colon: 69 (13.2) Left Side: 188 (36.1) Proximal to splenic flexure: 66 (12.7) All: 198 (38)	NR	195 (37.4)	113 (21.7)	76 (14.6)	NR	NR
	VEDO (Cohort 1 & 2)	746	40.1 (13.2)	313 (42)	6.8 (6.2)	358 (48)	8.6 (1.8)	Rectum& Sigmoid Colon: 94 (12.6) Left Side: 280 (37.5) Proximal to splenic flexure: 91 (12.2) All: 281 (37.7)	NR	274 (36.7)	141 (18.9)	123 (16.5)	NR	NR
	Placebo	149	41.2 (12.5)	57 (38.3)	7.1 (7.2)	73 (49)	8.6 (1.7)	Rectum & Sigmoid Colon: 22 (14.8) Left Side: 59 (39.6) Proximal the splenic flexure: 18 (12.1) All: 50 (33.6)	NR	58 (38.9)	18 (12.1)	26 (17.4)	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MER-C
GEMINI LTS[119] (Card et al. 2020)	VEDO OL	751	41.3 (13.20)	331 (44)	8.0 (6.79)	321 (43)	3.8 (2.91)	NR	NR	314 (42)	204 (27)	NR	NR	NR
GEMINI LTS[44] (Loftus et al. 2020)	VEDO OL	894	41.2 (13.6)	372 (41.6)	8.1 (7.0)	380 (46)	6.0 (1.5)	NR	NR	330 (36.9)	NR	NR	NR	NR
GEMINI LTS[120] (Danese et al. 2021)	VEDO OL	142	47.7 (11.8)	63 (44.4)	NR	28 (19.7)	0.5 (1.0)	NR	NR	5 (3.5)	26 (18.3)	2 (1.4)	NR	NR
VISIBLE I VEDO	VEDO 108 mg SC	106	38.1 (13.1)	41 (38.7)	8 (6.2)	40 (37.7)	9.0†	Proctosigmoiditis: 15 (14.2) Left Side: 46 (43.4) Extensive: 7 (6.6) Pancolitis: 37 (34.9)	NR	45(42.5)	NR	NR	NR	NR
	VEDO 300 mg IV	54	41.6 (14.1)	23 (42.6)	8.2 (5.9)	24 (44.4)	9.0†	Proctosigmoiditis: 7 (13) Left Side: 21 (38.9) Extensive: 7 (13) Pancolitis: 19 (35.2)	NR	21 (38.9)	NR	NR	NR	NR
	Placebo	56	39.4 (11.7)	22 (39.3)	7.4 (7.1)	20 (35.7)	9.0†	Proctosigmoiditis: 7 (12.5) Left Side: 24 (42.9) Extensive: 4 (7.1) Pancolitis: 21 (37.5)	NR	24 (42.9)	NR	NR	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MER-C
Motoya et al. (2019) VEDO	VEDO 300 mg	164	42.3 (14.4)	65 (39.6)	7.2 (6.2)	85 (51.8)	8.3 (1.5)	Total Colitis: 101 (61.6) Left Side: 63 (38.4)	<3 mg/L: 76 (46.3) ≥3 mg/L: 50 (61)	31 (18.9)	59 (36)	21 (12.8)	NR	NR
	Placebo	82	44 (16)	27 (32.9)	8.6 (8)	41 (50)	8.1 (1.5)	Total Colitis: 51 (62.2) Left Side: 31 (37.8)	<3 mg/L: 88 (53.7) ≥3 mg/L: 32 (39.0)	11 (13.4)	29 (35.4)	14 (17.1)	NR	NR
	VEDO 300 mg OL	46	42.4 (15.6)	20 (43.5)	9.2 (7.7)	24 (52.2)	8.3 (1.7)	Total Colitis: 32 (69.6) Left Side: 14 (30.4)	NR	13 (28.3)	17 (37)	6 (13)	NR	NR
EARNEST VEDO	VEDO 300 mg	51	42[†]	19 (37)	NR	15 (29)	NR	NR	≤250 µg/g: 15 (29) >250 µg/g: 36 (71)	NR	NR	NR	NR	NR
	Placebo	51	45[†]	13 (26)	NR	12 (24)	NR	NR	≤250 µg/g: 17 (33) >250 µg/g: 34 (67)	NR	NR	NR	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MER-C
ULTRA 1 ADA	ADA 80/40 mg	130	40[†]	52 (40)	6.91[†]	NA	9 (1.62)	Left Side: 36.9 Extensive: 53.8 Other: 9.2	6.4[†]	48 (36.9)	25 (19.2)	26 (20)	NR	NR
	ADA 160/80 mg	130	36.5[†]	47 (36.2)	6.06[†]	NA	8.8 (1.61)	Left Side: 46.9 Extensive: 46.2 Other: 6.9	3.3[†]	48 (36.9)	28 (21.5)	23 (17.7)	NR	NR
	Placebo	130	37[†]	48 (36.9)	5.35[†]	NA	8.7 (1.6)	Left Side: 32.3 Extensive: 56.2 Other: 11.5	3.2[†]	55 (41.5)	18 (13.8)	34 (26.1)	NR	NR
ULTRA 2 ADA	ADA	248	39.6 (12.5)	106 (42.7)	8.1 (7.09)	98 (39.1)	8.9 (1.5)	Pancolitis: 120 (48.4) Descending Colon: 96 (38.7) Other: 32 (12.9)	NR	150 (60.5)	NR	NR	93 (37.5)	NR
	Placebo	246	41.3 (13.2)	94 (38.2)	8.5 (7.37)	101 (41.1)	8.9 (1.8)	Pancolitis: 120 (48.8) Descending Colon: 96 (39) Other: 30 (12.2)	NR	140 (56.9)	NR	NR	80 (32.5)	NR
Suzuki et al. (2014) ADA	ADA 80/40 mg	87	44.4 (15)	37 (42.5)	7.8 (7.1)	NA	8.6 (1.4)	Pancolitis: 63 (70) Descending colon: 27 (30) Other: 0	0.22[†]	57 (63.3)	NR	NR	41 (45.6)	NR
	ADA 160/80 mg	90	42.5 (14.6)	29 (32.2)	8.3 (7.7)	NA	8.5 (1.4)	Pancolitis: 54 (62.1) Descending Colon: 32 (36.8) Other: 1 (1.1)	0.31[†]	63 (72.4)	NR	NR	38 (43.7)	NR
	Placebo	96	41.3 (13.6)	26 (27.1)	7.8 (6.6)	NA	8.5 (1.6)	Pancolitis: 59 (61.5) Descending Colon: 35 (36.5)	0.34[†]	58 (60.4)	NR	NR	52 (54.2)	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MER-C
								Other: 2 (2.1)						
UNIFI UST	UST 6 mg/kg	322	41.7 (13.7)	127 (39.4)	8.2 (7.8)	166 (51.6)	8.9 (1.5)	Left Side: 168/320 (52.5)	4.8†	168 (52.2)	89 (27.6)	NR	NR	NR
	Placebo	319	41.2 (13.5)	122 (38.2)	8 (7.2)	161 (50.5)	8.9 (1.6)	Left Side: 167/316 (52.8)	4.7†	157 (49.2)	89 (27.9)	NR	NR	NR
VARSITY VEDO	ADA 40 mg	386	40.5 (13.4)	170 (44)	6.4 (6.0)	81 (21.0)	8.7(1.5)	NR	NR	140 (36.3)	100 (25.9)	NR	NR	NR
	VEDO 300 mg	385	40.8 (13.7)	151 (39.2)	7.3 (7.2)	80 (20.8)	8.7(1.6)	NR	NR	139 (36.1)	101 (26.2)	NR	NR	NR
EFFICACI VEDO vs. IFX	VEDO 300 mg	78	NR	NR	NR	151 (100)	NR	NR	NR	NR	NR	NR	NR	NR
	IFX 5 mg/kg	73	NR	NR	NR		NR	NR	NR	NR	NR	NR	NR	NR
Naganuma et al. (2025) VEDO vs. IFX vs. UST	IFX 5 mg/kg	33	37†	9 (27.3)	2.9†	0	9.0†	Pancolitis: 23 (69.7) Left Side: 10 (30.3)	0.5†	NR	NR	NR	NR	NR
	VEDO 300 mg	34	50.5†	14 (41.2)	2.6†	0	9.0†	Pancolitis: 21 (61.8%) Left Side: 13 (38.2)	0.2†	NR	NR	NR	NR	NR
	UST 6 mg/kg	30	43†	13 (43.3)	6.0†	0	8.5†	Pancolitis: 21 (70%) Left Side: 9 (30)	0.2†	NR	NR	NR	NR	NR

ADA: adalimumab, AZA: azathioprine, CRP: C-reactive protein, CS: corticosteroid, IFX: infliximab, IMM: immunomodulators, IV: intravenous, LTS: long-term study, MERC: mercaptopurine, mg: milligrams, mg/dL: milligram per deciliter, mg/kg: milligram per kilogram, mg/L: milligram per liter, n: number, NA: not applicable, NR: not reported, OL: open-label, SC: subcutaneous, SD: standard deviation, UST: ustekinumab, VEDO: vedolizumab, µg/g: microgram per gram
*Race/Ethnicity include, but are not limited to, White (W), Black (B), Asian (A), American Indian (AI), Native Hawaiian (NH), and Hispanic/Latino (H/L). 'Others' refers to any of these that have no data.

†Median.
‡GEMINI I Cohort 1 (N=374) received 300 mg of vedolizumab or placebo intravenously at weeks 0 and 2. Cohort 2 (N=521) received open-label vedolizumab at weeks zero and two.

Table D3.3 Response, Remission, and Endoscopic Improvement in the Induction Phase

Induction Phase (Weeks 6-10)													
Trial	**Arm**	**Response**				**Remission**							
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
ACT 1 IFX	**Week 8**												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	84	121	69.4	<0.001	47	121	38.8	<0.001	75	121	62	<0.001
	Placebo	45	121	37.2	--	18	121	14.9	--	41	121	33.9	--
	Biologic-Experienced (Population Not Studied)												
ACT 2 IFX	**Week 8**												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	78	121	64.5	<0.001	41	121	33.9	<0.001	73	121	60.3	<0.001
	Placebo	36	123	29.3	--	7	123	5.7	--	38	123	30.9	--
	Biologic-Experienced (Population Not Studied)												
Jiang et al. (2015) IFX	**Week 8**												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	32	41	78.1	0	22	41	53.7	0.003	24	41	58.5	0.0020
	Placebo	15	41	36.6	--	9	41	21.9	--	10	41	24.4	--
	Biologic-Experienced (Population Not Studied)												
Kobayashi et al. (2016) IFX	**Week 8**												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	57	104	54.8	0.005	21	104	20.2	0.054	48	104	46.2	0.0060
	Placebo	37	104	35.6	--	11	104	10.6	--	29	104	27.9	--
	Biologic-Experienced (Population Not Studied)												
NCT01551290 IFX	**Week 8**												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	32	50	64.0	0.0021	11	50	22.0	0.1233	17	50	34.0	0.0451
	Placebo	16	49	33.0	--	5	49	10.0	--	8	49	16.0	--
	Biologic-Experienced (Population Not Studied)												

Induction Phase (Weeks 6-10)													
Trial	Arm	Response				Remission							
		n	N	%	p-value	n	N	%	p-value	n	N	%	p-value
ULTRA 1 ADA	**Week 8**												
	Overall – Biologic-Naïve												
	ADA 80/40 mg	67	130	51.5	NS	13	130	10	NS	49	130	37.7	NR
	ADA 160/80 mg	71	130	54.6	NS	24	130	18.5	0.031	61	130	46.9	NR
	Placebo	58	130	44.6	--	12	130	9.2	--	54	130	41.5	NR
	Biologic-Experienced (Population Not Studied)												
ULTRA 2 ADA	**Week 8**												
	Overall												
	ADA 160/80 mg	125	248	50.4	<0.005	41	248	16.5	< 0.05	102	248	41.1	<0.05
	PBO	85	246	34.6	--	23	246	9.3	--	78	246	31.7	--
	Biologic-Naïve												
	ADA 160/80 mg	89	150	59.3	<0.001	32	150	21.3	0.017	74	150	49.3	0.014
	PBO	56	145	38.6	--	16	145	11	--	51	145	35.2	--
	Biologic-Experienced												
	ADA 160/80 mg	36	98	36.7	0.228	9	98	9.2	0.559	28	98	28.6	0.772
	PBO	29	101	28.7	--	7	101	6.9	--	27	101	26.7	--
Suzuki et al. (2014) ADA	**Week 8**												
	Overall – Biologic-Naïve												
	ADA 80/40 mg	37	87	43	NS	12	87	14	NS	34	87	39	NS
	ADA 160/80 mg	45	90	50	0.044	9	90	10	NS	40	90	44	0.045
	PBO	34	96	35	--	11	96	11	--	29	96	30	--
	Biologic-Experienced (Population Not Studied)												
GEMINI I VEDO	**Week 6**												
	Overall												
	VEDO 300 mg	106	225	47.1	<0.001	38	225	16.9	0.001	92	225	40.9	0.001
	Placebo	38	149	25.5	--	8	149	5.4	--	37	149	24.8	--
	Biologic-Naïve												
	VEDO 300 mg	69	130	53.1	NR	30	130	23.1	NR	64	130	49.2	NR
	Placebo	20	76	26.3	NR	5	76	6.6	NR	19	76	25	NR
	Biologic-Experienced												
	VEDO 300 mg	32	82	39	NR	8	82	9.8	NR	25	82	30.5	NR
	Placebo	13	63	20.6	NR	2	63	3.2	NR	13	63	20.6	NR

Induction Phase (Weeks 6-10)													
Trial	Arm	Response				Remission							
		n	N	%	p-value	n	N	%	p-value	n	N	%	p-value
Motoya et al. (2019) VEDO	**Week 10**												
	Overall												
	VEDO 300 mg	65	164	39.6	0.2722	30	164	18.3	0.198	60	164	36.6	0.3168
	Placebo	27	82	32.9	--	10	82	12.2	--	25	82	30.5	--
	Biologic-Naïve												
	VEDO 300 mg	42	79	53.2	NR	22	79	27.8	NR	38	79	48.1	NR
	Placebo	15	41	36.6	NR	6	41	14.6	NR	13	41	31.7	NR
	Biologic-Experienced												
	VEDO 300 mg	23	85	27.1	NR	8	85	9.4	NR	22	85	25.9	NR
	Placebo	12	41	29.3	NR	4	41	9.8	NR	12	41	29.3	NR
VARSITY VEDO vs. ADA	**Week 6**												
	Overall												
	VEDO 300 mg	263	383	68.7	NR	154	383	40.2	NR	NR	NR	NR	NR
	ADA 40 mg	232	386	60.1	NR	124	386	32.1	NR	NR	NR	NR	NR
	Biologic-Naïve												
	VEDO 300 mg	NR	NR	70.1	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADA 40 mg	NR	NR	49.5	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Biologic-Experienced												
	VEDO 300 mg	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADA 40 mg	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
EARNEST* VEDO	**Week 14**												
	Overall												
	VEDO 300 mg	32	51	63	NR	16	51	31	0.01	NR	NR	NR	NR
	Placebo	17	51	33	NR	5	51	10	--	NR	NR	NR	NR
	Biologic-Naïve												
	VEDO 300 mg	NR	NR	NR	NR	5	18	27.8	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	2	20	10	NR	NR	NR	NR	NR
	Biologic-Experienced												
	VEDO 300 mg	NR	NR	NR	NR	11	33	33.3	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	3	31	9.7	NR	NR	NR	NR	NR
UNIFI UST	**Week 8**												
	Overall												

Induction Phase (Weeks 6-10)													
Trial	**Arm**	**Response**				**Remission**							
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	UST 6 mg/kg	199	322	61.8	<0.001	50	322	15.5	<0.001	87	322	27	<0.001
	Placebo	100	319	31.3	--	17	319	5.3	--	44	319	13.8	--
	Biologic-Naïve												
	UST 6 mg/kg	98	147	66.7	NR	27	147	18/4	NR	49	147	33.3	NR
	Placebo	54	151	35.8	NR	15	151	9.9	NR	32	151	21.2	NR
	Biologic-Experienced												
	UST 6 mg/kg	95	166	57.2	NR	21	166	12.7	NR	35	166	21.1	NR
	Placebo	44	161	27.3	NR	2	161	1.2	NR	11.0	161.0	6.8	NR
EFFICACI VEDO vs. IFX	**Week 14**												
	Overall – Biologic-Experienced												
	VEDO 300 mg	46	78	59	0.27	27	78	34.6	0.033	36	77	46.8	0.027
	IFX 5 mg/kg	36	72	50	--	14	73	19.2	--	21	72	29.2	--
	Biologic-Naïve (Population Not Studied)												
Naganuma et al. (2025) VEDO vs. IFX vs. UST	**Week 12**												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	16	33	48.5	--	*12*	33	36.4	0.5276 vs. UST 0.7297 vs. VED0	NR	NR	NR	NR
	VEDO 300 mg	20	34	58.8	0.397	*11*	34	32.4	--	NR	NR	NR	NR
	UST 6 mg/kg	22	30	73.3	0.047	*13*	30	43.3	0.3665 vs. VEDO	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)												

ADA: adalimumab, IFX: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, NS: not significant, UST: ustekinumab, VEDO: vedolizumab

*Modified Pouchitis Disease Activity Index defined response and remission.

Table D3.4. Response and Remission in the Maintenance Phase

Maintenance Phase (Weeks 30-60)																
Trial	**Arm**	**Response**				**Sustained Response†**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
ACT 1 IFX	**Week 54**																
	Overall – Biologic-Naïve																
	IFX 5 mg/kg	55	121	45.5	<0.001	47	121	38.8	<0.001	42	121	34.7	0.001	24	121	19.8	0.002
	Placebo	54	122	44.3	<0.001	45	122	36.9	<0.001	42	122	34.4	0.001	25	122	20.5	0.002
	Biologic-Experienced (Population Not Studied)																
ACT 2 IFX	**Week 30**																
	Overall – Biologic-Naïve																
	IFX 5 mg/kg	57	121	47.1	<0.001	50	121	41.3	<0.001	31	121	25.6	0.003	18	121	14.9	<0.001
	Placebo	32	123	26	--	19	123	15.4	--	13	123	10.6	--	3	123	2.4	--
	Biologic-Experienced (Population Not Studied)																
Jiang et al. (2015) IFX	**Week 30**																
	Overall – Biologic-Naïve																
	IFX 5 mg/kg	27	41	65.8	0.001	NR	NR	NR	NR	21	41	51.2	0.012	NR	NR	NR	NR
	Placebo	11	41	26.8	--	NR	NR	NR	NR	10	41	24.4	--	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)																
Kobayashi et al. (2016) IFX	**Week 30**																
	Overall – Biologic-Naive																
	IFX 5 mg/kg	48	104	46.2	0.033	NR	NR	NR	NR	22	104	21.2	0.373	NR	NR	NR	NR
	Placebo	33	104	31.7	--	NR	NR	NR	NR	17	104	16.3	--	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)																
NCT01551290 IFX	**Week 26**																
	Overall – Biologic-Naïve																
	IFX 5 mg/kg	29	50	58.0	0.6638	27	50	54.0	0.0032	14	50	28.0	0.0281	7	50	14	0.0926
	Placebo	26	49	53.0	--	12	49	24.0	--	5	49	10.2	--	2	49	4	--
	Biologic-Experienced (Population Not Studied)																
LIBERTY-UC IFX	**Week 54**																
	Overall																

Maintenance Phase (Weeks 30-60)																	
Trial	**Arm**	**Response**				**Sustained Response†**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	IFX 120 mg SC	158	294	53.7	NR	NR	NR	NR	NR	127	294	43.2	NR	NR	NR	NR	NR
	Placebo	45	144	31.3	NR	NR	NR	NR	NR	30	144	20.8	NR	NR	NR	NR	NR
	Biologic-Naïve																
	IFX 120 mg SC	146	265	55.1	NR	NR	NR	NR	NR	118	265	44.5	NR	NR	NR	NR	NR
	Placebo	43	131	32.8	NR	NR	NR	NR	NR	28	131	21.4	NR	NR	NR	NR	NR
	Biologic-Experienced																
	IFX 120 mg SC	12	29	41.4	NR	NR	NR	NR	NR	9	29	31	NR	NR	NR	NR	NR
	Placebo	2	13	15.4	NR	NR	NR	NR	NR	2	13	15.4	NR	NR	NR	NR	NR
ULTRA 1 OLE[121] **ADA**	**Week 52**																
	Overall – Biologic-Experienced																
	ADA 160/80 mg	245	575	42.6	NR	170	575	59.9	NR	139	575	24.2	NR	107	575	37.7	NR
	Biologic-Naïve (Population Not Studied)																
ULTRA 2 ADA	**Week 52**																
	Overall																
	ADA 40 mg	75	248	30.2	< 0.05	59	248	23.8	<0.001	43	248	17.3	<0.005	21	248	8.5	0.047
	Placebo	45	246	18.3	--	30	246	12.2	--	21	246	8.5	--	10	246	4.1	--
	Biologic-Naïve																
	ADA 40 mg	55	150	36.7	0.019	44	150	29.3	0.009	33	150	22.0	0.029	16	150	10.7	0.169
	Placebo	35	145	24.1	--	24	145	16.6	--	18	145	12.4	--	9	145	6.2	--
	Biologic-Experienced																
	ADA 40 mg	20	98	20.4	0.038	15	98	15.3	0.032	10	98	10.2	0.039	5	98	5.1	0.115
	Placebo	10	101	9.9	--	6	101	5.9	--	3	101	3.0	--	1	101	1.0	--
Suzuki et al. (2014) ADA	**Week 52**																
	Overall – Biologic-Naïve																
	ADA 40 mg	55	177	31	0.021	50	82	61	NR	41	177	23	0.001	38	82	46	NR
	Placebo	17	96	18	--	NR	NR	NR	NR	7	96	7	--	NR	NR	NR	NR
	Biologic-Naïve (Population Not Studied)																
Visible I VEDO	**Week 52**																
	Overall																

Maintenance Phase (Weeks 30-60)																	
Trial	**Arm**	**Response**				**Sustained Response†**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	VEDO 108 mg SC	68	106	64.2	<0.001	68	106	64.2	<0.001	49	106	46.2	<0.001	16	106	15.1	0.076
	VEDO 300 mg IV	39	54	72.2	NR	39	54	72.2	NR	23	54	42.6	NR	10	54	16.7	NR
	Placebo	17	56	28.6	--	17	56	28.6	--	8	56	14.3	--	3	56	5.4	--
	Biologic-Naïve																
	VEDO 108 mg SC	NR	NR	NR	NR	NR	NR	NR	NR	36	67	53.7	<0.001	NR	NR	NR	NR
	VEDO 300 mg IV	NR	NR	NR	NR	NR	NR	NR	NR	17	32	53.1	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	7	37	18.9	--	NR	NR	NR	NR
	Biologic-Experienced																
	VEDO 108 mg SC	NR	NR	NR	NR	NR	NR	NR	NR	13	39	33.3	0.023	NR	NR	NR	NR
	VEDO 300 mg IV	NR	NR	NR	NR	NR	NR	NR	NR	6	22	27.3	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	1	19	5.3	--	NR	NR	NR	NR
GEMINI I VEDO	**Week 52**																
	Overall																
	VEDO 300 mg q4w	65	125	52	<0.001	65	125	52	<0.001	56	125	44.8	<0.001	30	125	24	0.001
	VEDO 300 mg q8w	69	122	56.6	<0.001	69	122	56.6	<0.001	51	122	41.8	<0.001	25	122	20.5	0.008
	Placebo	30	126	23.8	--	30	126	23.8	--	20	126	15.9	--	11	126	8.7	--
	Biologic-Naïve																
	VEDO 300 mg q4w	41	73	56.2	NR	41	73	56.2	NR	35	73	47.9	NR	21	73	28.8	NR
	VEDO 300 mg q8w	47	72	65.3	NR	47	72	65.3	NR	33	72	45.8	NR	16	72	22.2	NR
	Placebo	21	79	26.6	NR	21	79	26.6	NR	15	79	19.0	NR	10	79	12.7	NR
	Biologic-Experienced																
	VEDO 300 mg q4w	17	40	42.5	NR	17	40	42.5	NR	14	40	35.0	NR	5	40	12.5	NR

Maintenance Phase (Weeks 30-60)																	
Trial	**Arm**	**Response**				**Sustained Response†**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	VEDO 300 mg q8w	20	43	46.5	NR	20	43	46.5	NR	16	43	37.2	NR	9	43	20.9	NR
	Placebo	6	38	15.8	NR	6	38	15.8	NR	2	38	5.3	NR	1	38	2.6	NR
Motoya et al. (2019) VEDO	**Week 60**																
	Overall																
	VEDO 300 mg	27	41	65.9	0.0067	27	41	65.9	0.0067	23	41	56.1	0.021	11	41	26.8	0.209
	Placebo	15	42	35.7	--	15	42	35.7	--	13	42	31	--	7	42	16.7	--
	Biologic-Naïve																
	VEDO 300 mg	16	24	66.7	NR	16	24	66.7	NR	13	24	54.2	NR	8	24	33.3	NR
	Placebo	10	28	35.7	NR	10	28	35.7	NR	10	28	35.7	NR	6	28	21.4	NR
	Biologic-Experienced																
	VEDO 300 mg	11	17	64.7	NR	11	17	64.7	NR	10	17	58.8	NR	3	17	17.6	NR
	Placebo	5	14	35.7	NR	5	14	35.7	NR	3	14	21.4	NR	1	14	7.1	NR
VARSITY VEDO vs. ADA	**Week 52**																
	Overall																
	VEDO 300 mg	211	383	55.1	NR	NR	NR	NR	NR	120	383	31.3	NR	70	383	18.3	NR
	ADA 40 mg	166	386	43.0	NR	NR	NR	NR	NR	87	386	22.5	NR	46	386	11.9	NR
	Biologic-Naïve																
	VEDO 300 mg	NR	NR	NR	NR	NR	NR	NR	NR	104	304	34.2	NR	NR	NR	NR	NR
	ADA 40 mg	NR	NR	NR	NR	NR	NR	NR	NR	74	305	24.3	NR	NR	NR	NR	NR
	Biologic-Experienced																
	VEDO 300 mg	NR	NR	NR	NR	NR	NR	NR	NR	16	79	20.3	NR	NR	NR	NR	NR
	ADA 40 mg	NR	NR	NR	NR	NR	NR	NR	NR	13	81	16.0	NR	NR	NR	NR	NR
EARNEST* VEDO	**Week 34**																
	Overall																
	VEDO 300 mg	26	51	51	NR	NR	NR	NR	NR	18	51	35	NR	NR	NR	NR	NR

Maintenance Phase (Weeks 30-60)																	
Trial	**Arm**	**Response**				**Sustained Response†**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	Placebo	15	51	29	NR	NR	NR	NR	NR	9	51	18	NR	NR	NR	NR	NR
	Biologic-Naïve																
	VEDO 300 mg	NR	NR	NR	NR	NR	NR	NR	NR	6	18	33.3	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	5	20	25	NR	NR	NR	NR	NR
	Biologic-Experienced																
	VEDO 300 mg	NR	NR	NR	NR	NR	NR	NR	NR	12	33	36.4	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	4	31	12.9	NR	NR	NR	NR	NR
UNIFI UST	**Week 52**																
	Overall																
	UST 90 mg q12w	NR	NR	NR	NR	117	172	68	<0.001	66	172	38.4	0.002	NR	40	65	NR
	UST 90 mg q8w	NR	NR	NR	NR	125	176	71	<0.001	77	176	43.8	<0.001	NR	38	58	NR
	Placebo	NR	NR	NR	NR	78	175	44.6	ref	42	175	24	ref	NR	45	38	NR
	Biologic-Naïve																
	UST 90 mg q12w	73	102	76.8	NR	73	95	76.8	NR	45	95	47.4	NR	21	30	70.0	NR
	UST 90 mg q8w	61	85	77.2	NR	61	79	77.2	NR	40	79	50.6	NR	12	16	75.0	NR
	Placebo	44	87	52.4	NR	44	84	52.4	NR	27	84	32.1	NR	9	25	36.0	NR
	Biologic-Experienced																
	UST 90 mg q12w	39	70	55.7	0.008	39	70	55.7	0.008	16	70	22.9	0.044	3	8	37.5	1
	UST 90 mg q8w	59	91	64.8	<0.001	59	91	64.8	<0.001	36	91	39.6	<0.001	10	20	50.0	0.751
	Placebo	34	88	38.6	--	34	88	38.6	--	15	88	17.0	--	8	20	40.0	--

ADA: adalimumab, IFX: infliximab, IV: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, NS: not significant, OLE: open-label extension, q4w: every 4 weeks, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

*Modified Pouchitis Disease Activity Index defined response and remission.

†Sustained response in treat-through trials is defined as having response at end of induction and end of maintenance. Note that for re-randomized trials, the rates of response are among induction responders, so "response" and "sustained response" rates in this table are equivalent.

Table D3.5. Endoscopic Improvement and Corticosteroid-Free Remission in Maintenance Phase

Maintenance Phase (Weeks 30-60)									
Trial	**Arm**	**Endoscopic Improvement**				**Corticosteroid-Free Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
ACT 1 **IFX**	**Week 54**								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	55	121	45.5	<0.001	18	70	25.7	0.0060
	Placebo	22	121	18.2	--	7	79	8.9	--
	Biologic-Experienced (Population Not Studied)								
ACT 2 **IFX**	**Week 30**								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	56	121	46.3	0.009	11	60	18.3	0.010
	Placebo	37	123	30.1	--	2	60	3.3	--
	Biologic-Experienced (Population Not Studied)								
Jiang et al. (2015) **IFX**	**Week 30**								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	22	41	53.7	0.003	NR	NR	NR	22
	Placebo	9	41	21.9	--	NR	NR	NR	9
	Biologic-Experienced (Population Not Studied)								
Kobayashi et al. (2016) **IFX**	**Week 30**								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	43	104	41.3	0.057	NR	NR	NR	43
	Placebo	30	104	28.8		NR	NR	NR	30
	Biologic-Experienced (Population Not Studied)								
NCT01551290 **IFX**	**Week 26**								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	20	50	40.0	0.1781	5	30	17.0	0.0428
	Placebo	13	49	27.0	--	1	39	3.0	--
	Biologic-Experienced (Population Not Studied)								
LIBERTY-UC **IFX**	**Week 54**								
	Overall								
	IFX 120 mg SC	129	294	43.9	<0.0001	108	294	36.7	NR
	Placebo	32	144	22.2	--	26	144	18	NR
	Biologic-Naïve								
	IFX 120 mg SC	NR	NR	NR	NR	39	107	36.4	NR

Maintenance Phase (Weeks 30-60)									
Trial	**Arm**	**Endoscopic Improvement**				**Corticosteroid-Free Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	Placebo	NR	NR	NR	NR	10	56	17.9	NR
	Biologic-Experienced								
	IFX 120 mg SC	NR	NR	NR	NR	5	13	38.5	NR
	Placebo	NR	NR	NR	NR	1	5	20	NR
ULTRA 1 OLE ADA	**Week 52**								
	Overall – Biologic-Experienced								
	ADA 160/80 mg	106	575	18.4	NR	NR	NR	NR	NR
	Biologic-Naïve (Population Not Studied)								
ULTRA 2 ADA	**Week 52**								
	Overall								
	ADA 40 mg	71	248	25	<0.05	20	248	13.3	0.035
	Placebo	38	246	15.4	--	8	246	5.7	--
	Biologic-Naïve								
	ADA 40 mg	47	150	31.3	0.02	15	248	13.6	0.0960
	Placebo	28	145	19.3	--	5	246	6.2	--
	Biologic-Experienced								
	ADA 40 mg	15	98	15.3	0.25	5	98	12.5	0.263
	Placebo	10	101	9.9	--	3	101	5.1	--
Suzuki et al. (2014) ADA	Week 52								
	Overall – Biologic-Naïve								
	ADA 40 mg	51	177	29	0.0200	17	177	14.2	NR
	Placebo	15	96	16	--	4	96	6.9	NR
	Biologic-Experienced (Population Not Studied)								
VISIBLE I VEDO	**Week 52**								
	Overall								
	VEDO 108 mg SC	60	106	56.6	<0.001	31	106	28.9	0.067
	VEDO 300 mg IV	29	54	53.7	NR	6	21	28.6	NR
	PBO	12	56	21.4	--	2	24	8.3	--
	Stratified Biologic-Naïve and Experienced Data Not Reported								
GEMINI I VEDO	**Week 52**								
	Overall								
	VEDO 300 mg q4w	70	125	56	<0.001	33	73	45.2	<0.001
	VEDO 300 mg q8w	63	122	51.6	<0.001	22	70	31.4	0.0100

Maintenance Phase (Weeks 30-60)									
Trial	**Arm**	**Endoscopic Improvement**				**Corticosteroid-Free Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	Placebo	25	126	19.8	--	10	72	13.9	--
	Biologic-Naïve								
	VEDO 300 mg q4w	44	73	60.3	NR	25	44	52.3	NR
	VEDO 300 mg q8w	43	72	59.7	NR	14	39	35.9	NR
	Placebo	19	79	21.1	NR	8	43	18.6	NR
	Biologic-Experienced								
	VEDO 300 mg q4w	19	40	47.5	NR	6	19	31.6	NR
	VEDO 300 mg q8w	18	43	41.9	NR	6	26	23.1	NR
	Placebo	3	381	7.9	NR	1	23	4.3	NR
GEMINI I[122] (Loftus 2020) **VEDO**	***Week 52***								
	Overall								
	VEDO 300 mg q4w	NR	NR	NR	NR	32	313	10.2	NR
	VEDO 300 mg q8w	NR	NR	NR	NR	5	67	7.5	NR
	Placebo	NR	NR	NR	NR	1	74	1.4	NR
	Biologic-Naïve								
	VEDO 300 mg q4w	NR	NR	NR	NR	25	154	16.2	NR
	VEDO 300 mg q8w	NR	NR	NR	NR	4	40	10	NR
	Placebo	NR	NR	NR	NR	0	41	0	NR
	Biologic-Experienced								
	VEDO 300 mg q4w	NR	NR	NR	NR	7	129	5.4	NR
	VEDO 300 mg q8w	NR	NR	NR	NR	0	21	0	NR
	Placebo	NR	NR	NR	NR	1	29	3.4	NR
Motoya et al. (2019) **VEDO**	**Week 60**								
	Overall								
	VEDO 300 mg	26	41	63.4	0.0060	6	41	46.2	0.1571
	Placebo	14	42	33.3	--	3	42	20	--
	Biologic-Naïve								
	VEDO 300 mg	15	24	62.5	NR	4	24	44.4	NR
	Placebo	10	28	35.7	NR	2	28	22.2	NR
	Biologic-Experienced								
	VEDO 300 mg	11	17	64.7	NR	2	17	50	NR
	Placebo	4	14	28.6	NR	1	14	16.7	NR
VARSITY	**Week 52**								

Maintenance Phase (Weeks 30-60)									
Trial	**Arm**	**Endoscopic Improvement**				**Corticosteroid-Free Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
VEDO vs. ADA	***Overall***								
	VEDO 300 mg	152	383	39.7	NR	14	383	12.6	NR
	ADA 40 mg	107	386	27.7	NR	26	386	21.8	NR
	Biologic-Naïve								
	VEDO 300 mg	131	304	43.1	NR	13	87	14.9	NR
	ADA 40 mg	90	305	29.5	NR	20	92	21.7	NR
	Biologic-Experienced								
	VEDO 300 mg	21	79	26.6	NR	1	24	4.2	NR
	ADA 40 mg	17	81	21	NR	6	27	22.2	NR
UNIFI UST	**Week 44**								
	Overall								
	UST 90 mg q12w	75	172	43.6	0.0020	65	172	37.8	0.0020
	UST 90 mg q8w	90	176	51.1	<0.001	74	176	42	<0.001
	Placebo	50	175	28.6	--	41	175	23.4	--
	Biologic-Naïve								
	UST 90 mg q12w	52	95	54.7	NR	49	102	48	0.0280
	UST 90 mg q8w	46	79	58.2	NR	40	85	47.1	0.0340
	Placebo	30	84	35.7	NR	27	87	31	--
	Biologic-Experienced								
	UST 90 mg q12w	18	70.0	25.7	NR	16	70	22.9	0.0260
	UST 90 mg q8w	41	91.0	45.1	NR	34	91	37.4	<0.001
	Placebo	20.0	88.0	22.7	NR	14	88	15.9	ref

ADA: adalimumab, IFX: infliximab, IV: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, NS: not significant, OLE: open-label extension, q4w: every 4 weeks, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

Table D3.6. IBDQ and EQ-5D outcomes in Induction Phase

Induction Phase (Weeks 6-10)															
Trial	**Arm**	**IBDQ Score**					**IBDQ Response/ Remission**				**EQ-5D (Visual Analog Scale)**				
		Data Type	**Value**	**Data Type**	**Value**	**p-value**	**n**	**N**	**%**	**p-value**	**Data Type**	**Value**	**Data Type**	**Value**	**p-value**
ACT 1 IFX	**Week 8**														
	Overall – Biologic-Naïve														
	IFX 5 mg/kg	Mean	42.04	95% CI:	35.4-48.0	<0.05	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	Mean	20.9	95% CI:	16.0-25.8	--	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)														
ACT 2 IFX	**Week 8**														
	Overall – Biologic-Naïve														
	IFX 5 mg/kg	Mean	38.9	95% CI:	31.9-44.8	<0.05	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	Mean	19.9	95% CI:	15.0-24.8	-	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)														
GEMINI I VEDO	**Week 6**														
	Overall														
	VEDO 300 mg	NR	NR	NR	NR	NR	65	225	28.62	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	21	149	13.48	NR	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported														
EARNEST VEDO	**Week 14**														
	Overall														
	VEDO 300 mg	CFB	21.1	SD	29	NR	20	51	39	NR	NR	NR	NR	NR	NR
	Placebo	CFB	16.7	SD	27	NR	16	51	31	NR	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported														
UNIFI UST	**Week 8**														
	Overall														

Induction Phase (Weeks 6-10)															
Trial	Arm	IBDQ Score					IBDQ Response/ Remission				EQ-5D (Visual Analog Scale)				
		Data Type	Value	Data Type	Value	p-value	n	N	%	p-value	Data Type	Value	Data Type	Value	p-value
	UST 6 mg/kg	Mean	161.9	SD	35.64	--	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	Mean	143.5	SD	39.96	--	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported														

ADA: adalimumab, CFB: change from baseline, CI: confidence interval, IBDQ: Inflammatory Bowel Disease Questionnaire, IFX: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, SD: standard deviation, UST: ustekinumab, VEDO: vedolizumab

Table D3.7. IBDQ and EQ-5D Outcomes in Maintenance Phase

Induction Phase (Weeks 6-10)															
Trial	Arm	IBDQ Score					IBDQ Response/ Remission				EQ-5D (Visual Analog Scale)				
		Data Type	Value	Data Type	Value	p-value	n	N	%	p-value	Data Type	Value	Data Type	Value	p-value
ACT 1 IFX	**Week 8**														
	Overall – Biologic-Naïve														
	IFX 5 mg/kg	Mean	32.8	95% CI:	25.8-38.8	<0.05	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	Mean	12.8	95% CI:	6.8-17.9	--	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)														
ACT 2 IFX	**Week 8**														
	Overall – Biologic-Naïve														
	IFX 5 mg/kg	Mean	31.9	95% CI:	24.9-37.8	<0.05	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	Mean	17.9	95% CI:	11.8-22.8	--	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)														
ULTRA 2 ADA	**Week 52**														
	Overall														
	ADA 40 mg	NR	NR	NR	NR	NR	65	248	26.2	0.0070	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	40	246	16.3	--	NR	NR	NR	NR	NR
	Biologic-Naïve														
	ADA 40 mg	NR	NR	NR	NR	NR	48	150	32	0.0390	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	31	145	21.4	--	NR	NR	NR	NR	NR

	Biologic-Experienced														
	ADA 40 mg	NR	NR	NR	NR	NR	17	98	17.3	0.0780	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	9	101	8.9	--	NR	NR	NR	NR	NR
Suzuki et al. (2014) ADA	**Week 52**														
	Overall – Biologic-Naïve														
	ADA 40 mg	NR	NR	NR	NR	NR	45	177	25.4	<0.01	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	12	96	12.5	--	NR	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)														
VISIBILE I VEDO	**Week 52**														
	Overall														
	VEDO 108 mg SC	LS Mean	43.9	95% CI:	30.6-57.1	<0.001	NR	NR	NR	NR	LS Mean	17.6	95% CI:	11-24.3	<0.001
	VEDO 300 mg IV	LS Mean	37.1	95% CI:	21.9-52.4	<0.001	NR	NR	NR	NR	LS Mean	13.1	95% CI:	5.5-20.8	0.0010
	Placebo	NR	NR	NR	NR	--	NR	NR	NR	NR	NR	NR	NR	NR	--
	Stratified Biologic-Naïve and Experienced Data Not Reported														
GEMINI I VEDO	**Week 52**														
	Overall														
	VEDO 300 mg q4w	Mean	49	SE	3.3	NR	NR	NR	NR	NR	Mean change	19.4	SE	1.7	NR
	VEDO 300 mg q8w	Mean	48.4	SE	3.4	NR	NR	NR	NR	NR	Mean change	19	SE	1.7	NR
	Placebo	Mean	27.3	SE	3.3	NR	NR	NR	NR	NR	Mean change	9.7	SE	1.7	NR
	Biologic-Naïve														
	VEDO 300 mg q4w	Mean	25.8	95% CI:	14.7-36.9	NR	NR	NR	NR	NR	Mean change	11.1	95% CI:	5.5-16.7	NR
	VEDO 300 mg q8w	Mean	25.9	95% CI:	14.6-37.3	NR	NR	NR	NR	NR	Mean change	10.6	95% CI:	4.9-16.3	NR
	Placebo	--	--	--	--	NR	NR	NR	NR	NR	--	--	--	--	NR
	Biologic-Experienced														
	VEDO 300 mg q4w	Mean	13.4	95% CI:	-3.4-30.2	NR	NR	NR	NR	NR	Mean change	6.9	95% CI:	-2.0-15.7	NR
	VEDO 300 mg q8w	Mean	14.1	95% CI:	-2.5-30.5	NR	NR	NR	NR	NR	Mean change	6.8	95% CI:	-1.8-15.5	NR
	Placebo	--	--	--	--	NR	NR	NR	NR	NR	--	--	--	--	NR

VARSITY VEDO vs. ADA	**Week 52**														
	Overall														
	VEDO 300 mg	CFB	66.1	NR	NR	NR	192	383	50.1	NR	NR	NR	NR	NR	NR
	ADA 40 mg	CFB	60.4	NR	NR	NR	156	386	40.4	NR	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported														
EARNEST VEDO	**Week 34**														
	Overall														
	VEDO 300 mg	CFB	33.1	SD	34.4	NR	22	51	43	NR	NR	NR	NR	NR	NR
	Placebo	CFB	23.1	SD	21.6	NR	10	51	20	NR	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported														
UNIFI UST	**Week 44**														
	Overall														
	UST 90 mg q12w	Mean	172.3	SD	40.97	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	UST 90 mg q8w	Mean	178.2	SD	32.71	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	Mean	159.3	SD	40.67	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported														

ADA: adalimumab, CFB: change from baseline, CI: confidence interval, IBDQ: Inflammatory Bowel Disease Questionnaire, IFX: infliximab, IV: intravenous, LS: least squares, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, q4w: every 4 weeks, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, SD: standard deviation, SE: standard error, UST: ustekinumab, VEDO: vedolizumab

Table D3.8. Additional Outcomes: Partial Mayo Scores and Change in CRP Concentration in Induction Phase

Induction Phase (Weeks 6-10)								
Trial	**Arm**	**Partial Mayo Score**					**Change in CRP Concentration (mg/L)**	
		Data Type	**Value**	**Data Type**	**Value**	**p-value**	**Data Type**	**Value**
ACT 1 IFX	**Week 8**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	Median	2	IQR	1.0-4.0	NR	NR	NR
	Placebo	Median	5	IQR	3.0-6.0	NR	NR	NR
	Biologic-Experienced (Population Not Studied)							
ACT 2 IFX	**Week 8**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	Median	2	IQR	1.0-4.0	NR	NR	NR
	Placebo	Median	5	IQR	3.0-7.0	NR	NR	NR
	Biologic-Experienced (Population Not Studied)							
Jiang et al. (2015) IFX	**Week 8**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	Median	2	IQR	1.0-4.0	NR	NR	NR
	Placebo	Median	5	IQR	3.0-7.0	NR	NR	NR
	Biologic-Experienced (Population Not Studied)							
NCT01551290 IFX	**Week 8**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	NR	NR	NR	NR	NR	Mean CFB, median	-5.0, -1.3
	Placebo	NR	NR	NR	NR	NR	Mean CFB, median	-1.5, -0.2
	Biologic-Experienced (Population Not Studied)							
ULTRA 1 ADA	**Week 8**							
	Overall – Biologic-Naïve							
	ADA 80/40 mg	NR	NR	NR	NR	NR	Median (range)	-0.49 (-115.76, 88.03)
	ADA 160/80 mg	NR	NR	NR	NR	NR	Median (range)	-0.77 (-95.09, 130.41)
	Placebo	NR	NR	NR	NR	NR	Median (range)	-0.09 (-274.79, 88.71)
	Biologic-Experienced (Population Not Studied)							
GEMINI I VEDO	**Week 6**							
	Overall							

Induction Phase (Weeks 6-10)								
Trial	**Arm**	**Partial Mayo Score**					**Change in CRP Concentration (mg/L)**	
		Data Type	**Value**	**Data Type**	**Value**	**p-value**	**Data Type**	**Value**
	VEDO 300 mg	Mean	4.13	SE	0.29	<0.001	NR	NR
	Placebo	Mean	5.23	SE	0.37	--	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported							
UNIFI UST	**Week 8**							
	Overall							
	UST 6 mg/kg	Mean	3.3	SD	2.17	NR	Mean (SD)	6.40 (14.873)
	Placebo	Mean	4.7	SD	2.27	NR	Mean (SD)	10.72 (18.279)
	Stratified Biologic-Naïve and Experienced Data Not Reported							

ADA: adalimumab, CFB: change from baseline, CRP: C-reactive protein, IFX: infliximab, IQR: interquartile range, mg: milligrams, mg/kg: milligram per kilogram, mg/L: milligram per liter, n: number, NR: not reported, SD: standard deviation, UST: ustekinumab, VEDO: vedolizumab

Table D3.9. Additional Outcomes: Partial Mayo Scores and Change in CRP Concentration in Maintenance Phase

Induction Phase (Weeks 6-10)								
Trial	**Arm**	**Partial Mayo Score**					**Change in CRP Concentration (mg/L)**	
		Data Type	**Value**	**Data Type**	**Value**	**p-value**	**Data Type**	**Value**
ACT 1 IFX	**Week 54**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	Median	3	IQR	1.0-6.0	NR	NR	NR
	Placebo	Median	5	IQR	4.0-7.0	NR	NR	NR
	Biologic-Experienced (Population Not Studied)							
ACT 2 IFX	**Week 30**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	Median	4	IQR	1.0-6.0	NR	NR	NR
	Placebo	Median	6	IQR	3.0-7.0	NR	NR	NR
	Biologic-Experienced (Population Not Studied)							
Jiang et al. (2015) IFX	**Week 30**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	Median	3	IQR	1.0-5.0	NR	NR	NR
	Placebo	Median	6	IQR	3.0-7.0	NR	NR	NR
	Biologic-Experienced (Population Not Studied)							
NCT01551290 IFX	**Week 26**							
	Overall – Biologic-Naïve							
	IFX 5 mg/kg	NR	NR	NR	NR	NR	Mean CFB, median	-1.6, -0.6
	Placebo	NR	NR	NR	NR	NR	Mean CFB, median	2.4, 0
	Biologic-Experienced (Population Not Studied)							
VISIBLE I VEDO	**Week 52**							
	Overall – Biologic-Naïve							
	VEDO 108 mg SC	Mean	*1.8*	SD	1.9	NR	NR	NR
	VEDO 300 mg IV	Mean	*1.71*	SD	2.1	NR	NR	NR
	Placebo	Mean	*4.09*	SD	2.5	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported							
GEMINI I VEDO	**Week 52**							
	Overall							
	VEDO 300 mg q4w	Mean	2.61	SD	2.36-2.84	<0.001	NR	NR
	VEDO 300 mg q8w	Mean	2.61	SD	2.36-2.84	<0.001	NR	NR
	Placebo	Mean	4.39	SD	4.14-4.66	NR	NR	NR

Induction Phase (Weeks 6-10)								
Trial	**Arm**	**Partial Mayo Score**					**Change in CRP Concentration (mg/L)**	
		Data Type	**Value**	**Data Type**	**Value**	**p-value**	**Data Type**	**Value**
	Stratified Biologic-Naïve and Experienced Data Not Reported							
VARSITY VEDO vs. ADA	**Week 52**							
	Overall							
	VEDO 300 mg	NR	NR	NR	NR	NR	Mean (SD)	-5.34 (18.35)
	ADA 40 mg	NR	NR	NR	NR	NR	Mean (SD)	-3.91 (17.77)
	Stratified Biologic-Naïve and Experienced Data Not Reported							
UNIFI UST	**Week 44**							
	Overall							
	UST 90 mg q12w	Mean	2.3	SD	2.47	NR	Mean (SD)	4.46 (6.761)
	UST 90 mg q8w	Mean	1.9	SD	2.09	NR	Mean (SD)	4.3 (6.903)
	Placebo	Mean	3.5	SD	2.75	NR	Mean (SD)	6.06 (10.684)
	Stratified Biologic-Naïve and Experienced Data Not Reported							

ADA: adalimumab, CFB: change from baseline, CRP: C-reactive protein, IFX: infliximab, IQR: interquartile range, IV: intravenous, mg: milligrams, mg/kg: milligram per kilogram, mg/L: milligram per liter, n: number, NR: not reported, q4w: every 4 weeks, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, SD: standard deviation, UST: ustekinumab, VEDO: vedolizumab

Note: italicized data was calculated.

Table D3.10. Safety in the Induction Phase

Induction Phase (Weeks 6-10)											
Trial	**Arm**	**N**	**Any AEs**	**Related AEs**	**D/C due to AE**	**Death**	**SAEs**	**Infusion / Injection Site Reaction**	**Infections**	**Serious Infections**	**Malignancy**
Kobayashi et al. (2016) IFX	IFX 5 mg/kg	104	81.7	NR	4.8	NR	8.7	10.6	31.7	1	NR
	Placebo	104	82.7	NR	7.7	NR	12.5	8.7	33.7	1.9	NR
ULTRA 1 ADA	ADA 80/40 mg	130	53.8	NR	6.2	0	3.8	5.4	20	1.5	NR
	ADA 160/80 mg	223	50.2	NR	5.4	0	4	5.8	14.3	0	NR
	Placebo	223	48.4	NR	5.4	0	7.6	3.1	15.7	1.3	NR
Suzuki et al. (2014) ADA	ADA 80/40 mg	87	56.3	16.1	0	NR	2.3	5.7	12.6	0	NR
	ADA 160/80 mg	90	44.4	13.3	6.7	NR	4.4	7.8	18.9	3.3	1.1
	Placebo	96	46.9	10.4	4.2	NR	7.3	2.1	15.6	0	0
GEMINI I VEDO	VEDO 300 mg	225	45	NR	6.7	2.2	3	<1	14	<1	0
	Placebo	149	46	NR	0	0	7	<1	15	2	0
Motoya et al. (2019) VEDO	VEDO 300 mg	164	50	10.4	4.9	0	6.1	3	NR	0.6	0.6
	Placebo	82	52.4	14.6	2.4	0	4.9	2.4	NR	2.4	0
UNIFI UST	UST 6 mg/kg	320	50.6	NR	0.3	0.3	3.4	0.9	15.9	0.3	0
	Placebo	319	48	NR	0.94	0	6.9	1.9	15.4	1.6	0
EFFICACI VEDO vs. IFX	VEDO 300 mg	78	70.51	NR	NR	NR	NR	NR	NR	NR	NR
	IFX 5 mg/kg	73	63.9	NR	NR	NR	NR	NR	NR	NR	NR
Naganuma et al. (2025) IFX vs. VEDO vs. UST	IFX 5 mg/kg	34	32.4	14.7	2.9	0	2.9	2.9	5.9	NR	NR
	VEDO 300 mg	36	36.1	16.7	5.6	0	5.6	0	8.3	NR	NR
	UST 6 mg/kg	34	8.8	5.9	0	0	0	0	0	NR	NR

ADA: adalimumab, AEs: adverse events, D/C: discontinuation, IFX: infliximab, mg: milligrams, mg/kg: milligram per kilogram, N: number, NA: not applicable, NR: not reported, SAEs: serious adverse events, UST: ustekinumab, VEDO: vedolizumab

Note: data presented as percentages.

*In the induction trial, ustekinumab or placebo was administered as a single IV infusion at week zero; therefore, patients could not be discontinued from further administration of ustekinumab or placebo.

Table D3.11. Hepatic and Thrombotic Adverse Events in the Induction Phase

Induction Phase (Weeks 6-10)				
Trial	**Arm**	**N**	**Hepatic**	**Thrombotic**
Suzuki et al. (2014) ADA	ADA 80/40 mg	87	NR	NR
	ADA 160/80 mg	90	0	NR
	Placebo	96	1	NR
Motoya et al. (2019) VEDO	VEDO 300 mg	164	NR	0.6
	Placebo	82	NR	NR
UNIFI UST	UST 6 mg/kg	322	0	NR
	Placebo	319	0.3	NR

ADA: adalimumab, mg: milligrams, mg/kg: milligram per kilogram, N: number, NR: not reported, UST: ustekinumab, VEDO: vedolizumab

Note: data presented as percentages.

Table D3.12. Safety in the Maintenance Phase

Maintenance Phase (Weeks 30-60)											
Trial	**Arm**	**N**	**Any AEs**	**Related AEs**	**D/C due to AE**	**Death**	**SAEs**	**Infusion / Injection Site Reaction**	**Infections**	**Serious Infections**	**Malignancy**
ACT 1 IFX	IFX 5 mg/kg	121	87.6	NR	8.3	NR	21.5	9.9	43.8	2.5	NR
	Placebo	121	85.1	NR	9.1	NR	25.6	10.7	38.8	4.1	NR
ACT 2 IFX	IFX 5 mg/kg	121	81.8	NR	1.7	NR	10.7	11.6	27.3	2.5	NR
	Placebo	123	73.2	NR	9.8	NR	19.5	8.1	23.6	0.8	NR
Jiang et al. (2015) IFX	IFX 5 mg/kg	41	41.5	NR	2.4	NR	7.3	7.3	14.6	2.4	NR
	Placebo	41	39	NR	4.9	NR	9.8	4.9	12.2	0	NR
Kobayashi et al. (2016) IFX	IFX 5 mg/kg	104	96.2	NR	6.7	NR	17.3	15.4	59.6	1	NR
	Placebo	104	90.4	NR	7.7	NR	18.3	10.6	49	1.9	NR
NCT01551290 IFX	IFX 5 mg/kg	50	66.0	16.0	8.0	0	14.0	NR	26.0	0	NR
	Placebo	49	63.3	10.2	4.1	0	8.2	NR	14.3	0	NR
LIBERTY-UC IFX	IFX 120 mg SC	296	67.6	19.3	3.4	0	6.4	NR	28	NR	0.37
	Placebo	140	59.3	15	2.9	0	2.9	NR	25.7	NR	0
ULTRA 2 ADA	ADA 40 mg	257	82.9	39.3	4.7	0	12.1	12.1	45.1	1.6	0.8
	Placebo	260	83.8	33.1	9.6	0	12.3	3.8	39.6	1.9	0
Suzuki et al. (2014) ADA	ADA 40 mg	177	538*	91*	22*	NR	33*	20*	134*	8*	2*
	Placebo	96	237*	34*	6*	NR	14*	4*	70*	2*	0*
VISIBLE I VEDO	VEDO 108 mg SC	106	65.1	26.4	4.7	0	9.4	4.7	19.8	2.12	0
	VEDO 300 mg IV	54	75.9	16.7	3.7	0	13	0	27.8	0	0
	Placebo	56	76.8	17.9	8.9	0	10.7	0	25	0	0
GEMINI I VEDO	VEDO 300 mg q4w	125	81	NR	4.8	NR	9	11	72	2	NR
	VEDO 300 mg q8w	122	82	NR	5.7	NR	8	6	71	2	NR
	Placebo	126	84	NR	11.9	NR	16	2	71	3	NR
Motoya et al. (2019) VEDO	VEDO 300 mg	41	87.8	9.8	2.4	0	9.8	0	NR	2.4	NR
	Placebo	42	78.6	14.3	14.3	0	7.1	0	NR	2.4	NR
EARNEST VEDO	VEDO 300 mg	51	92	24	2	0	6	NR	NR	NR	0
	Placebo	51	86	22	10	0	8	NR	NR	NR	3.9

Maintenance Phase (Weeks 30-60)											
Trial	**Arm**	**N**	**Any AEs**	**Related AEs**	**D/C due to AE**	**Death**	**SAEs**	**Infusion / Injection Site Reaction**	**Infections**	**Serious Infections**	**Malignancy**
VARSITY VEDO vs. ADA	VEDO 300 mg	383	62.7	NR	4.4	0.3	11	NR	23.4	1.6	0.26
	ADA 40 mg	386	69.2	NR	6.5	0	13.7	NR	34.6	2.2	0
UNIFI UST	UST 90 mg q12w	172	69.2	NR	5.2	0	7.6	0.6	33.7	3.5	NR
	UST 90 mg q8w	176	77.3	NR	2.8	0	8.5	2.8	48.9	1.7	1.14
	Placebo	175	78.9	NR	11.4	0	9.7	2.3	46.3	2.3	0.6

ADA: adalimumab, AEs: adverse events, D/C: discontinuation, IFX: infliximab, IV: intravenous, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, q4w: every 4 weeks, q8w: every 8 weeks, q12w: every 12 weeks, SAEs: serious adverse events, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

Note: data are presented as percentages.

*Events.

Table D3.13. Hepatic and Thrombotic Adverse Events in the Maintenance Phase

Maintenance Phase (Weeks 30-60)				
Trial	**Arm**	**N**	**Hepatic**	**Thrombotic**
Suzuki et al. (2014) ADA	ADA 40 mg	177	2.8	NR
	Placebo	96	3.125	NR
VISIBLE I VEDO	VEDO 108 mg SC	160	0.625	NR
	VEDO 300 mg IV			NR
	Placebo	52	0	NR
VARSITY VEDO vs. ADA	VEDO 300 mg	383	NR	0.26
	ADA 40 mg	386	NR	0.26
UNIFI UST	UST 90 mg q12w	172	NR	NR
	UST 90 mg q8w	176	NR	NR
	Placebo	175	0.6	NR

ADA: adalimumab, IV: intravenous, mg: milligrams, mg/kg: milligram per kilogram, N: number, NR: not reported, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

Note: data presented as percentages.

Table D3.14. Adverse Events from Open-Label Extensions and Long-Term Studies

Trial	Arm	Duration	N	AEs	SAEs	≥1 UC-related Hospitalization, Colectomy or Procedure	UC-Related Hospitalization	Colectomy
VISIBLE OLE[43,62]	Any VEDO	≤ 97.9 months	288	69	14	NR	8.3	1
GEMINI LTS	VEDO	≥ 1 year	846	NR	NR	16.8	NR	NR

AEs: adverse events, OLE: open-label extension, LTS: long-term study, N: number, SAEs: serious adverse events, UC: ulcerative colitis, VEDO: vedolizumab

Ulcerative Colitis – RWEs

Table D3.15. Study Design of Included Observational Studies

Study	Design	Location	Population	Comparison
Long et al. (2019)[45]	Retrospective database study	USA	- N=3562 - No biologic therapy in prior 12 months	ADA vs. IFX vs. VEDO
Dubinsky et al. (2018)[46]	Retrospective database study	USA	- N=26505 - TNF-naïve	VEDO vs. TNFs
Bressler et al. (2021)[47]	Multicenter, multi-country retrospective cohort study	USA, Canada, Greece	- N=604 - Biologic naïve	VEDO vs TNFs
Singh et al. (2022)[49]	Retrospective database analysis (medical and pharmacy claims)	USA	- N=5566 - TNF- or VEDO-naïve	VEDO vs. TNFs
Singh et al. (2022)[48]	Retrospective database analysis (medical and pharmacy claims)	USA	- N=5987 - TNF- or VEDO-naïve	VEDO vs. TNFs
Lukin et al. (2022)[50]	Multicenter, retrospective, observational cohort study	North America	- N=722 - Naïve or experienced	VEDO vs. TNFs
Kochhar et al. (2023)[51]	Retrospective cohort study	USA	- N=2141 - Switched to a second-line therapy	VEDO vs. UST

Study	Design	Location	Population	Comparison
Kirchgesner et al. (2022)[52]	Health care claims databases cohort study	USA and France	- N=14654 - Naïve or experienced	VEDO vs. TNFs
Karlqvist et al. (2024)[53]	Nationwide registry study	Sweden	- N=44012 - Naïve or experienced	VEDO vs. TNFs
Farkas et al. (2025)[54]	Multicenter, retrospective study	Europe, Israel, and Canada	- N=683 - Failed first-line anti-TNF	VEDO, UST, TOFA
Dalal et al. (2023)[55]	Retrospective cohort study	USA	- N=805 - Biologic naïve	VEDO, IFX, ADA
Cohen et al. (2020)[56]	Retrospective database study	Global	- N=14042 - Naïve or experienced	VEDO
Koliani-Pace et al. (2019)[57]	Retrospective database study	USA	- N=1566 - Naïve or experienced	VEDO

ADA: adalimumab, IFX: infliximab, N: number, TNF: tumor necrosis factor, TOFA: tofacitinib, USA: United States of America, UST: ustekinumab, VEDO: vedolizumab

Table D3.16. Response and Remission

Trial	Arm	Response				Remission			
		n	N	%	p-value	n	N	%	p-value
Bressler et al. (2021) VEDO vs. Anti-TNFs	**Month 24**								
	Overall – Biologic-Naïve								
	VEDO	*16*	18	88.3	0.64	9	18	65.9	0.09
	Anti-TNF	*34*	39	86.2	--	10	39	48.6	--
	Biologic-Experienced (Population Not Studied)								
Lukin et al. (2022) VEDO vs. IFX vs. Anti-TNFs	**~ Month 12***								
	Overall								
	VEDO	NR	NR	NR	NR	187	453	41.2	NR
	IFX	NR	NR	NR	NR	61	163	37.4	NR
	Anti-TNF	NR	NR	NR	NR	100	266	37.6	NR
	Biologic-Naïve								
	VEDO	NR	NR	NR	NR	74	143	51.7	NR
	Anti-TNF	NR	NR	NR	NR	65	158	41.1	NR
	Biologic-Experienced								
	VEDO	NR	NR	NR	NR	113	310	36.5	NR
	Anti-TNF	NR	NR	NR	NR	35	108	32.4	NR

Trial	Arm	Response				Remission			
		n	N	%	p-value	n	N	%	p-value
Koliani-Pace et al. (2019) VEDO	**Month 12**								
	Overall – VICTORY Consortium								
	VEDO (Era 1)†	NR	NR	NR	NR	*87*	182	48	NR
	VEDO (Era 2)‡	NR	NR	NR	NR	138	255	54	NR
	Biologic-Naïve – VICTORY Consortium								
	VEDO	NR	NR	NR	NR	139	*243*§	57	NR
	Biologic-Experienced – VICTORY Consortium								
	VEDO	NR	NR	NR	NR	93	*194*§	48	NR

Anti-TNFs: Tumor Necrosis Factor Antagonists, IFX: infliximab, n: number, NR: not reported, VEDO: vedolizumab

Note: italicized data indicates data has been calculated.

*Median follow-up of 333 days.

†Era 1 data was collected in May 2014 through June 2015.

‡Era 2 data was collected in July 2015 through June 2017.

§Calculated from the baseline characteristics of the VICTORY consortium cohort.

Table D3.17. Endoscopic Improvement, Corticosteroid-free Remission, and Treatment Persistence

Trial	Arm	N	Endoscopic Improvement		Corticosteroid-free Remission		Treatment Persistence	
			%	p-value	%	p-value	%	p-value
Long et al. (2019) ADA vs. IFX vs. VEDO	**Month 12**							
	Overall – Biologic-Experienced							
	ADA	1291	NR	NR	39.4	NR	NR	NR
	IFX	810	NR	NR	43.9	NR	NR	NR
	VEDO	103	NR	NR	41.4	NR	NR	NR
	Biologic-Naive (Population Not Studied)							
Bressler et al. (2021) VEDO vs. Anti-TNFs	**Month 24**							
	Overall – Biologic-Naïve							
	VEDO	380	86.6	0.66	NR	NR	76.3	<0.01
	Anti-TNF	224	80.6	--	NR	NR	52.4	--
	Biologic-Experienced (Population Not Studied)							
Lukin et al. (2022) VEDO vs. IFX vs. Anti-TNFs	**~Month 12***							
	Overall							
	VEDO	243	NR	NR	29.6	NR	NR	NR
	IFX	103	NR	NR	25.8	NR	NR	NR
	Anti-TNF	97	NR	NR	28.9	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported							
Farkas et al. (2025) VEDO vs. UST	**Month 36**							
	Overall – Biologic-Experienced							
	VEDO	492	NR	NR	NR	NR	37.8	0.05
	UST	94	NR	NR	NR	NR	54.7	--
	Biologic-Naïve (Population Not Studied)							
Dalal et al. (2023) ADA vs. IFX vs. VEDO	**Month 48**							
	Overall – Biologic-Naïve							
	ADA	103	NR	NR	30.1	<0.01	NR	NR
	IFX	87	NR	NR	51.7	<0.01	NR	NR
	VEDO	23	NR	NR	52.2	<0.01	NR	NR
	Biologic-Experienced (Population Not Studied)							
Koliani-Pace et al. (2019) VEDO	**Month 12**							
	Overall – VICTORY Consortium							
	VEDO (Era 1)[†]	252	43	NR	26	NR	NR	NR
	VEDO (Era 2)[‡]		62	NR	33	NR	NR	NR

Trial	Arm	N	Endoscopic Improvement		Corticosteroid-free Remission		Treatment Persistence	
			%	p-value	%	p-value	%	p-value
	Biologic-Naïve							
	VEDO	NR	59	NR	41	NR	NR	NR
	Biologic-Experienced							
	VEDO	NR	47	NR	38	NR	NR	NR

ADA: adalimumab, Anti-TNFs: Tumor Necrosis Factor Antagonists, IFX: infliximab, n: number, NR: not reported, VEDO: vedolizumab

Note: italicized data indicates data has been calculated.

*Median follow-up of 333 days.

†Era 1 data was collected in May 2014 through June 2015.

‡Era 2 data was collected in July 2015 through June 2017.

Table D3.18. Safety in RWEs

Trial	Arm	N	Any AEs	Related AEs	D/C due to AE	Death	SAEs	Serious Infections	Malignancy	Hospitalizations	Surgery
Long et al. (2019) ADA vs. IFX vs. VEDO	**Month 12**										
	ADA	1291	NR	NR	NR	NR	NR	NR	NR	12.9	NR
	IFX	810	NR	NR	NR	NR	NR	NR	NR	18.3	NR
	VEDO	103	NR	NR	NR	NR	NR	NR	NR	9.7	NR
Bressler et al. (2021) VEDO vs. Anti-TNFs	**Month 24**										
	VEDO	376	NR	NR	NR	NR	4.8	1.7	0.53	NR	NR
	Anti-TNF	221	NR	NR	NR	NR	12.5	2.6	0.45	NR	NR
Singh et al. (2022) VEDO vs. Anti-TNFs	**Month 12**										
	VEDO	671	NR	NR	NR	NR	NR	IR: 4.6/100-py	NR	NR	NR
	Anti-TNF	1950	NR	NR	NR	NR	NR	IR: 6.5/100-py	NR	NR	NR
Lukin et al. (2022) VEDO vs. IFX vs. Anti-TNFs	**Month 12**										
	VEDO	453	NR	NR	NR	NR	57.4	4.6	NR	NR	NR
	IFX	163	NR	NR	NR	NR	19	11.7	NR	NR	NR
	Anti-TNFs	266	NR	NR	NR	NR	16.9	10.2	NR	NR	NR
Kochhar et al. (2023) VEDO vs. UST	**Month 24**										
	VEDO	1077	NR	NR	NR	NR	NR	NR	3.3	NR	3
	UST	716	NR	NR	NR	NR	NR	NR	2.3	NR	1.7
Kirchgesner et al. (2022) VEDO vs. Anti-TNFs	**Month 12**										
	VEDO	2066	NR	NR	NR	NR	NR	IR: 18/100-py	NR	NR	NR
	Anti-TNF	5119	NR	NR	NR	NR	NR	IR: 18.4/100-py	NR	NR	NR
Karlqvist et al. (2024) VEDO vs. Anti-TNFs	**Month 12**										
	VEDO	647	NR	NR	NR	NR	NR	IR: 3.74/100-py	NR	NR	NR
	Anti-TNF	647	NR	NR	NR	NR	NR	IR: 3.42/100-py	NR	NR	NR
Dalal et al. (2023)	**Month 48**										
	ADA	180	21	NR	NR	NR	NR	NR	NR	NR	NR

Trial	Arm	N	Any AEs	Related AEs	D/C due to AE	Death	SAEs	Serious Infections	Malignancy	Hospitalizations	Surgery
ADA vs. IFX vs. VEDO	IFX	175	38	NR	NR	NR	NR	NR	NR	NR	NR
	VEDO	76	12	NR	NR	NR	NR	NR	NR	NR	NR
Cohen et al. (2020) VEDO	**Month 48**										
	VEDO	14042	100	NR	Events: 46†	Events: 3580†	NR	Events: 427†	Events: 117†	Events: 83†	Events: 92†
Koliani-Pace et al. (2019) VEDO	**Month 12**										
	VEDO (Era 1)‡	182	NR	NR	NR	NR	NR	NR	NR	14.3	10.7
	VEDO (Era 2)§	255	NR	NR	NR	NR	NR	NR	NR	4.7	6

ADA: adalimumab, AEs: adverse events, Anti-TNFs: Tumor Necrosis Factor Antagonists, D/C: discontinuation, IFX: infliximab, IR: incidence rate, n: number, NR: not reported, py: person-years, SAEs: serious adverse events, VEDO: vedolizumab

*Colectomy.

†Total number of events 34259.

‡Era 1 data was collected in May 2014 through June 2015.

§Era 2 data was collected in July 2015 through June 2017.

Crohn's Disease – RCTs

Table D3.19. Study Design of Included RCTs

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
Infliximab					
LIBERTY-CD[38] MAINT (54 weeks)	Experienced (9%)	- IFX 5 mg/kg IV at weeks 0, 2, and 6 (n=343)	- IFX 120mg SC q2w (n=231) - Placebo SC q2w (n=112)	- CDAI score of 220–450 - SES-CD of >6 points for ileal-colonic CD or >4 points including ulcer score from ≥1 segment for ileal or colonic CD	- Prior treatment with ≥2 biologics, JAK inhibitors, and/or IFX - Previous inadequate response or intolerance to anti-TNFs
Adalimumab					
CLASSIC-I[100] IND (4 weeks)	Naïve (100%)	- ADA 160 mg at week 0 and 80 mg at week 2 (n=76) - Placebo at weeks 0 and 2 (n=74)	--	- CD for ≥4 months - CDAI score of 220–450 - Radiologic or endoscopic diagnosis	- History of malignancy, active TB, listeriosis, or HIV - Had symptomatic obstructive strictures - Underwent surgical bowel resection within 6 months - Previously received IFX or any anti-TNFs
CLASSIC-II[101] MAINT (56 weeks)	Naïve (100%)	--	- ADA 40 mg q2w (n=19) - Placebo (n=18)	- Completed CLASSIC-I	--
Sandborn et al. (2007c)[102] IND (4 weeks)	Experienced (100%)	- ADA 160 mg at week 0 and 80 mg at week 2 (n=159) - Placebo at weeks 0 and 2 (n=166)	--	- CD for ≥4 months -CDAI score of 220–450 - Radiologic or endoscopic presence of CD - Prior intolerance or loss of response to IFX	- Primary nonresponse to IFX - Received IFX or any anti-TNF within the past 8 weeks - History of short bowel syndrome - Had symptomatic stricture, or bowel resection within the past 6 months - Undergone ostomy or ileoanal pouch
Watanabe et al. (2012)[103] IND + MAINT (4/52 weeks)	Naïve (42.2%) Experienced (57.8%)	- ADA 160/80 mg at baseline and week 2 (n=33) - Placebo at	- ADA 40 mg EOW (n=26) - Placebo (n=9)	- CDAI score of 220–450 - Diagnosis of ileal, colonic or ileocolonic CD	- Primary non-response to prior anti-TNFs - Persistent chronic infections or recent infections

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
		baseline and week 2 (n=22)			
Chen et al. (2020)[104] **IND + MAINT (8/18 weeks)**	Naïve (100%)	- ADA 160/80mg (n=102) - Placebo (n=103)	- ADA 40 mg EOW - Placebo	- Biologic naïve - CDAI score of >220– <450 - Elevated hs-CRP (>3mg/l) - Did not improve with conventional therapy of oral CS and/or IMMs	- Had symptomatic obstructive strictures, internal or external fistula - Undergone surgical bowel resection within 6 months
CHARM 2007[105,123] **MAINT (56 weeks)**	Naïve (50.4%) Experienced (49.6%)	--	- ADA 40 mg EOW - Placebo	- CD of ≥4 months - CDAI score of 220–450	- History of UC, symptomatic obstructive disease, or bowel resection within the past 6 months - History of ostomy, extensive small bowel resection, or short bowel syndrome
CHARM Extension[124,125] **MAINT (4 years)**	Naïve (50.4%) Experienced (49.6%)	--	- ADA 40 mg EOW	- All ADA mITT population from CHARM	--
Vedolizumab					
GEMINI II[106,126] **IND + MAINT (6/54 weeks)**	Naïve (38.2%) Experienced (61.8%)	- VEDO 300mg at weeks 0 and 2 (n=220) - Placebo (n=148)	- VEDO 300mg q4w - VEDO 300mg q8w - Placebo	- CD for ≥3 months - CDAI score of 220–450 - No response or unacceptable side effects to anti-TNFs, CSs, or IMMs	- History of a stoma, > 3 small-bowel resections, short-bowel syndrome, extensive colonic resection, intestinal stricture, abdominal abscess, active/latent tuberculosis, or cancer
GEMINI III[107,127] **IND (10 weeks)**	Naïve (24%) Experienced (76%)	- VEDO 300 mg at weeks 0 and 2 (n=209) - Placebo (n=207)	--	- CD with known involvement of the ileum and/or colon - CDAI score of 220–400 - Inadequate response, loss of response, or intolerance to anti-TNFs, IMMs, or CSs	- Previous VEDO, natalizumab, efalizumab, or rituximab exposure
GEMINI LTS[44,119,120] **(510 weeks)**	Naïve (63.3%) Experienced (36.7%)	--	- OL VEDO 300 mg q4w weeks (n=1349)	- Previous treatment in NCT00619489, GEMINI II, or GEMINI III	--

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
Watanabe et al. (2020)[66] IND + MAINT (6/54 weeks)	Naïve (22.9%) Experienced (77.1%)	- VEDO 300 mg IV infusion at weeks 0, 2, and 6 (n=79) - Placebo (n=78)	- VEDO 300 mg (n=12) - Placebo (n=12)	- Ileal, colonic or ileocolonic CD - CDAI score of 220–450 -Treatment failure or intolerance to CSs, IMMs, or anti-TNFs	- Total colectomy, with prior small intestine resections in ≥3 locations
VISIBLE 2[65] MAINT (52 weeks)	Naïve (42.5%) Experienced (57.5%)	--	- VEDO 108 mg SC q2w (n=134) - Placebo (n=275)	- Inadequate response to or intolerance of CSs, IMMs, and/or anti-TNFs - CDAI score of 220–450 - Involvement of the ileum and/or colon	- Abdominal abscess, extensive colonic resection, subtotal or total colectomy - History of ≥3 small bowel resections or diagnosis of short bowel syndrome
VISIBLE OLE[128,129] MAINT (48 weeks)	Naïve (41.6%) Experienced (58.4%)	--	- VEDO 108 mg SC q2w (n=458)	- Previous treatment in VISIBLE 2	--
Ustekinumab					
CERTIFI[108] IND + MAINT (8/36 weeks)	Experienced (100%)	- UST 6 mg/kg (n=131) - Placebo (n=132)	- UST 270 mg SC - Placebo	- Ages +18 - CD for ≥3 months - CDAI score of 220–450 - Primary or secondary nonresponse, or had unacceptable side effects to anti-TNFs	- Undergone bowel resection within 6 months - Had short-bowel syndrome, or a clinically significant stricture that could require surgery or preclude the use of the CDAI
UNITI-1[109] IND (6 weeks)	Experienced (100%)	- UST 6 mg/kg (n=249) - Placebo (n=247)	--	- Ages +18 - CD for ≥3 months - CDAI score of 220–450 - Previous treatment with ≥1 anti-TNFs - Primary or secondary nonresponse, or had unacceptable side effects to anti-TNFs	- Undergone bowel resection within 6 months -Received IFX, ADA, or certolizumab pegol ≤8 weeks before - History of or ongoing chronic or recurrent infectious disease - Previously received a biologic agent targeting IL-12 or IL-23, including UST or briakinumab

Trial (IND/MAINT Timepoints)	Naïve (%) Experienced (%)	Treatment Arms (n)		Inclusion Criteria	Exclusion Criteria
		Induction	Maintenance		
UNITI-2[109] **IND (8 weeks)**	Naïve 68% Experienced 32%	- UST 6 mg/kg (n=209) - Placebo (n=210)	--	- CDAI score of 220-450 - Treatment failure with or unacceptable side effects to IMMs - Could have previously received ≥1 TNF antagonists if no unacceptable side effects and/or primary/ secondary nonresponse to treatment	-Any kind of bowel resection within 6 months - Received IFX, ADA or certolizumab pegol ≤8 weeks before study
IM-UNITI[109] **MAINT (44 weeks)**	Experienced (100%)	--	- UST 90 mg, SC q8w (n=132) - UST 90 mg, SC q12w (n=132) - Placebo (n=133)	- Patients who received UST at start of UNITI-1 or UNITI-2, and completed week 8 visit	- Undergone CD-related surgery - Protocol-specified changes to concomitant medications due to CD (lack of efficacy) since start of UNITI-1 or -2
Head-to-Head					
SEAVUE[110] **MAINT (56 weeks)**	Naïve (100%)	- UST 6 mg/kg IV on day 0, then 90 mg SC once every 8 weeks (n=191) - ADA 160 mg SC on day 0, 80 mg SC at 2 weeks, then 40 mg SC q2w(n=195)		- CDAI of 220–450 - ≥1 ulcer at baseline (SES-CD ≥3 on ileocolonoscopy) - Biologic naïve - No response or intolerance to conventional therapy or were CS dependent	- Confounding CD complications or other comorbidities - Ongoing infection or malignancy - History of recurrent infection or serious opportunistic infection

ADA: adalimumab, CD: Crohn's disease, CDAI: Crohn's Disease Activity Index, cm: centimeter, CSs: corticosteroids, EOW: every other week, HIV: human immunodeficiency virus, hs-CRP: high sensitivity C-reactive protein, IFX: infliximab, IMMs: immunomodulators, IND: induction, IV: intravenous, JAK: Janus kinase, MAINT: maintenance, mg: milligrams, mg/kg: milligram per kilogram, mITT: modified intention-to-treat, n: number, q2w: every 2 weeks, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, SES-CD: Simple Endoscopic Score for Crohn's Disease, TNF: tumor necrosis factor, UC: ulcerative colitis, UST: ustekinumab, VEDO: vedolizumab

Table D3.20. Baseline Characteristics

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	CDAI Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MERC
LIBERTY-CD IFX	IFX 120 mg SC	231	36[†]	97 (42)	4.34 (5.18)	NR	311.95 (58.4)	NR	18.89 (36.95)	99 (42.9)	*71 (30.7)*	NR	63 (27.3)	4 (1.7)
	Placebo	112	29[†]	43 (38.4)	4.45 (5.78)	NR	311.95 (58.4)	NR	21.29 (32.98)	44 (39.3)	40 (35.7)	NR	36 (32.1)	2 (1.8)
CLASSIC-I ADA	ADA 160/80 mg	76	39 (11)	40 (53)	NR	NA	295 (52)	Colonic: 22 (29) Ileal: 40 (53) Ileocolonic: 8 (11) Perianal: 1 (1) Small Bowel: 2 (3) Unclassifiable: 3 (4)	1.4 (1.9)	24 (32)	22 (29)	NR	11 (14)	10 (13)
	Placebo	74	37 (13)	37 (50)	NR	NA	296 (60)	Colonic: 14 (19) Ileal: 50 (68) Ileocolonic: 7 (9) Unclassifiable: 3 (4)	1.8 (2.6)	25 (34)	22 (30)	NR	13 (18)	8 (11)
CLASSIC-II ADA	ADA 40 mg EOW	19	34 (12)	12 (63)	7.73 (6.5)	NA	106 (33)	NR	0.8 (0.8)	8 (47)	4 (21)	NR	4 (21)	0 (0)
	Placebo	18	36 (13)	12 (67)	8.24 (8.3)	NA	107 (62)	NR	0.2 (0.2)	10 (56)	3 (17)	NR	1 (6)	1 (6)
	ADA OL	204	40 (12)	104 (51)	9.58 (8.8)	NA	245 (73)	NR	1.3 (2.9)	74 (36)	67 (33)	NR	33 (16)	25 (12)
Sandborn et al. (2007c) ADA	ADA 160/80 mg	159	39 (12)	109 (69)	NR	159 (100)	313 (58)	Colonic: 105 (66) Ileal: 112 (70) Perianal: 27 (17) Rectum: 36 (23) Gastroduodenal:	*1.9 (2.5)*	55 (35)	73 (46)	NR	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	CDAI Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MERC
								5 (3) Jejunum: 6 (4) Other: 5 (3)						
	Placebo	166	37 (12)	101 (61)	NR	166 (100)	313 (66)	Colonic: 113 (68) Ileal: 124 (75) Perianal: 31 (19) Rectum: 37 (22) Gastroduodenal: 16 (10) Jejunum: 4 (2) Other: 6 (4)	2 (3.7)	73 (44)	85 (51)	NR	NR	NR
Watanabe et al. (2012) ADA	ADA 160/80 mg	33	32.0 (9.6)	13 (39.4)	11.0 (7.1)	19 (57.6)	300.5 (66.5)	NR	2.2 (2.0)	8 (24.2)	10 (30.3)	NR	NR	NR
	Placebo	23	30.4 (6.9)	7 (30.4)	7.9 (4.7)	13 (56.5)	308.1 (63.8)	NR	2.5 (2.0)	5 (21.7)	8 (34.8)	NR	NR	NR
Chen et al. (2020) ADA	ADA	102	33.2 (10.2)	35 (34)	3.1 (3.2)	NA	272.1 (48.1)	Colonic: 19 (19) Ileal: 22 (22) Ileocolonic: 60 (59) Upper Disease: 9 (9)	*2.4 (2.5)*	31 (30)	61 (60)	NR	60 (59)	0 (0)
	Placebo	103	32.6 (9.5)	30 (29)	2.3 (2.7)	NA	274.7 (49.1)	Colonic: 24 (23) Ileal: 19 (18) Ileocolonic: 60 (58) Upper Disease: 10 (10)	*2.7 (3.2)*	32 (31)	65 (63)	NR	59 (57)	2 (2)
CHARM 2007 ADA	ADA	499	36.7 (11.6)	311 (62.3)	NR	238 (47.7)	316.6 (62.5)	Colonic: 375 (75.2) Ileal: 357 (71.5)	2.4 (3.7)	210 (42.1)	240 (48.1)	NR	165 (33.1)	38 (7.6)

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	CDAI Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MERC
								Gastrodudenal: 30 (6) Other: 68 (13.6)						
GEMINI II VEDO	VEDO 300 mg	220	36.3 (11.6)	115 (52.3)	9.2 (8.2)	111 (50.5)	327 (71)	Colonic: 62 (28.2) Ileal: 37 (16.8) Ileocolonic: 121 (55)	*1.53*[†]	67 (30.5)	37 (16.8)	38 (17.3)	NR	NR
	Placebo	148	38.6 (13.2)	79 (53.4)	8.2 (7.8)	72 (48.6)	322 (67)	Colonic: 43 (29.1) Ileal: 21 (14.2) Ileocolonic: 84 (56.8)	*1.37*[†]	45 (30.4)	25 (16.9)	26 (17.6)	NR	NR
	VEDO 300 mg OL	747	35.6 (12.0)	401 (53.7)	9.2 (7.6)	506 (67.7)	325 (78)	Colonic: 211 (28.2) Ileal: 123 (16.5) Ileocolonic: 413 (55.3)	*1.02*[†]	269 (36.0)	119 (15.9)	125 (16.7)	NR	NR
GEMINI III VEDO	VEDO 300 mg	209	36.9*	118 (56)	8.4*	158 (76)	313.9 (53.2)	Colonic: 33 (16) Ileal: 48 (23) Ileocolonic: 128 (61)	1.9 (2.32)	110 (53)	71 (34)	NR	NR	NR
	Placebo	207	34.8*	118 (57)	8.0*	157 (76)	301.3 (55.0)	Colonic: 52 (25) Ileal: 29 (14) Ileocolonic: 126 (61)	1.85 (2.20)	108 (52)	69 (33)	NR	NR	NR
GEMINI LTS[119] (Card et al. 2020) VEDO	VEDO 300 mg	1034	38.3 (12.64)	549 (53)	10.0 (8.42)	640 (62)	NR	NR	NR	452 (44)	317 (31)	NR	NR	NR
GEMINI LTS[44] (Loftus	VEDO 300 mg	1349	37.8 (12.7)	743 (55)	10.1 (8.3)	898 (66.6)	314.0 (63.2)	NR	NR	545 (40.4)	NR	NR	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	CDAI Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MERC
et al. 2020) VEDO														
GEMINI LTS[120] (Danese et al. 2021) VEDO	VEDO 300 mg	169	42.5 (11.8)	74 (43.8)	13.4 (6.7)	62 (36.7)	NR	NR	*0.22*[†]	7 (4.1)	32 (18.9)	2 (1.2)	NR	NR
Watanabe et al. (2020) VEDO - IND	VEDO 300 mg	79	33.9 (12.3)	28 (35.4)	9.0 (6.2)	61 (77.2)	303.9 (63.2)	Colonic: 11 (13.9) Ileal: 13 (16.5) Ileocolonic: 55 (69.6)	2.2 (2.2)	13 (16.5)	NR	9 (11.4)	NR	NR
	Placebo	78	32.6 (10.9)	26 (33.3)	9.1 (6.5)	62 (79.5)	295.0 (64.8)	Colonic: 19 (24.4) Ileal: 9 (11.5) Ileocolonic: 50 (64.1)	2.9 (3.2)	7 (9.0)	NR	11 (14.1)	NR	NR
Watanabe et al. (2020) VEDO - MAINT	VEDO 300 mg	12	36.7 (16.8)	6 (50)	9.0 (4.9)	8 (66.7)	319.8 (79.3)	Colonic: 5 (41.7) Ileal: 2 (16.7) Ileocolonic: 4 (41.7)	2.0 (1.6)	2 (16.7)	NR	3 (25.0)	NR	NR
	Placebo	12	35.2 (13)	3 (25)	7.5 (6.6)	7 (58.3)	303.3 (81.7)	Colonic: 1 (8.3) Ileal: 2 (16.7) Ileocolonic: 9 (75)	2.4 (2.5)	3 (25.0)	NR	0 (0.0)	NR	NR
VISIBLE 2 VEDO	VEDO 108 mg SC	275	38.2 (13.9)	118 (42.9)	9.5 (8.3)	168 [61.1]	318.0	Colonic: 55 (20) Ileal: 66 (24) Ileocolonic: 122 (44.4) Other: 31 (11.3)	NR	64 (23.3)	51 (18.5)	31 (11.3)	NR	NR
	Placebo	134	36.1 (12.9)	68 (50.7)	8.2 (8.4)	71 (53.0)	309.0	Colonic: 55 (20) Ileal: 66 (24)	NR	31 (23.1)	34 (25.4)	13 (9.7)	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	CDAI Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MERC
								Ileocolonic: 122 (44.4) Other: 31 (11.3)						
CERTIFI UST	UST 6 mg/kg	131	39.4 (13.2)	83 (63)	12.7 (8.9)	130 (99)	338.0 (67.3)	NR	*1.26*[†]	59 (45.0)	35 (26.7)	NR	NR	NR
	Placebo	132	39.5 (13.1)	68 (52)	12.4 (9.1)	131 (99)	312.4 (64.2)	NR	*0.93*[†]	73 (55.3)	30 (22.7)	NR	NR	NR
UNITI-1 UST	UST 6 mg/kg	249	37.3 (12.5)	148 (59)	12.7 (9.2)	246 (99)	327.6 (62.0)	Colonic: 40 (16.1) Ileal: 37 (14.9) Ileocolonic: 171 (68.7) Perianal: 107 (43)	*0.99*[†]	NR	NR	NR	NR	NR
	Placebo	247	37.3 (11.8)	129 (52)	12.1 (8.4)	246 (99.6)	319.0 (59.7)	Colonic: 48 (19.5) Ileal: 28 (11.4) Ileocolonic: 166 (67.5) Perianal: 107 (43.5)	*0.85*[†]	NR	NR	NR	NR	NR
UNITI-2 UST	UST 6 mg/kg	209	38.4 (13.1)	119 (56.9)	8.7 (8.4)	*65 (31.1)*	302.2 (58.9)	Colonic: 43 (20.6) Ileal: 49 (23.4) Ileocolonic: 117 (56) Perianal: 61 (29.2)	*0.78*[†]	NR	NR	NR	NR	NR
	Placebo	210	40.2 (13.1)	111 (52.9)	10.4 (9.8)	*79 (37.6)*	302.2 (61.7)	Colonic: 37 (17.6) Ileal: 44 (21)	*0.85*[†]	NR	NR	NR	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	CDAI Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MERC
								Ileocolonic: 129 (61.4) Perianal: 57 (27,1)						
IM-UNITI UST	UST 90 mg SC q8w	132	37.3 (12.5)	74 (56)	12.7 (9.2)	*81 (60.9)*	327.6 (62.0)	Colonic: 29 (22) Ileal: 19 (14.4) Ileocolonic: 84 (63.6) Perianal: 46 (34.8)	*0.91*[†]	NR	NR	NR	NR	NR
	UST 90 mg SC q12w	132	39.1 (13.8)	76 (58)	8.7 (8.5)	*79 (59.8)*	304.1 (57.0)	Colonic: 23 (17.4) Ileal: 26 (19.7) Ileocolonic: 83 (62.9) Perianal: 39 (29.5)	*0.88*[†]	NR	NR	NR	NR	NR
	Placebo	133	37.3 (11.8)	74 (56)	12.1 (8.4)	*80 (60.6)*	319.0 (59.7)	Colonic: 28 (21.1) Ileal: 19 (14.3) Ileocolonic: 86 (64.7) Perianal: 43 (32.3)	*0.96*[†]	NR	NR	NR	NR	NR
SEAVUE UST vs. ADA	UST 6 mg/kg	191	37.0 (13.2)	101 (53)	5.4 (8.4)	NA	301.6 (61.6)	Colonic: 26 (14) Ileal: 60 (32) Ileocolonic: 102 (54) Perianal: 50 (27)	*1.5 (2.4)*[†]	112 (58.6)	112 (71)	NR	NR	NR
	ADA 160/80 mg	195	37.4 (13)	100 (51)	5.8 (7.1)	NA	300 (56)	Colonic: 34 (17) Ileal: 55 (28)	*1.2 (1.8)*[†]	121 (62)	126 (60)	NR	NR	NR

Trial	Arm	N	Age, Mean Years (SD)	Female, n (%)	Disease Duration, Mean Years (SD)	Prior TNF Use, n (%)	CDAI Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)	Concomitant Medication, n (%)				
										CS	IMM	CS + IMM	AZA	MERC
								Ileocolonic: 103 (53) Perianal: 41 (21)						

ADA: adalimumab, AZA: azathioprine, CDAI: Crohn's Disease Activity Index, CRP: C-reactive protein, CS: corticosteroid, EOW: every other week, IFX: infliximab, IMM: immunomodulators, LTS: long-term study, MERC: mercaptopurine, mg: milligrams, mg/dL: milligram per deciliter, mg/kg: milligram per kilogram, mg/L: milligram per liter, n: number, NA: not applicable, NR: not reported, OL: open-label, SC: subcutaneous, SD: standard deviation, UST: ustekinumab, VEDO: vedolizumab

Note: italicized data indicates data was calculated. Baseline CRP data was converted to mg/dL.

*Race/Ethnicity include, but are not limited to, White (W), Black (B), Asian (A), American Indian or Alaskan Native (AI/AN), Native Hawaiian or Other Pacific Islander (NHPI), and Hispanic/Latino (H/L). 'Others' refers to any of these that have no data.

†Median.

‡Week four non-randomized responders. Data was pooled between the placebo, ADA 40 mg every week, and ADA 40 mg every other week arms.

Table D3.21. Response and Remission in the Induction Phase

Induction Phase (Weeks 4-10)									
Trial	**Arm**	**Response**				**Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
LIBERTY-CD IFX	**Week 10**								
	Overall								
	IFX 120 mg SC	229	231	99.1	NR	174	231	75	NR
	Placebo	112	112	100	NR	91	112	81	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported								
CLASSIC-I ADA	**Week 4**								
	Overall – Biologic Naïve								
	ADA 160/80 mg	38	76	50	0.001	27	76	36	NR
	Placebo	19	74	25	--	9	74	12	NR
	Biologic-Experienced (Population Not Studied)								
Chen et al. (2020)* ADA	**Week 4**								
	Overall – Biologic Naïve								
	ADA 160/80 mg	69	102	68	<0.001	38	102	37	<0.001
	Placebo	28	103	27	--	7	103	7	--
	Biologic-Experienced (Population Not Studied)								
Sandborn et al. (2007) ADA	**Week 4**								
	Overall – Biologic-Experienced								
	ADA 160/80 mg	61	159	38	NR	34	159	21	<0.001
	Placebo	41	166	25	NR	12	166	7	--
	Biologic-Naïve (Population Not Studied)								
Watanabe et al. (2012)	**Week 4**								
	Overall								
	ADA 160/80 mg	15	33	46	<0.05	11	33	33	NR
	Placebo	4	23	17	--	3	23	13	NR
	Biologic-Naïve								
	ADA 160/80 mg	7	14	50	NR	6	14	43	NR
	Placebo	2	10	20	NR	2	10	20	NR
	Biologic-Experienced								
	ADA 160/80 mg	8	19	42	> 0.05	5	19	26	> 0.05
	Placebo	2	13	15	--	1	13	8	--
GEMINI II	**Week 6**								

Induction Phase (Weeks 4-10)									
Trial	**Arm**	**Response**				**Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
VEDO	***Overall***								
	VEDO 300 mg	69	220	31.4	0.23	32	220	14.5	0.02
	Placebo	38	148	25.7	--	10	148	6.8	--
	Biologic-Naïve								
	VEDO 300 mg	46	109	42	NR	61	109	56	NR
	Placebo	23	76	30	NR	30	76	40	NR
	Biologic-Experienced								
	VEDO 300 mg	25	105	23.8	NR	11	105	10.5	NR
	Placebo	16	70	22.9	NR	3	70	4.3	NR
GEMINI III VEDO	**Week 6**								
	Overall								
	VEDO 300 mg	*82*	209	39.2	0.0002	*40*	209	19.1	0.048
	Placebo	*47*	207	22.7	--	*25*	207	12.1	--
	Biologic-Naïve								
	VEDO 300 mg	*20*	51	39.2	NR	*16*	51	31.4	NR
	Placebo	*12*	50	24	NR	*6*	50	12	NR
	Biologic-Experienced								
	VEDO 300 mg	*62*	158	39.2	0.001	*24*	158	15.2	NR
	Placebo	*35*	157	22.3	--	*19*	157	12.1	NR
	Week 10								
	Biologic-Naïve								
	VEDO 300 mg	*26*	51	51	NR	*18*	51	35.3	NR
	Placebo	*11*	50	22	NR	*8*	50	16	NR
	Biologic-Experienced								
	VEDO 300 mg	*73*	158	46.8	<0.0001	*42*	158	26.6	NR
	Placebo	*39*	157	24.8	--	*19*	157	12.1	NR
Ogata et al. (2019) VEDO	Week 6								
	Overall								
	VEDO 300 mg	21	79	26.6	NR	NR	NR	NR	NR
	Placebo	13	78	16.7	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported								
	Week 6								
	Overall								

Induction Phase (Weeks 4-10)									
Trial	**Arm**	**Response**				**Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
	VEDO 300 mg	19	79	24.1	NR	11	79	13.9	NR
	Placebo	10	78	12.8	NR	10	78	12.8	NR
	Biologic-Naïve								
	VEDO 300 mg	*7*	18	38.9	NR	*7*	18	38.9	NR
	Placebo	*4*	16	25	NR	*3*	16	18.8	NR
	Biologic-Experienced								
	VEDO 300 mg	12	61	19.7	NR	4	61	6.6	NR
	Placebo	6	62	9.7	NR	7	62	11.3	NR
Watanabe et al. (2020) VEDO	**Week 10**								
	Overall								
	VEDO 300 mg	21	79	26.6	NR	14	79	17.7	NR
	Placebo	13	78	16.7	NR	8	78	10.3	NR
	Biologic-Naïve								
	VEDO 300 mg	*9*	18	50	NR	*9*	18	50	NR
	Placebo	*4*	16	25	NR	*2*	16	12.5	NR
	Biologic-Experienced								
	VEDO 300 mg	12	61	19.7	NR	5	61	8.2	NR
	Placebo	9	62	14.5	NR	6	62	9.7	NR
CERTIFI UST	**Week 8**								
	Overall – Biologic-Experienced								
	UST 6 mg/kg	52	131	39.7	0.005	16	131	12.2	0.68
	Placebo	31	132	23.5	--	14	132	10.6	--
	Biologic-Naïve (Population Not Studied)								
UNITI-1 UST	**Week 6**								
	Overall – Biologic-Experienced								
	UST 6 mg/kg	84	249	33.7	0.003	46	249	18.5	0.002
	Placebo	53	247	21.5	--	22	247	8.9	--
	Biologic-Naïve (Population Not Studied)								
UNITI-2 UST	**Week 6**								
	Overall								
	UST 6 mg/kg	116	209	55.5	<0.001	73	209	34.9	<0.001
	Placebo	60	209	28.7	--	37	209	17.7	--
	Stratified Biologic-Naïve and Experienced Data Not Reported								

Induction Phase (Weeks 4-10)									
Trial	**Arm**	**Response**				**Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
SEAVUE UST vs. ADA	**Week 8**								
	Overall – Biologic-Naïve								
	UST 6 mg/kg	130	191	68	NR	96	191	50	NR
	ADA 160/80 mg	129	195	66	NR	94	195	48	NR
	Biologic-Experienced (Population Not Studied)								

ADA: adalimumab, IFX: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

Note: italicized data indicates data has been calculated.

*Response data defined as CDAI 70-point response.

Table D3.22. Response and Remission in the Maintenance Phase

Maintenance Phase (Weeks 30-60)																	
Trial	**Arm**	**Response**				**Sustained Response**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
LIBERTY-CD IFX	**Week 54**																
	Overall																
	IFX 120 mg SC	152	231	66	<0.0001	163	231	70.6	NR	144	231	62	NR	120	231	51.9	NR
	Placebo	43	112	38	--	48	112	42.9	NR	36	112	32	NR	33	112	29.5	NR
	Biologic-Naïve																
	IFX 120 mg SC	205	65.4	205	<0.0001	NR	NR	NR	NR	126	205	61.5	<0.0001	NR	NR	NR	NR
	Placebo	41	103	39.8	--	NR	NR	NR	NR	34	103	33	--	NR	NR	NR	NR
	Biologic-Experienced																
	IFX 120 mg SC	18	26	69.2	0.016	NR	NR	NR	NR	18	26	69.2	0.016	NR	NR	NR	NR
	Placebo	2	9	22.2	--	NR	NR	NR	NR	2	9	22.2	--	NR	NR	NR	NR
CLASSIC-II ADA	**Week 56**																
	Overall – Biologic-Naïve																
	ADA 40 mg	*15*	19	79	>0.05	NR	NR	NR	NR	15	19	79	<0.05	NR	NR	NR	NR
	Placebo	*10*	18	56	--	NR	NR	NR	NR	8	18	44	--	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)																
CHARM ADA	**Week 56**																
	Overall																
	ADA 40 mg EOW	71	172	41.3	0.001	NR	NR	NR	NR	62	172	36	0.001	NR	NR	NR	NR
	Placebo	28	170	16.5	--	NR	NR	NR	NR	20	170	12	--	NR	NR	NR	NR
	Biologic-Naïve																
	ADA 40 mg EOW	NR	NR	NR	NR	NR	NR	NR	NR	36	87	42	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	12	89	14	NR	NR	NR	NR	NR
	Biologic-Experienced																
	ADA 40 mg EOW	NR	NR	NR	NR	NR	NR	NR	NR	26	85	31	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	8	81	10	NR	NR	NR	NR	NR

Maintenance Phase (Weeks 30-60)																	
Trial	**Arm**	**Response**				**Sustained Response**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
Watanabe et al. (2012) ADA	**Week 52**																
	Overall																
	ADA 160/80 mg	*10*	25	39.8	<0.05	NR	NR	NR	NR	*10*	25	40	<0.05	NR	NR	NR	NR
	Placebo	*2*	25	9.1	--	NR	NR	NR	NR	*3*	25	10	--	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported																
GEMINI II VEDO	**Week 52**																
	Overall																
	VEDO 300 mg q8w	67	154	43.5	0.01	NR	NR	NR	NR	34	66	52	NR	16	66	24	NR
	Placebo	46	153	30.1	--	NR	NR	NR	NR	19	71	27	NR	14	71	20	NR
	Biologic-Naïve																
	VEDO 300 mg q8w	40	66	61	NR	NR	NR	NR	NR	34	66	52	NR	16	66	24	NR
	Placebo	27	71	38	NR	NR	NR	NR	NR	19	71	27	NR	14	71	20	NR
	Biologic-Experienced																
	VEDO 300 mg q8w	24	82	29.3	NR	NR	NR	NR	NR	60	154	39	<0.001	33	154	21.4	>0.05
	Placebo	16	78	20.5	NR	NR	NR	NR	NR	33	153	21.6	--	22	153	14.4	--
VISIBLE 2 VEDO	**Week 52**																
	Overall																
	VEDO 108 mg SC	143	275	52	0.17	NR	NR	NR	NR	132	275	48	NR	NR	NR	NR	NR
	Placebo	60	134	44.8	--	NR	NR	NR	NR	46	134	34.3	NR	NR	NR	NR	NR
	Biologic-Naïve																
	VEDO 108 mg SC	58	107	54	NR	NR	NR	NR	NR	52	107	49	NR	NR	NR	NR	NR
	Placebo	30	63	48	NR	NR	NR	NR	NR	27	63	43	NR	NR	NR	NR	NR
	Biologic-Experienced																
	VEDO 108 mg SC	85	168	51	NR	NR	NR	NR	NR	80	168	48	NR	NR	NR	NR	NR
	Placebo	30	71	50	NR	NR	NR	NR	NR	19	71	27	NR	NR	NR	NR	NR

Maintenance Phase (Weeks 30-60)																	
Trial	**Arm**	**Response**				**Sustained Response**				**Remission**				**Sustained Remission**			
		n	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**	**n**	**N**	**%**	**p-value**
Watanabe et al. (2020) VEDO	**Week 60**																
	Overall																
	VEDO 300 mg	7	12	58.3	NR	4	12	33.3	NR	5	12	41.7	NR	NR	NR	NR	NR
	Placebo	1	12	8.3	NR	3	12	25	NR	2	12	16.7	NR	NR	NR	NR	NR
	Biologic-Naïve																
	VEDO 300 mg	3	4	75	NR	NR	NR	NR	NR	2	4	50	NR	1	4	25	NR
	Placebo	1	5	20	NR	NR	NR	NR	NR	2	5	40	NR	3	5	60	NR
	Biologic-Experienced																
	VEDO 300 mg	4	8	50	NR	NR	NR	NR	NR	3	8	37.5	NR	3	8	37.5	NR
	Placebo	0	7	0	NR	NR	NR	NR	NR	0	7	0	NR	0	7	0	NR
IM-UNITI UST	**Week 44**																
	Overall – Biologic-Experienced																
	UST 90mg q8w	76	128	59.4	0.02	NR	NR	NR	NR	68	128	53.1	0.005	59	128	46.1	<0.001
	Placebo	58	131	44.3	--	NR	NR	NR	NR	47	131	35.9	--	34	131	26	--
	Biologic-Naïve (Population Not Studied)																
SEAVUE* UST vs. ADA	**Week 52**																
	Overall – Biologic-Naïve																
	UST 6 mg/kg	138	191	72	0.18	124	191	65	0.29	124	191	65	0.42	97	191	51	0.83
	ADA 160/80 mg	129	195	66	--	119	195	61	--	119	195	61	--	101	195	52	--
	Biologic-Experienced (Population Not Studied)																

ADA: adalimumab, EOW: every other week, IFX: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, q8w: every 8 weeks, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

Note: italicized data indicates data has been calculated.

*Durable clinical response at week 52 was defined as a ≥100-point decrease from baseline in CDAI or CDAI.

Table D3.23. Endoscopic Response, Endoscopic Remission, and Corticosteroid-Free Remission in Maintenance Phase

Maintenance Phase (Weeks 30-60)										
Trial	**Arm**	**Endoscopic Response**			**Endoscopic Remission**			**Corticosteroid-Free Remission**		
		n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
LIBERTY-CD IFX	**Week 54**									
	Overall									
	IFX 120 mg SC	118	231	51.1	80	231	34.6	40	99	40.4
	Placebo	20	112	17.9	80	231	34.6	40	99	40.4
	Biologic-Naïve									
	IFX 120 mg SC	106	205	34.6	71	205	34.6	31	88	35.2
	Placebo	19	103	18.4	19	103	18.4	10	41	24.4
	Biologic-Experienced									
	IFX 120 mg SC	12	26	46.2	9	26	34.6	9	11	81.8
	Placebo	1	9	11.1	1	9	11.1	0	3	0
CHARM ADA	**Week 56**									
	Overall									
	ADA 40 mg EOW	NR	NR	NR	NR	NR	NR	17	58	29
	Placebo	NR	NR	NR	NR	NR	NR	4	66	6
	Stratified Biologic-Naïve and Experienced Data Not Reported									
GEMINI II VEDO	**Week 52**									
	Biologic-Naïve									
	VEDO 300 mg q8w	NR	NR	NR	NR	NR	NR	15	38	39.5
	Placebo	NR	NR	NR	NR	NR	NR	11	40	27.5
	Biologic-Experienced									
	VEDO 300 mg q8w	NR	NR	NR	NR	NR	NR	10	41	24.4
	Placebo	NR	NR	NR	NR	NR	NR	0	38	0
	Overall Population Data Not Reported									
Watanabe et al. (2020) VEDO	**Week 60**									
	Biologic-Naïve									
	VEDO 300 mg	NR	NR	NR	NR	NR	NR	1	2	50
	Placebo	NR	NR	NR	NR	NR	NR	0	2	0
	Biologic-Experienced									
	VEDO 300 mg	NR	NR	NR	NR	NR	NR	1	3	33.3
	Placebo	NR	NR	NR	NR	NR	NR	0	1	0

Maintenance Phase (Weeks 30-60)										
Trial	**Arm**	**Endoscopic Response**			**Endoscopic Remission**			**Corticosteroid-Free Remission**		
		n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
	Overall Population Data Not Reported									
VISIBLE 2 VEDO	**Week 52**									
	Overall									
	VEDO 108 mg SC	NR	NR	NR	NR	NR	NR	43	95	45.3
	Placebo	NR	NR	NR	NR	NR	NR	8	44	18.2
	Stratified Biologic-Naïve and Experienced Data Not Reported									
	Overall Population Data Not Reported									
IM-UNITI UST	**Week 44**									
	Overall – Biologic-Experienced									
	UST 6 mg/kg	NR	NR	NR	NR	NR	NR	60	128	46.9
	Placebo	NR	NR	NR	NR	NR	NR	39	131	29.8
	Biologic-Naïve (Population Not Studied)									
SEAVUE UST vs. ADA	**Week 52**									
	Overall – Biologic-Naïve									
	UST 6 mg/kg	75	179	42	51	179	29	117	191	61
	ADA 160/80 mg	66	179	37	55	179	31	111	195	57
	Biologic-Experienced (Population Not Studied)									

ADA: adalimumab, EOW: every other week, IFX: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, q8w: every 8 weeks, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

Table D3.24. IBDQ and CDAI Scores in Induction Phase

Induction Phase (Weeks 4-10)						
Trial	**Arm**	**N**	**IBDQ**		**CDAI**	
			Mean Score (SD)	**Mean Increase**	**Mean Score (SD)**	**Mean Decrease**
LIBERTY-CD IFX	**Week 10**					
	Overall					
	IFX 120 mg SC	231	NR	NR	102.3 (64.8)	NR
	Placebo	112	NR	NR	104.27 (61.9)	NR

Induction Phase (Weeks 4-10)						
Trial	**Arm**	**N**	**IBDQ**		**CDAI**	
			Mean Score (SD)	**Mean Increase**	**Mean Score (SD)**	**Mean Decrease**
	Stratified Biologic-Naïve and Experienced Data Not Reported					
CLASSIC-I ADA	**Week 4**					
	Overall – Biologic-Naïve					
	ADA 160/80 mg	76	*60*	*67*	*193*	*102*
	Placebo	74	*33*	*98*	*239*	*57*
	Biologic-Experienced (Population Not Studied)					
Sandborn et al. (2007c) ADA	**Week 4**					
	Overall – Biologic-Experienced					
	ADA 160/80 mg	159	150	30	226	87
	Placebo	166	139	15	264	49
	Biologic-Naive (Population Not Studied)					
Watanabe et al. (2012) ADA	**Week 4**					
	Overall					
	ADA 160/80 mg	33	NR	NR	NR	101.3
	Placebo	23	NR	NR	NR	37.5
	Stratified Biologic-Naïve and Experienced Data Not Reported					
GEMINI II[130] VEDO	**Week 6**					
	Overall					
	VEDO 300 mg	220	CFB (SE): 23.1 (2.28) 23.1		NR	NR
	Placebo	158	CFB (SE): 16.5 (2.75) 16.5		NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported					
GEMINI III[130] VEDO	**Week 6**					
	Overall					
	VEDO 300 mg	209	CFB (SE): 24.1 (2.14)		NR	NR
	Placebo	207	CFB (SE): 14.9 (2.16)		NR	NR
	Biologic-Experienced					
	VEDO 300 mg	158	CFB (SE): 24 (2.42)		NR	NR
	Placebo	157	CFB (SE): 14.6 (2.45)		NR	NR
	Biologic-Naïve Data Not Reported					
VISIBLE 2 VEDO	**Week 6**					
	Overall					

Induction Phase (Weeks 4-10)						
Trial	**Arm**	**N**	**IBDQ**		**CDAI**	
			Mean Score (SD)	**Mean Increase**	**Mean Score (SD)**	**Mean Decrease**
	VEDO 108 mg SC	275	162.7	52.2	NR	NR
	Placebo	134	161.2	55	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported					
CERTIFI UST	**Week 6**					
	Overall – Biologic-Experienced					
	UST 6 mg/kg	131	NR	NR	NR	75.1
	Placebo	132	NR	NR	NR	34.3
	Biologic-Naïve (Population Not Studied)					

ADA: adalimumab, CDAI: Crohn's Disease Activity Index, CFB: change from baseline, IBDQ: Inflammatory Bowel Disease Questionnaire, IFX: infliximab, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, SC: subcutaneous, SD: standard deviation, SE: standard error, UST: ustekinumab, VEDO: vedolizumab

Note: italicized data indicates data has been digitized and/or calculated.

Table D3.25. IBDQ and CDAI Scores in Maintenance Phase

Maintenance Phase (Weeks 30-60)					
Trial	**Arm**	**N**	**IBDQ**		**CDAI**
			Mean Score	**Mean Increase**	**Median Decrease (95% CI:)**
CLASSIC-II ADA	**Week 56**				
	Overall – Biologic-Naïve				
	ADA 40 mg EOW	19	*178.4*	*9.6*	150.8 (-202, 299.8)
	Placebo	18	*162.4*	*28.6*	119.6 (-174, -65.1)
	Biologic-Experienced (Population Not Studied)				
Watanabe et al. (2012) ADA	**Week 52**				
	Overall				
	ADA 160/80 mg	25	170.1*	27.9*	83.7
	Placebo	25	NR	1.8*	9.1
	Stratified Biologic-Naïve and Experienced Data Not Reported				
GEMINI II[130] VEDO	**Week 52**				
	Overall				
	VEDO 300 mg q8w	154	CFB (SE): 50.7 (3.88)		NR
	Placebo	153	CFB (SE): 35.5 (3.81)		NR
	Stratified Biologic-Naïve and Experienced Data Not Reported				
VISIBLE 2 VEDO	**Week 52**				
	Overall				
	VEDO 108 mg SC	275	NR	63.3	NR
	Placebo	134	NR	55.1	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported				
IM-UNITI UST	**Week 44**				
	Overall – Biologic-Experienced				
	UST 90 mg q8w	128	NR	NR	*-6* (NR)†
	Placebo	131	NR	NR	*74* (NR)†
	Biologic-Naïve (Population Not Studied)				

ADA: adalimumab, CDAI: Crohn's Disease Activity Index, CFB: change from baseline, CI: confidence interval, EOW: every other week, IBDQ: Inflammatory Bowel Disease Questionnaire, mg: milligrams, mg/kg: milligram per kilogram, n: number, NR: not reported, q8w: every 8 weeks, SC: subcutaneous, SE: standard error, UST: ustekinumab, VEDO: vedolizumab

Note: italicized data indicates data has been digitized and/or calculated.

*Median.

†Median change from baseline CDAI score.

Table D3.26. Safety in the Induction Phase

Induction Phase (Weeks 4-10)										
Trial	**Arm**	**N**	**All-Cause D/C of Trial**	**Any AEs**	**D/C due to AE**	**Death**	**SAEs**	**Infections**	**Serious Infections**	**Malignancy**
CLASSIC-I ADA	**Week 4**									
	ADA 160/80 mg	76	3	75	0	NR	4	21	3	NR
	Placebo	74	8	74	3	NR	4	16	0	NR
Chen et al. (2020) ADA	**Week 4**									
	ADA 160/80 mg	102	4	37	2	0	2	8	0	0
	Placebo	103	5	37	4	0	1	9	0	0
Sandborn et al. (2007c) ADA	**Week 4**									
	ADA 160/80 mg	159	3	57	1	NR	1	16	0	0
	Placebo	166	6	73	2	NR	5	24	2	0
Watanabe et al. (2012) ADA	**Week 4**									
	ADA 160/80 mg	33	NR	51.5	3	0	3	12.1	0	NR
	Placebo	22	NR	52.2	4.3	0	8.7	8.7	0	NR
GEMINI II VEDO	**Week 6**									
	VEDO 300 mg	220	9.5	56	4.1	NR	9	15	0.5	0
	Placebo	148	7.4	59	5	NR	6	18	1	0
GEMINI III VEDO	**Week 10**									
	VEDO 300 mg	209	6.2	56	2	0	6	19	<1	NR
	Placebo	207	7.2	60	4	0	8	17	0	NR
Watanabe et al. (2020) VEDO	**Week 10**									
	VEDO 300 mg	79	7.5	62	3.8	0	10.1	NR	NR	NR
	Placebo	78	15.4	53.8	15.4	0	12.8	NR	NR	NR
UNITI-1 UST	**Week 8**									
	UST 6 mg/kg	249	5.6	65.9	NR	NR	7.2	25.7	2.8	NR
	Placebo	247	2.8	64.9	NR	NR	6.1	23.7	1.2	NR
CERTIFI UST	**Week 8**									
	UST 6 mg/kg	131	6.1	61.1	0.8	0	6.9	22.1	3.8	NR
	Placebo	132	14.4	71.2	3.8	0	8.3	24.2	0.8	NR

ADA: adalimumab, AEs: adverse events, D/C: discontinuation, mg: milligrams, mg/kg: milligram per kilogram, N: number, NR: not reported, SAEs: serious adverse events, UST: ustekinumab, VEDO: vedolizumab

Note: data presented as percentages. Italicized data indicates data has been digitized and/or calculated.

Table D3.27. Safety in the Maintenance Phase

Maintenance Phase (Weeks 30-60)										
Trial	**Arm**	**N**	**All-Cause D/C of Trial**	**Any AEs**	**D/C due to AE**	**Death**	**SAEs**	**Infections**	**Serious Infections**	**Malignancy**
LIBERTY-CD IFX	**Week 54**									
	IFX 120 mg SC	231	15	72.3	3.5	0.4	6.7	31.1	NR	0
	Placebo	112	22	61.9	5.4	0	7.6	18.1	NR	1
CLASSIC-II ADA	**Week 56**									
	ADA 160/80 mg	19	16	79	5.3	NR	5	74	0	0
	Placebo	18	28	100	5.6	NR	11	83	0	5.6
Watanabe et al. (2012) ADA	**Week 52**									
	ADA 160/80 mg	25	*4*	80	24	0	8	60	4	0
	Placebo	25	*12*	84	24	0	24	36	8	0
GEMINI II VEDO	**Week 52**									
	VEDO 300 mg q8w	154	52.6	88	*7.8*	NR	18	42	3.9	0.6
	Placebo	153	58.2	84	*9.8*	NR	15	45	3.3	0
VISIBLE 2 VEDO	**Week 52**									
	VEDO 108 mg SC	275	38.9	73.5	4	0	8.4	31.3	1.5	0.7
	Placebo	135	45.2	76.1	9	0	10.4	34.3	4.5	2.2
Watanabe et al. (2020) VEDO	**Week 60**									
	VEDO 300 mg	12	41.7	75	16.7	0	16.7	NR	NR	NR
	Placebo	12	66.7	83.3	33.3	0	33.3	NR	NR	NR
IM-UNITI UST	**Week 44**									
	UST 90 mg q8w	132	11	81.7	NR	0	9.9	48.1	2.3	NR
	Placebo	133	9.8	83.5	NR	0	15	49.6	2.3	NR
CERTIFI UST	**Week 36**									
	UST 270 mg SC	72	6.9	75	1.4	0	12.5	31.9	2.8	1.4
	Placebo	73	13.7	84.9	6.8	0	16.4	39.7	4.1	0
SEAVUE UST vs. ADA	**Week 52**									
	UST 6 mg/kg	195	23.6	78	11	0	16	41	3	0.5
	ADA 160/80 mg	191	15	80	6	0	13	34	2	0

ADA: adalimumab, AEs: adverse events, D/C: discontinuation, mg: milligrams, mg/kg: milligram per kilogram, N: number, NR: not reported, q8w: every 8 weeks, SAEs: serious adverse events, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

Note: data presented as percentages. Italicized data has been digitized and/or calculated.

Table D3.28. Adverse Events from Open-Label Extension and Long-Term Studies

Trial	Arm	N	All-Cause D/C of Trial	Any AEs	D/C due to AE	Death	SAEs	Infections	Serious Infections	Malignancy	CD-Related Hospitalization	Bowel Surgeries
GEMINI LTS[44] (Loftus et al. 2020)	VEDO 300 mg	1349	NR	96	17	0.4	40.6	69.7	10.8	6.8	29.1*	NR
GEMINI LTS[120] (Danese et al. 2021)	VEDO 300 mg	169	15.4	49.1	1.2	0.6	10.7	NR	NR	NR	NR	NR
VISIBLE OLE[128]	VEDO 108 mg SC†	158	NR	NR	NR	NR	NR	NR	NR	NR	9.5	3.2
	Placebo/VEDO 108 mg SC‡	68	NR	NR	NR	NR	NR	NR	NR	NR	16.2	2.9
	VEDO 300 mg IV/108 mg SC§	118	NR	NR	NR	NR	NR	NR	NR	NR	14.4	4.2

AEs: adverse events, CD: Crohn's disease, D/C: discontinuation, IV: intravenous, LTS: long-term study, mg: milligrams, mg/kg: milligram per kilogram, N: number, NR: not reported, OLE: open-label extension, SAEs: serious adverse events, SC: subcutaneous, VEDO: vedolizumab

Note: data presented as percentages. Italicized data has been digitized and/or calculated.

*Events, out of 887 total events.

†Randomized participants who were treated with VEDO 108 mg SC in VISIBLE I or 2, and in VISIBLE OLE.

‡Randomized participants who were treated with placebo in VISIBLE I or 2, and switched to VEDO 108 mg SC in VISIBLE OLE.

§Randomized participants who were treated with VEDO 300 mg IV in VISIBLE I or 2 until week 14, and switched to VEDO 108 mg SC in VISIBLE OLE.

Crohn's Disease – RWEs

Table D3.29. Study Design of Included Observational Studies

Study	Design	Location	Population	Comparison
Garcia et al. (2024)[67]	Multicenter registry study	Spain	- N=835 - Previous anti-TNF failure or intolerance	VEDO vs. UST
Bohm et al. (2020)[68]	Multicenter, retrospective cohort, study	North America	- N=1266 - Naïve or experienced	VEDO, IFX, TNF-agonists
Cohen et al. (2020)[56]	Retrospective database study	Global	- N=14191 - Naïve or experienced	VEDO
Karlqvist et al. (2024)[53]	Nationwide registry study	Sweden	- N=44012 - Naïve or experienced	VEDO vs. TNFs
Kirchgesner et al. (2022)[52]	Health care claims databases cohort study	USA and France	- N=21366 - Naïve or experienced	VEDO vs. TNFs
Koliani-Pace et al. (2019)[57]	Retrospective database study	USA	- N=3661 - Naïve or experienced	VEDO
Macaluso et al. (2021)[69]	Database cohort study	Italy	- N=585 - Naïve or experienced	VEDO vs. ADA
Singh et al. (2022)[49]	Retrospective database analysis (medical and pharmacy claims)	USA	- N=5566 - TNF- or VEDO-naïve	VEDO vs. TNFs
Singh et al. (2022)[48]	Retrospective database analysis (medical and pharmacy claims)	USA	- N=6251 - TNF- or VEDO-naïve	VEDO vs TNFs
Singh et al. (2023)[70]	Database cohort study	USA	- N=2965 - Naïve or experienced	VEDO, UST, TNFs
Supovec et al. (2025)[71]	Cohort study	Slovenia	- N=588 - Biologic naïve	VEDO, UST, TNFs
Vu et al. (2023)[72]	Prospective cohort study	USA	- N=1122 - Biologic naïve	VEDO vs. UST
Dubinsky et al. (2018)[46]	Retrospective database study	USA	- N=26,505 - TNF-naïve	VEDO vs. TNFs

ADA: adalimumab, IFX: infliximab, N: number, TNF: tumor necrosis factor, USA: United States of America, UST: ustekinumab, VEDO: vedolizumab

Table D3.30. Response and Remission

Trial	Arm	Response				Remission				
		n	N	%	p-value	n	N	%	p-value	Hazard Ratios (95% CI:)*
Garcia et al. (2024) VEDO vs. UST	**Week 208**									
	Overall – Biologic-Experienced									
	VEDO	13	152	8.5	NS	12	152	7.8	NS	At 12 months: 1.73 (1.1-2.7)
	UST	28	445	6.2	NS	25	445	5.6	NS	
	Biologic-Naïve (Population Not Studied)									
Bohm et al. (2020) VEDO vs. IFX vs. Anti-TNFs	**Month 12**									
	Overall									
	VEDO vs. IFX	NR	NR	NR	NR	NR	NR	NR	NR	1.361 (0.789-2.347)
	VEDO vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	NR	1.861 (1.059-3.272)
	VEDO vs. IFX vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	NR	1.654 (1.029-2.659)
	Biologic-Naïve									
	VEDO vs. IFX	NR	NR	NR	NR	NR	NR	NR	NR	0.557 (0.331-0.937)
	VEDO vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	NR	0.969 (0.612-1.536)
	VEDO vs. IFX vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	NR	0.821 (0.588-1.146)
	Biologic-Experienced									
	VEDO vs. IFX	NR	NR	NR	NR	NR	NR	NR	NR	0.692 (0.472-1.014)
	VEDO vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	NR	1.022 (0.714-1.404)
	VEDO vs. IFX vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	NR	0.932 (0.707-1.228)
Koliani-Pace et al. (2019) VEDO	**Month 12**									
	Overall									
	VEDO (Era 1)†	NR	NR	NR	NR			31	0.03	NR
	VEDO (Era 2) ‡	NR	NR	NR	NR			40	--	NR
	Biologic-Naïve									
	VEDO	NR	NR	NR	NR			58	<0.01‡	NR
	Biologic-Experienced									
	VEDO	NR	NR	NR	NR			33	--	NR
	Week 52									

Trial	Arm	Response				Remission				
		n	N	%	p-value	n	N	%	p-value	Hazard Ratios (95% CI:)*
Macaluso et al. (2021) VEDO vs. ADA	***Overall***									
	VEDO	150	277	54	0.334	NR	NR	NR	NR	NR
	ADA	213	308	69.1	--	NR	NR	NR	NR	NR
	Stratified Biologic-Naïve and Experienced Data Not Reported									

ADA: adalimumab, CI: confidence interval, IFX: infliximab, N: number, NR: not reported, TNF: tumor necrosis factor, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

*Hazard ratios are inverse probability weighting average treatment effect (IPW ATE).

†Era 1 data was collected in May 2014 through June 2015 from the VICTORY consortium.

‡Era 2 data was collected in July 2015 through June 2017 from the VICTORY consortium.

§P-value against biologic-experienced.

Table D3.31. Endoscopic Improvement, Corticosteroid-free Remission, and Treatment Persistence

Trial	Arm	N	Endoscopic Improvement			Corticosteroid-free Remission				Treatment Persistence	
			%	Cumulative Rate	p-value	%	p-value	Cumulative Rates, p-value	Hazard Ratio (95% CI:)*	n	n, at Risk
Garcia et al. (2024) VEDO vs. UST	**Week 208**										
	Overall – Biologic-Experienced										
	VEDO	207	NR	NR	NR	7.8	NR	NR	NR	NR	NR
	UST	628	NR	NR	NR	5.6	NR	NR	NR	NR	NR
	Biologic-Naïve (Population Not Studied)										
Bohm et al. (2020) VEDO vs. IFX vs. Anti-TNF	**Month 12**										
	Overall										
	VEDO vs. IFX	NR	NR	NR	NR	NR	NR	NR	0.695 (0.295-1.641)	NR	NR
	VEDO vs. Anti-TNF SC	NR	NR	NR	NR	NR	NR	NR	1.717 (0.665-4.432)	NR	NR
	VEDO vs. IFX vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	1.250 (0.677-2.310)	NR	NR
	VEDO	659	NR	NR	NR	NR	NR	NR	NR	417	NR
	Anti-TNF SC	302	NR	NR	NR	NR	NR	NR	NR	261	NR
	Biologic-Naïve										
	VEDO vs. IFX	NR	NR	NR	NR	NR	NR	NR	1.156 (0.504-3.309)	NR	NR
	VEDO vs. Anti-TNF SC	NR	NR	NR	NR	NR	NR	NR	5.608 (1.471-21.374)	NR	NR
	VEDO vs. IFX vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	2.002 (0.763-5.255)	NR	NR
	Biologic-Experienced										
	VEDO vs. IFX	NR	NR	NR	NR	NR	NR	NR	0.452 (0.145-1.408)	NR	NR
	VEDO vs. Anti-TNF SC	NR	NR	NR	NR	NR	NR	NR	1.398 (0.424-4.611)	NR	NR
	VEDO vs. IFX vs. Anti-TNFs SC	NR	NR	NR	NR	NR	NR	NR	1.014 (0.469-2.192)	NR	NR
	Month 12										
	Overall										

Trial	Arm	N	Endoscopic Improvement			Corticosteroid-free Remission				Treatment Persistence	
			%	Cumulative Rate	p-value	%	p-value	Cumulative Rates, p-value	Hazard Ratio (95% CI:)*	n	n, at Risk
Koliani-Pace et al. (2019) VEDO	VEDO (Era 1)†	182	NR	42	<0.01	NR	NR	27	NR	NR	NR
	VEDO (Era 2)‡	255	NR	58	--	NR	NR	21	NR	NR	NR
	Biologic-Naïve										
	VEDO	143	NR	54	NR	NR	NR	48, p=0.01§	NR	NR	NR
	Biologic-Experienced										
	VEDO	294	NR	47	NR	NR	NR	23, p=0.01§	NR	NR	NR
Macaluso et al. (2021) VEDO vs. ADA	**Week 52**										
	Overall										
	VEDO	277	31.8	NR	0.850	44.7	NR	NR	NR	NR	147
	ADA	308	33.8	NR	--	61.3	NR	NR	NR	NR	186
	Stratified Biologic-Naïve and Experienced Data Not Reported										
Supovec et al. (2025) VEDO vs. UST vs. Anti-TNF	**Week 208**										
	Overall										
	VEDO	59	NR	NR	NR	NR	NR	NR	NR	NR	5
	UST	55	NR	NR	NR	NR	NR	NR	NR	NR	10
	Anti-TNF	473	NR	NR	NR	NR	NR	NR	NR	NR	176
	Stratified Biologic-Naïve and Experienced Data Not Reported										

ADA: adalimumab, CI: confidence interval, IFX: infliximab, N: number, NR: not reported, TNF: tumor necrosis factor, SC: subcutaneous, UST: ustekinumab, VEDO: vedolizumab

*Hazard ratios are inverse probability weighting average treatment effect (IPW ATE).

†Era 1 data was collected in May 2014 through June 2015 from the VICTORY consortium.

‡Era 2 data was collected in July 2015 through June 2017 from the VICTORY consortium.

§P-value for biologic-naïve against biologic-experienced.

Table D3.32. Safety in RWEs

Trial	Arm	N	Any AEs	D/C due to AE	Death	SAEs	Infections	Serious Infections	Malignancy	Hospitalizations	Surgery
Garcia et al. (2024) VEDO vs. UST	**Week 208**										
	VEDO	207	3.6	1.6	0.5	1.1	7.2	2.9	NR	NR	NR
	UST	628	8	2	0	1.6	8	1.9	NR	NR	NR
Bohm et al. (2020) VEDO vs. IFX vs. Anti-TNF	**Month 12**										
	VEDO	659	NR	NR	0.2	0.5	NR	7.1	NR	NR	NR
	Anti-TNF SC	302	NR	NR	0.3	8.3	NR	15.6	NR	NR	NR
	IFX	305	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cohen et al. (2020) VEDO	**Week 208**										
	VEDO	14191	37662*	93*	NR	5230*	3064*	710*	83*	92*	134*
Karlqvist et al. (2024) VEDO vs. Anti-TNF	**Month 12**										
	VEDO	1221	NR	NR	NR	NR	NR	63*	NR	NR	NR
	Anti-TNF	1180	NR	NR	NR	NR	NR	38*	NR	NR	NR
Kirchgesner et al. (2022) VEDO vs. Anti-TNF	**Month 12**										
	VEDO	NR	NR	NR	NR	NR	NR	98*	NR	NR	NR
	Anti-TNF	NR	NR	NR	NR	NR	NR	439*	NR	NR	NR
Koliani-Pace et al. (2019) VEDO	**Month 12**										
	VEDO (Era 1)†	1013	NR	NR	NR	NR	NR	NR	NR	14.6	17.8
	VEDO (Era 2)‡	116	NR	NR	NR	NR	NR	NR	NR	16.6	16.8
Macaluso et al. (2021) VEDO vs. ADA	**Week 52**										
	VEDO	277	58*	NR	NR	NR	NR	NR	NR	NR	NR
	ADA	308	70*	NR	NR	NR	NR	NR	NR	NR	NR
Vu et al. (2023)	**Month 12**										
	VEDO	578	NR	NR	NR	NR	NR	NR	NR	NR	7.3
	UST	544	NR	NR	NR	NR	NR	NR	NR	NR	9.9

ADA: adalimumab, AEs: adverse events, Anti-TNFs: Tumor Necrosis Factor Antagonists, D/C: discontinuation, IFX: infliximab, IR: incidence rate, n: number, NR: not reported, SAEs: serious adverse events, VEDO: vedolizumab

*Number of events.

†Era 1 data was collected in May 2014 through June 2015 from the Truven MarketScan Database.

‡Era 2 data was collected in July 2015 through June 2017 from the Truven MarketScan Database.
§Cumulative rate.

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Trial, NCT, & Trial Sponsor	Study Design	Arms	Inclusion Criteria & Patient Population	Primary Outcome(s)	Estimated Completion Date
PANORAMA **NCT06581328** **Takeda**	Phase IV study evaluating moderate to severely active ulcerative colitis or Crohn's disease and the use of VEDO SC within a community setting. N=400	- VEDO IV 300 mg at week 0 and 2, then VEDO SC 108 mg q2w from week 6-12.	- Adults diagnosed with CD or UC. - For CD: CDAI 220-450 and SES-CD ≥6. - For UC: complete Mayo score of 6-12 with endoscopy subscore of 2-3.	- Percentage of CD participants with PRO-2 remission at week 14. - Percentage of UC participants with PRO-2 remission at week 14.	June 2028
NCT05428345 **Takeda**	A prospective, non-interventional, post-marketing study of adult participants with moderately to severely active UC or CD, who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or an Anti-TNF in South Korea. N=600.	- Observational review of South Korean adults treated with VEDO SC.	- Adults with moderately to severely active UC or CD, who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or an anti-TNF. - Evidence of therapeutic benefit after ≥2 VEDO IV infusions.	- Percentage of participants with serious adverse events (SAEs), adverse drug reactions (ADRs), serious ADRs, AEs of special interest (AESIs), unexpected AEs or ADRs up to week 52.	November 2027
NCT06045754 **Takeda**	Phase IV, open-label study to evaluate the efficacy and safety of dual targeted therapy with VEDO IV and ADA SC or VEDO IV and UST IV/SC in moderate to severe	Part A: - VEDO + ADA: VEDO IV 300 mg at weeks 0, 2 and 6, then q8w until week 22. ADA SC 160/80/40 mg at weeks 0, 2 and 4,	- Adults with CD for ≥3 months. - SES-CD ≥6 (moderate to severely active CD). - Inadequate response with, lost response to, or were intolerant to either	- Part A: percentage of participants with endoscopic response based on SES-CD score at week 26. - Part B: percentage of participants with endoscopic	June 2027

Trial, NCT, & Trial Sponsor	Study Design	Arms	Inclusion Criteria & Patient Population	Primary Outcome(s)	Estimated Completion Date
	CD. N=100	respectively, then 40 mg q2w until week 26. - VEDO + UST: VEDO IV 300 mg at weeks 0, 2 and 6, then q8w until week 22. UST IV 520, 390, or 260 mg (weight-based), then SC 90 mg 8 weeks after initial IV dose, then q8w until Week 24. Part B - VEDO: participants who achieve therapeutic benefit in Part A will receive VEDO IV 300 mg monotherapy, q8w week 30-46.	interleukin antagonist or an anti-TNF.	response based on SES-CD score at week 52.	
NCT03221036 **Takeda**	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of VEDO IV infusion treatment in Chinese subjects with moderately to severely active UC. N=402	- VEDO IV 300 mg - Placebo	- Adults with UC for ≥3 months. - Complete Mayo score of 6-12 with endoscopic subscore of ≥2 (moderately to severely active UC). - UC extending proximal to the rectum (≥15 cm of involved colon).	- Percentage of participants with clinical response at week 10. - Percentage of participants with clinical remission at week 60.	January 2028

Trial, NCT, & Trial Sponsor	Study Design	Arms	Inclusion Criteria & Patient Population	Primary Outcome(s)	Estimated Completion Date
			- Inadequate response with, lost response to, or were intolerant to either CSs, IMMs, or anti-TNFs.		
NCT05837897 **Takeda**	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group induction study followed by OLE period to examine the efficacy and safety of VEDO IV infusion treatment in Chinese subjects with moderately to severely active UC. N=402	- VEDO IV 300 mg, during induction and OLE phases. - Placebo	- Adults with CD for ≥3 months. - PRO-2 score of 14-34 and SES-CD score of ≥6 (moderately to severely active CD). - CD involvement of the ileum and/or colon. - Inadequate response with, lost response to, or were intolerant to either CSs, IMMs, or anti-TNFs.	- Percentage of participants with clinical response at week 14.	May 2031
VEDIAN **NCT06180382** **Takeda**	Phase IV multicenter, randomized, controlled study comparing VEDO to ADA dose intensification in patients with CD with loss of response or biomarker activity to ADA on first line with therapeutic drug concentration. N=220	- ADA SC, with optimization either 80 mg every 14 days or same dose of 40 mg every 7 days. - VEDO IV 300 mg at baseline, 14 days, 42 days, and 60 days, followed by 108 mg SC q2w.	- Patients with CD who had primary response to ADA or biosimilar with loss of response to ADA (40 mg q2w) with therapeutically adequate levels of ADA (> 7.5 µg/mL).	- Proportion of clinical and biomarker remission (composite score) at 24 weeks.	January 2027

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

ADA: adalimumab, Anti-TNFs: TNF-antagonists, CD: Crohn's disease, CDAI: Crohn's Disease Activity Index, CSs: corticosteroids, IMMs: immunomodulators, IV: intravenous, mg: milligrams, N: number, OLE: open-label extension, PRO-2: 2-item Patient-Reported Outcome Measure, SES-CD: Simple Endoscopic Score for CD, q2w: every 2 weeks, q8w: every 8 weeks, SC: subcutaneous, UC: ulcerative colitis, UST: ustekinumab, VEDO: vedolizumab, µg/mL: micrograms per milliliter

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	Caregiver productivity impacts included for infliximab IV administration.
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Notes: An "x" indicates that the impact was included in the analysis; Adapted from Sanders et al[131]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[132]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps three and four.
6. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Impact of Patient Involvement on Model Development

We discussed the preliminary model structure and assumptions with seven members of the patient community. The discussions consisted of three one-hour sessions held virtually over the Zoom meeting platform. Session One (combined for patients with UC and CD) and Session Two (separately for patients with UC and CD) were completed prior to the posting of the Model Analysis Plan. The third session (Session Three) was an optional discussion for participants that took place following completion of the Draft Evidence Report and prior to submission to CMS. The aim of the discussions was to work with patients on a proposed draft analysis plan to ensure that the patient's experience with Entyvio and therapeutic alternatives, and goals for treatment were reflected in the economic analysis structure, data, and key assumptions.

Session Three was an opportunity for ICER to share the findings from the economic analysis and the impact of patient engagement in the modeling effort. Five of seven patients participated in Session Three.

The first session provided background information on the role of cost-effectiveness analysis in health technology assessment and the opportunities to inform the CMS drug price negotiation process, and provided a summary of the draft analysis plan for the review of Entyvio. The second session consisted of a semi-structured group discussion with open-ended questions to ensure that

the draft analysis plan reflected the perspectives and experiences of patients living with UC and CD. The third session consisted of a recap of material presented during Sessions One and Two, provided an overview of how patient input impacted the model development, and shared draft results of the analysis. Session Three also provided an opportunity for participants to highlight if the model reflected their experience and expectations for treatment, if there was anything that we missed including based on discussions from Sessions One and Two, and if there were any surprises or additional considerations they wanted to share for inclusion in the CMS submission.

Discussion Questions During Session Two Included the Following:

Stages of Disease

- Do the health states described match your experience living with UC or CD? Are there any states that we missed?
- Do you experience or think about your disease differently?

Outcomes of Interest

- If treatment could improve any aspect of your disease, what types of improvements would be most impactful in your life? For example, keeping you in remission or not having to have colectomy (UC) or surgery (CD)?

Treatments of Interest

- What are the advantages and disadvantages of intravenous and subcutaneous forms of administration?
- Do you experience burden with at-home administration (e.g., time, uncertainty, remembering to do the injection)?
- How does each form of administration impact your caregiver (if relevant)?
- What additional costs do you experience when you receive the intravenous form of administration (e.g., travel, parking, time)?

Key Data Inputs for the Model (health-related quality of life)

- How would you describe changes in your quality of life between when you are in remission compared to when you did not have UC or CD?
- If you are responding to treatment, but not in remission, how does your quality of life compare to when you were in remission or in active disease?

- How did your quality of life around the time of surgery compare to when you were in remission on treatment or did not have UC or CD? Are there additional quality of life impacts that you experience because of colectomy (UC) or surgery (CD)?

Key Data Inputs for the Model (medical costs)

- When you are responding to treatment, but not in remission, about how often would you see your physician, visit the ER, or have an inpatient or outpatient visit (outside of any visits you have for medication).

- How does this compare to when you are experiencing active disease?

Key Data Inputs for the Model (non-medical costs and caregiver impacts)

- In addition to medical-related costs, do you experience other financial impacts? How does UC or CD impact your ability to do the things you want to do on a day-to-day basis - for example, with paid work, volunteering, or household activities? How does this differ depending on whether you are in remission, responding to treatment without remission, or in active disease?

- How do your caregiver support needs differ when you are in remission, responding to treatment without remission, or in active disease?

Additional Consideration

- Some patients may experience symptoms outside of their digestive tract (e.g., joint pain, mouth sores, skin conditions, etc.). If you have experienced any of these additional symptoms, how did the management of your condition change (e.g., medication switch, or new medication added, etc.)? Did treatment help with these additional symptoms?

Final Thoughts

- Are there any choices that we have made for the Model Analysis Plan that you disagree with?

- What have we not yet discussed that you were hoping to share?

- What is the most important thing that you don't want ICER to miss as we finalize our Model Analysis Plan for Entyvio?

Discussion Questions During Session Three Included the Following:

- Were there any choices that ICER made for the model analysis that you disagree with?
- What surprised you when we presented the results?
- What would you like CMS to know about UC or CD, your experience, and your expectations for treatment when they review the evidence?

During Session Three, participants indicated that Session One and Two discussions on experiences and expectations for treatment were very robust and appropriately considered in the model analysis plan. There was an expressed appreciation for incorporating participant perspectives in the analysis and they were grateful that there is an organization dedicated to compiling the data, comparing how well each drug works, and listening to their experiences. Participants found it interesting to hear how their input impacted the outcomes of the model and some were surprised that the drugs were all found to be very similar. Despite being somewhat surprised with the results, more than one participant indicated that it "*validated*" the feeling that you don't know *"…what is going to work for you until you're there…"* and it is often unclear why a drug stops working. Participants shared additional experiences with switching between drugs, shared the challenges with vein access for IV administration, and highlighted the importance of physicians setting realistic expectations about how well a drug may or may not work given the variability between patients in how they respond to medications, and asked for confirmation that all potential side effects were taken into consideration in the model. One participant also asked about potential implications for the analysis because of not including guselkumab in the analysis.

Overview and Model Structure

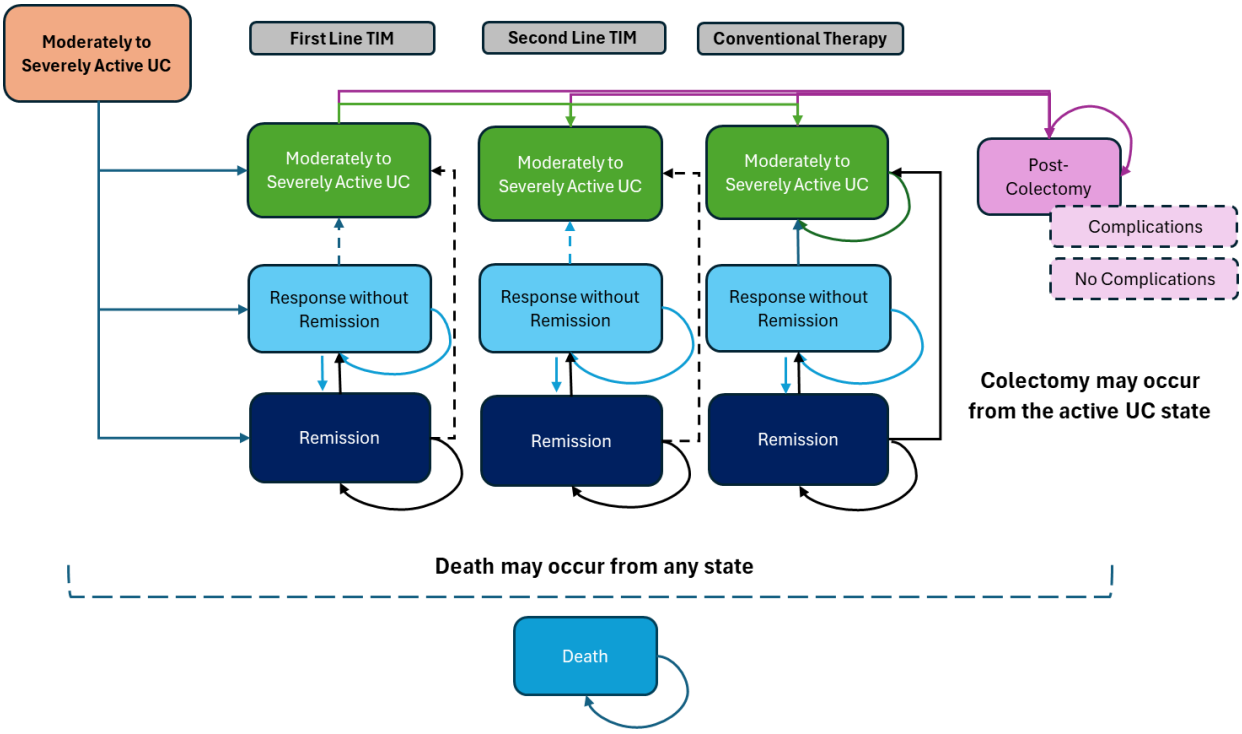
We developed two separate *de novo* decision analytic models for this evaluation, one for UC and one for CD. The analytic structure was primarily informed by ICER's prior model for the assessment of targeted immune modulators for UC in 2020,[91] other prior economic models of treatments for UC and CD, and key clinical trials as well as important observational studies. Costs and outcomes were discounted at 3% per year.

Both models focused on a hypothetical cohort of Medicare patients with moderately to severely active UC or CD who initiated treatment with Entyvio, infliximab, or ustekinumab. Model cycle length was eight weeks based on what was observed in prior published economic models and key clinical trials (i.e., based on timing of clinical endpoint assessment, frequency of treatment administration, and the induction and maintenance periods of treatment).

Ulcerative Colitis

For UC (Figure E1.1A), the Markov model consisted of health states for moderately to severely active disease, clinical response without remission, clinical response with remission, post-colectomy (with and without complications), and death. All patients entered the model receiving an induction period of treatment with Entyvio, infliximab, or ustekinumab. Following induction, patients who achieved clinical response (with or without remission) continued to receive their initial treatment. Patients who did not achieve clinical response during induction, or who did not continue to respond to treatment during the maintenance phase, transitioned to subsequent therapy. Patients could also discontinuation treatment due to adverse events (AEs) while responding to treatment or in remission. These patients also transitioned to subsequent therapy. When Entyvio was compared to infliximab, we assumed that the subsequent line of therapy was ustekinumab, and when Entyvio was compared to ustekinumab, we assumed that the subsequent line of therapy was infliximab. Patients who did not respond to or who did not continue to respond to subsequent therapy moved to conventional therapy. Conventional therapy transition probabilities were based on the placebo arms of relevant clinical trials and for costing purposes and model simplicity, conventional therapy was defined as an induction period of prednisone followed by mercaptopurine or azathioprine. Patients with active disease had a per-cycle probability of colectomy, and after colectomy moved to the post-colectomy health state. The model also included a risk of chronic pouchitis for a percentage of patients following colectomy. All patients in the post-colectomy health state remained in this state until death.

Figure E1.1 A. Model Schematic (UC)



TIM: Targeted immunotherapy, UC: ulcerative colitis

Figure E1.1A. Notes: All patients entered the model with moderately to severely active UC. Within each line of therapy (first and second line), there was an induction and a maintenance phase where patients were at risk of moving between the moderately to severely active, response without remission, and remission health states. Dotted arrows from 'Response without Remission' to 'Moderately to Severely Active UC' and 'Remission' to 'Moderately to Severely Active UC' health states within the first and second line of therapy indicate that patients who follow this trajectory transition to the next line of therapy immediately upon entering the active health state. Movement to subsequent lines of therapy was dependent on response to treatment and discontinuation due to AEs and patients who remained in the active UC state had a per cycle probability of colectomy. After colectomy, patients moved to the post-colectomy health state with a risk of short-term and long-term complications and remained there until death. Death occurred from any state.

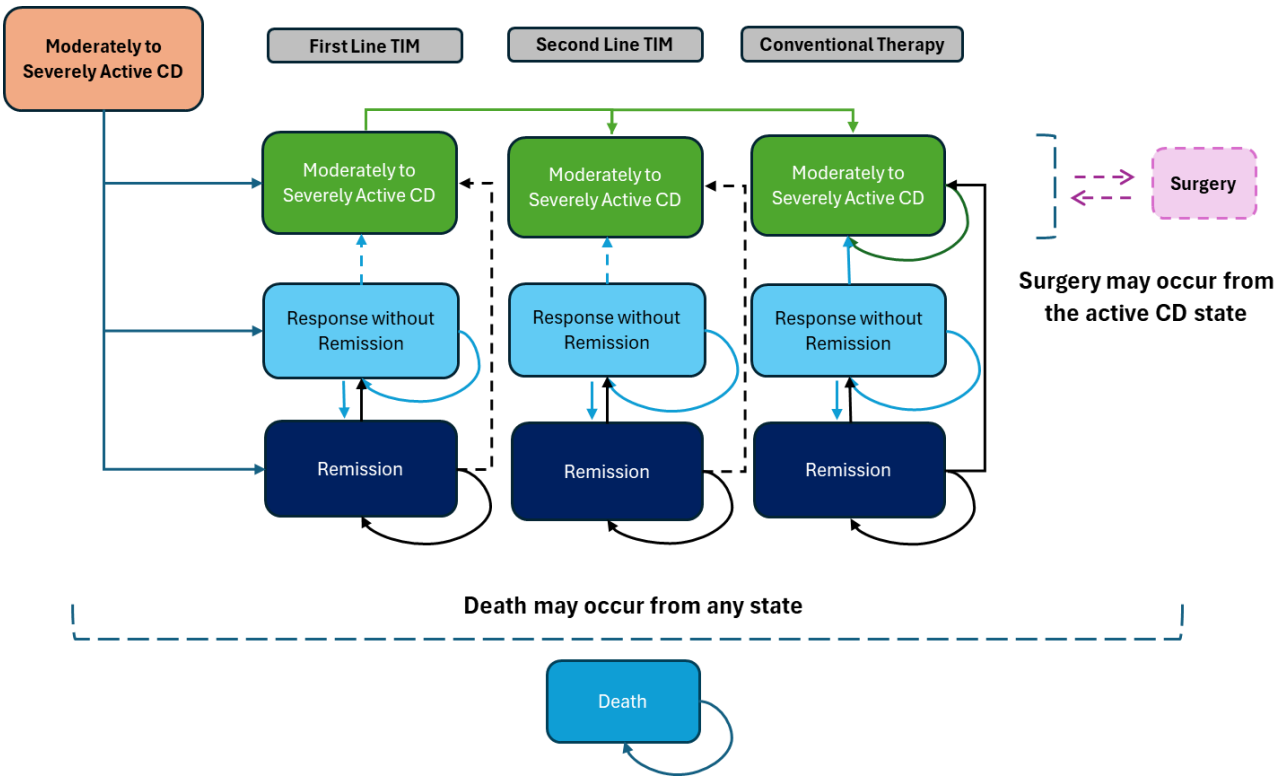
Crohn's Disease

For CD (Figure E1.1B), the Markov model consisted of a similar set of health states as for UC, including moderately to severely active disease, clinical response without remission, clinical response with remission, and death. All patients entered the model receiving an induction period with Entyvio, infliximab, or ustekinumab. Following induction, patients who achieved clinical response (with or without remission) continued to receive their initial treatment. Patients who did not achieve clinical response during induction, or who did not continue to respond to treatment during the maintenance phase, transitioned to subsequent therapy. Patients could also discontinue treatment due to adverse events (AEs) while responding to treatment or in remission. These

patients also transitioned to subsequent therapy. As with the UC model, when Entyvio was compared to infliximab, we assumed that the subsequent line of therapy was ustekinumab, and when Entyvio was compared to ustekinumab, we assumed that the subsequent line of therapy was infliximab. Patients who did not respond to or who did not continue to respond to subsequent therapy moved to conventional therapy. Conventional therapy transition probabilities were based on the placebo arms of relevant clinical trials and for costing purposes and model simplicity, conventional therapy was defined as an induction period of prednisone followed by mercaptopurine or azathioprine. Patients with moderately to severely active CD had a risk of surgery in each model cycle, and this was captured as a transient episode with additional costs and associated impacts on health outcomes. Following surgery, patients remained on the same therapy and in the same health state.

For both models, patients remained in the model until they die. All patients could transition to death from all causes from any of the alive health states. In addition, patients had an acute risk of death from colectomy (for patients with UC) and surgery (for patients with CD).

Figure E1.1 B. Model Schematic (CD)



CD: Crohn's disease, TIM: Targeted immunotherapy

Figure 2.1 B. Notes: All patients entered the model with moderately to severely active CD. Within each line of therapy (first and second line), there was an induction and a maintenance phase where patients were at risk of moving between the moderately to severely active, response without remission, and remission health states. Dotted arrows from 'Response without Remission' to 'Moderately to Severely Active UC' and 'Remission' to 'Moderately to Severely Active UC' health states within the first and second line of therapy indicate that patients who follow this trajectory transition to the next line of therapy immediately upon entering the active health state. Movement to a subsequent line of therapy was dependent on response to treatment and discontinuation due to AEs and patients who remained in the active CD state had a per cycle probability of surgery (bowel resection). After surgery, patients remained on the same treatment and in the same health state. Death occurred from any state.

Target Population

The population of focus for the economic evaluation included Medicare patients with moderately to severely active UC or CD with and without prior use of biologics and without extraintestinal manifestations (EIMs) at baseline. Baseline population characteristics (Table E1.2) for both models was informed by manufacturer submitted data consisting of the demographic characteristics of people with IBD on Medicare Fee For Service (Takeda data on file).[133] In a scenario analysis, we

explored the impact of focusing on a 65 and older Medicare population. For the threshold price analysis, we assumed that 55% of the population had CD.[77]

Table E1.2. Base-Case Model Cohort Characteristics

	UC	CD	Primary Source
	Value (SD)	Value (SD)	
Mean Age, Years (Overall) (Base Case)	71 (11)	65 (14)	Takeda data on file[133]
Mean Age, Years (≥65) (Scenario Analysis)	74 (5)	74 (5)	Takeda data on file[133]
Female, %	53%	60%	Takeda data on file[133]
Patient Weight, kg	73.4	70.0	GEMINI-I[41], [63,64]

CD: Crohn's disease, kg: kilograms, UC: ulcerative colitis

Treatment Strategies

The list of interventions was developed based on input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The intervention of interest for this review was Entyvio (Entyvio®) (IV and SC versions) based on the expectation of inclusion in the CMS drug price negotiations for implementation in 2028.

The comparators for Entyvio were:

- Infliximab (IV biosimilar, SC Zymfentra®)
- Ustekinumab (IV and SC biosimilars)

Comparators were selected based on discussions with patient organizations, clinicians, manufacturers, and payers on what represented the most relevant alternatives to Entyvio and the availability of biosimilar alternatives.

E2. Model Inputs and Assumptions

Our model included several assumptions as stated below.

Table 2.1. Key Model Assumptions

Assumption	Rationale
Patients were assumed to enter the model receiving Entyvio or a comparator (infliximab or ustekinumab) and moved through two subsequent lines of therapy including a second biologic and conventional therapy.	It was not our intent to identify the cost-effectiveness of all possible treatment sequences, of which there are many. Our focus was to estimate the cost-effectiveness of Entyvio as a first line treatment option and as such, subsequent treatment options were intended to be similar between intervention and comparator agents. Subsequent treatment options were selected based on what represented the most relevant options for the Medicare population while retaining the focus of the model to be on initial therapy.
Patients who remained in the Moderately to Severely Active UC or CD disease state in each model cycle or who discontinued due to AEs were assumed to progress to the next line of therapy.	Clinical experts indicated that a lack of response to treatment is typically managed by moving patients to the next line of therapy.
A pooled treatment effect was used to capture the efficacy of treatment for patients who had previously received biologic therapy and those that had not and applied regardless of line of therapy.	The inclusion criteria of key clinical trials included patients with prior biologic exposure and those that had not, and it was expected that the treatment effect was representative of the combined populations. Furthermore, there was no data to differentiate treatment effect by line of therapy.
The treatment effects observed in the clinical trials were generalizable to what would be observed in a population of only Medicare-aged beneficiaries.	Treatment efficacy data specific to the Medicare population was not available. For all other inputs, we have prioritized using data specific to a Medicare-eligible population, where possible.
For patients with UC, we assumed that patients who received a colectomy remained in the post-colectomy remission health state for life. The model assumed that some patients experienced post-colectomy complications.	Evidence indicated that a colectomy offers improvement with sustained remission. We also heard during the focused sessions with patients that a post-colectomy health state does not always equate to sustained remission without complications. Short term and long-term complications post-colectomy were included in the model.
For patients with CD, we assumed that patients who have surgery (bowel resection) experienced additional costs and impacts on health-related quality of life and remained on current treatment in their current health state. Risk of perianal fistula was not included in the model.	Clinical experts indicated that surgery would help address the acute episode but was not expected to change the course of the disease to warrant a change in treatment. Surgery for perianal fistula is expected to be independent of disease course and therefore was anticipated to occur at the same rate regardless of treatment strategy.

Assumption	Rationale
The cost and quality of life impacts from new onset extraintestinal manifestations (EIM) were assumed to be captured in the health state costs and utilities used for the model.	We heard during the focused sessions with patients that EIMs were common for patients with UC and CD. The health state costs and utilities used in the model are likely to capture the impacts of new-onset EIMs and as such, including additional impacts would likely have resulted in double counting. Additionally, there was limited evidence to suggest that there was a differential rate of new-onset EIMs between treatments. In the CD model, we conducted a scenario analysis to account for additional pharmacy costs for treatment that may not have been included in the health state costs used in the model based on literature that suggested that there was a statistically significant difference in the rate of new-onset EIMs for patients in an active versus an inactive disease state.

CD: Crohn's disease, EIM: extraintestinal manifestations, UC: ulcerative colitis

Model Inputs

Clinical Inputs

The clinical inputs for the models included transition probabilities to model disease activity, discontinuation to inform treatment switching, adverse events, and mortality. Efficacy data for Entyvio, infliximab, and ustekinumab were derived from the results of an ICER Network Meta-Analyses (NMA) of RCTs of biologic therapies for moderate to severe UC and CD. A pooled treatment effect was used to capture the efficacy of treatment for patients who had previously received biologic therapy and those who had not. Data from the placebo arms of the included trials was used to represent conventional therapy.

Transition Probabilities

Induction Phase

Transition probabilities for the induction phase of treatment were derived for each intervention and comparator using the relative risks calculated from ICER's NMA (see Section 3.2 and 3.3 of the main report) and applied to the placebo group transition probabilities from the same NMA, which represented conventional therapy. Conventional therapy post-induction health state distribution for the UC and CD models is outlined in Tables E2.2, and E2.3 respectively, and risk ratios for post-induction health state distribution for each treatment are outlined in Tables E2.4 (UC) and E2.5 (CD).

Table E2.2. Conventional Therapy Post-Induction Health State Distribution (UC)

Health State	Moderately to Severely Active	Clinical Response without Remission	Clinical Response with Remission	Source
Moderately to Severely Active*	66%	25%	9%	ICER NMA

ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis, UC: ulcerative colitis

*Represents the percentage of patients who started in the moderately to severely active state and then either stayed in the same state or moved to another state (clinical response without remission or clinical response with remission) at the end of the induction phase. Post-induction health state distribution was conditional on survival.

Table E2.3. Conventional Therapy Post-Induction Health State Distribution (CD)

Health State	Moderately to Severely Active	Clinical Response without Remission	Clinical Response with Remission	Source
Moderately to Severely Active*	73%	14%	13%	ICER NMA

CD: Crohn's disease, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis

*Represents the percentage of patients who started in the moderately to severely active health state and then either stayed in the same state or moved to another state (clinical response without remission, or clinical response with remission) at the end of the induction phase. Post-induction health state distribution was conditional on survival.

Table E2.4. Risk Ratios for Post-Induction Health State Distribution (UC)

	Clinical Response without Remission, Value (95% CrI)	Clinical Response with Remission, Value (95% CrI)	Source
Conventional Therapy	Reference	Reference	
Entyvio	1.77 (1.46, 2.14)	2.81 (1.97, 4)	ICER NMA
Infliximab	1.71 (1.38, 2.09)	2.62 (1.76, 3.82)	ICER NMA
Ustekinumab	1.91 (1.47, 2.43)	3.27 (1.96, 5.21)	ICER NMA

CrI: credible interval, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis, UC: ulcerative colitis

Table E2.5. Risk Ratios for Post-Induction Health State Distribution (CD)

	Clinical Response without Remission, Value (95% CrI)	Clinical Response with Remission, Value (95% CrI)	Source
Conventional Therapy	Reference	Reference	
Entyvio	1.49 (1.15, 1.86)	1.7 (1.21, 2.31)	ICER NMA
Infliximab	1.82 (1.46, 2.31)	2.25 (1.66, 3.15)	ICER NMA *Assumption
Ustekinumab	1.78 (1.47, 2.14)	2.18 (1.68, 2.8)	ICER NMA

CD: Crohn's disease, CrI: credible interval, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis

*No data was available to inform the RR for post-induction response or remission for infliximab. Results from the ICER NMA for adalimumab were used as a proxy given the similar mechanisms of action and based on results during the maintenance phase showing no statistically significant differences between infliximab and adalimumab (RR 1.01 for both remission and response for infliximab vs adalimumab [see Tables 3.10 and 3.11 in Section 3.3 of the Main Report]).

Maintenance Phase

Transition probabilities for the maintenance phase were conditional upon achieving response with or without remission during the induction phase, and as with the induction phase, were derived for each intervention and comparator using the relative risks calculated from ICER's NMA and applied to the placebo group transition probabilities from the same NMA which represented conventional therapy. No data was available to differentiate between transition probabilities for patients who respond with or without remission during maintenance, so the same maintenance transition probabilities were applied for both groups. Sandborn 2012 (UC) and Sandborn 2007 (CD),[97,134] both treat-through trials, were used to calculate the probability of clinical remission and clinical response without remission among placebo non-responders during the maintenance phase. Conventional therapy transition probabilities during the maintenance phase are included in Table E2.6 (UC) and Table E2.7 (CD), and risk ratios for the transition probabilities during the maintenance phase are included and outlined in Tables E2.8 (UC) and E2.9 (CD).

Table E2.6. Conventional Therapy Transition Probabilities During the Maintenance Phase (Eight-Week Cycles) (UC)

Health State*	Moderately to Severely Active	Clinical Response without Remission	Clinical Response with Remission	Source
Moderately to Severely Active	91%	7%	2%	ICER Clinical Review, Sandborn 2012 [30,97]
Clinical Response without Remission	68%	14%	19%	ICER NMA, Assumption
Clinical Response with Remission	68%	14%	19%	ICER NMA, Assumption

NMA: network meta-analysis, ICER: Institute for Clinical and Economic Review, UC: ulcerative colitis

Note: Due to rounding, row totals may not equal 100%.

*The health states depicted in the rows of the table represent the starting health state. Each cell represents the percentage of patients who moved from the starting state (represented in the row heading) to the ending state (represented in the column heading) during each cycle. Transition probabilities were conditional on survival.

Table E2.7. Conventional Therapy Transition Probabilities During the Maintenance Phase (Eight-week cycles) (CD)

Health State*	Moderately to Severely Active	Clinical Response without Remission	Clinical Response with Remission	Source
Moderately to Severely Active	94%	4%	2%	ICER Clinical Review, Sandborn 2007†[134]
Clinical Response without Remission	68%	7%	24%	ICER NMA, Assumption
Clinical Response with Remission	68%	7%	24%	ICER NMA, Assumption

CD: Crohn's disease, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis
Note: Due to rounding, row totals may not equal 100%
*The health states depicted in the rows of the table represent the starting health state. Each cell represents the percentage of patients who move from the starting state (represented in the row heading) to the ending state (represented in the column heading) during each cycle. Transition probabilities are conditional on survival.
†Calculated based on data from Table 2 and Figure 2 of Sandborn 2007. Assumes that 50% of patients who did not have remission at week 6 but achieved remission at week 26 were responding at week 6. Converted to 8-week transition probabilities.

Table E2.8. Risk Ratios for Transition Probabilities During the Maintenance Phase (UC)

	Clinical Response without Remission* (95% CrI)	Clinical Response with Remission* (95% CrI)	Source
Conventional Therapy	Reference	Reference	
Entyvio	1.67 (1.02, 2.33)	2.05 (1.03, 3.4)	ICER NMA
Infliximab	1.64 (1.11, 2.16)	1.99 (1.16, 2.97)	ICER NMA
Ustekinumab	1.92 (1.53, 2.37)	2.52 (1.8, 3.42)	ICER NMA

CrI: credible interval, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis, UC: ulcerative colitis
*The risk ratios represent the relative effectiveness of treatment in achieving clinical response with remission and clinical response without remission compared to conventional therapy (regardless of response with or without remission during the induction phase).

Table E2.9. Risk Ratios for Transition Probabilities During the Maintenance Phase (CD)

	Clinical Response without Remission* (95% CrI)	Clinical Response with Remission* (95% CrI)	Source
Conventional Therapy	Reference	Reference	
Entyvio	1.5 (1.06, 2.2)	1.53 (1.06, 2.3)	ICER NMA
Infliximab	2.03 (1.15, 2.96)	2.11 (1.16, 3.16)	ICER NMA
Ustekinumab	1.73 (1.12, 2.46)	1.78 (1.13, 2.59)	ICER NMA

CD: Crohn's disease, CrI: credible interval, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis
*The risk ratio represents the relative effectiveness of treatment in achieving clinical response with remission and clinical response without remission compared to conventional therapy (regardless of response during the induction phase unless data allow).

Rate of Colectomy (Ulcerative Colitis)

Patients with UC were at risk of colectomy from the active disease state. The probability of having a colectomy was constant each cycle over the lifetime of the model, and patients who underwent a colectomy subsequently entered the post-colectomy health state. Risk of colectomy was based on a systematic review and meta-analysis of population-based cohort studies that captured the cumulative incidence of colectomies for patients with newly diagnosed UC.[135] The per cycle probability was based on a 10-year risk of colectomy (with or without an ileal pouch–anal anastomosis) of 9.6% (95% CI: 6.3–14.2) and converted to an annual probability of 1.54% (or 0.15% per eight-week cycle). Short-term complications with one-time cost and utility implications and acute mortality from colectomy were also captured (Table E2.10). Costs for short-term complications from colectomy were captured in the one-time colectomy procedure costs outlined in the *Cost Inputs* section which were based on the frequency of procedures with major complications or comorbidities, with complications or comorbidities, and without complications or comorbidities. Based on data from a prospective surgical database in the US, ACS-NSQIP (American College of Surgeons National Surgical Quality Improvement Program Participant), specifically for individuals ≥65 years of age. We assumed a one-time disutility for 37.2% of patients experiencing an acute complication based on the predominant complication reported (intra-abdominal infection).[136] This was applied for one model cycle (eight weeks), assuming a six to eight week recovery time.[137]

We heard during the focused sessions with patients that a post-colectomy health state did not always equate to sustained remission without complications or sustained remission without treatment. It was unclear if continued treatment was a result of complications from surgery, a new diagnosis of CD, extraintestinal manifestations, or something else. We assumed that a percentage of patients had long-term complications from colectomy (chronic pouchitis; 20.3%)[138] based on a retrospective study of patients experiencing recurrent pouchitis following a colectomy with ileal pouch-anal anastomosis and incurred ongoing costs and utility impacts in the post-colectomy health state. The same study found that some patients without complications from the procedure remained on biologic therapy following colectomy due to a new diagnosis of CD.[138] We assumed that the costs and quality of life impacts for these patients were already captured in the health state costs and utilities in the post-colectomy health state. Importantly, our UC model did not focus on the cases of post-colectomy CD that may have occurred for patients originally diagnosed with UC. We relied on the CD model to understand the costs and health outcomes associated with the treatments of interest for patients with CD regardless of how they were diagnosed.

The utility for patients with chronic pouchitis was 0.40 based on a US-based time-trade-off study with 48 participants and structured interviews supported by visual aids.[139] Costs of chronic pouchitis was based on year two costs from Barnes 2022 which compared US administrative claims data for patients with and without pouchitis for the first two years after colectomy with ileal pouch-anal anastomosis between 2007 and 2016.[138] Costs were inflated to 2024 US dollars.

The rate of acute and chronic complications from colectomy and their associated cost and quality of life impacts are outlined in Table E2.10.

Table E2.10. Complications from Colectomy for UC

Parameter	Value (SD)	Source
Probability of short-term acute complications from colectomy	37.2%*	Bollegala 2017[136]
Disutility of short-term acute complications from colectomy	-0.13 (0.25)†	Worbes-Cerezo 2019[137]
Probability of chronic pouchitis post-colectomy	20.3%	Barnes 2022[138]
Utility of chronic pouchitis post-colectomy	0.40‡	Arseneau 2006[139]
Annual costs of chronic pouchitis post-colectomy	$12,812	Barnes 2022[138]

SD: standard deviation, UC: ulcerative colitis

*Calculated based on a weighted average of complications for total and partial colectomy, open and laparoscopic, where applicable, for elderly patients. Costs for acute complications were included in the average cost of a colectomy outlined in the *Cost Inputs* section below.

†Assuming intra-abdominal infection (Bollegala 2017)[136] and applied for one model cycle (8 weeks) based on Worbes-Cerezo 2019[137] suggesting that recovery from surgery may take 6-8 weeks.

‡Applied for lifetime of the model for percentage of patients with chronic pouchitis within the post-colectomy health state.

Rate of Surgeries (Crohn's Disease)

Patients with CD were at risk of surgery for small-bowel resection *only* in the moderately to severely active CD health state. The probability of surgery was constant in each cycle while patients were in this health state, and patients who underwent surgery stayed in the same health state, but incurred costs and quality of life decrements associated with surgery. The probability of surgery was based on a systematic review and meta-analysis of population-based cohort studies that captured the cumulative incidence of surgeries for patients with newly diagnosed CD.[135] The per cycle probability was based on a 10-year risk of surgery (intestinal resections) of 26.2% (95% CI: 23.4 to 29.4) and converted to an annual probability of 2.99% (or 0.47% per 8-week cycle). Clinical experts indicated that surgery for perianal fistula was common among patients with CD, however, incidence was expected to be independent of disease course and therefore anticipated to occur at the same rate regardless of treatment strategy. As such, we did not include this event in the model.

The rate of acute complications from surgery and quality of life impacts are outlined in Table E2.11.

Table E2.11. Complications from Surgery for CD

Parameter	Value (SD)	Source
Probability Of Short-Term Acute Complications from Small-Bowel Resection	38.1%*	Bollegala 2017[136]
Disutility Of Short-Term Acute Complications from Small-Bowel Resection	-0.13 (0.25)†	Worbes-Cerezo 2019[137]

CD: Crohn's disease, SD: standard deviation

*Calculated based on a weighted average of complications for total and partial colectomy, open and laparoscopic, where applicable, for elderly patients. Costs for acute complications were included in the average cost of surgery outlined in the *Cost Inputs* section below

†Applied for one model cycle (8 weeks) based on Worbes-Cerezo 2019[137] that suggested recovery from surgery takes 6-8 weeks.

Development of Extra-Intestinal Manifestations

We heard during the focused sessions with patients that extra-intestinal manifestations were common and were present even during times of remission. Importantly, the health state costs and utilities identified for the model were likely to capture the impacts of extraintestinal manifestations and as such, including additional costs and quality of life impacts were not included in the base case analysis because it would likely result in double counting. Additionally, there was limited evidence to suggest a differential rate of new-onset extraintestinal manifestations between treatments,[140] and we specified our population of focus as patients who did not have extraintestinal manifestations at baseline that would preferentially favor a particular treatment choice. However, a study by Vavricka 2011 demonstrated that patients with active CD were at greater risk of extraintestinal manifestations compared to patients without active disease (58.5% vs. 40.4%, p=0.003).[141] To account for the possibility of excluding EIM related pharmacy costs, we conducted a scenario analysis in the CD model that captured the additional pharmacy costs associated with treating the most common type of extra-intestinal manifestations (peripheral arthritis)[142] for some patients (18.1%)[141] in the active disease state *only*. We assumed that patients remained on their current treatment and additional quality of life impacts were not included as they were assumed to be captured in the health state utility values. Unlike CD, there was no evidence to suggest that patients with active UC are at greater risk of EIMs compared to patients without active disease,[141] so we did not conduct the same scenario analysis for the UC model.

Discontinuation

Patients who did not achieve clinical response during induction, or who did not continue to respond to treatment during the maintenance phase of treatment discontinued treatment and moved to the next line of therapy. In addition to discontinuation due to loss of efficacy, discontinuation due to adverse events (AEs) were included for patients who were responding to treatment (with or without remission). These rates were based on conventional therapy rates from the ICER clinical

review converted to a per-cycle probability and adjusted by the ICER NMA derived relative risks for each of the intervention and comparators (Table E2.12 [UC] and Table E2.13 [CD]). Discontinuation rates observed in the phase of the trials were extrapolated beyond one year under the assumption that the same discontinuation rates apply for the remainder of time on treatment. Patients who discontinued treatment due to AEs also moved to the next line of therapy.

Table E2.12. Discontinuation due to AEs (UC)

Treatment	Induction	Maintenance	Source and Notes
	Value (95% CI:)	**Value (95% CI:)**	
Conventional Therapy	2.97% (1.57%, 5.53%)	1.58% (1.32%, 1.89%)	ICER Clinical Review
RR vs. Conventional Therapy			
	Value (95% CrI)	**Value (95% CrI)**	
Entyvio	0.75 (0.26, 2.32)	0.46 (0.21, 0.95)	ICER NMA
Infliximab	0.61 (0.18, 1.80)	0.79 (0.3, 2.08)	ICER NMA
Ustekinumab	0.26 (0.01, 2.39)	0.24 (0.05, 0.94)	ICER NMA

AE: adverse event, CI: confidence interval, CrI: credible interval, NMA: network meta-analysis, UC: ulcerative colitis, RR: relative risk

Table E2.13. Discontinuation due to AEs (CD)

Treatment	Induction	Maintenance	Source and Notes
	Value (95% CI:)	**Value (95% CI:)**	
Conventional Therapy	4.65% (2.73%,7.81%)	1.62% (1.00%,2.60%)	ICER Clinical Review
	Value (95% CrI)	**Value (95% CrI)**	
RR vs. Conventional Therapy			
Entyvio	0.48 (0.16, 1.34)	0.57 (0.16, 1.92)	ICER NMA
Infliximab	0.40 (0.09, 1.42)*	2.23 (0.46, 9.43)	ICER NMA, Assumption*
Ustekinumab	0.15 (0.0, 1.74)	0.21 (0.02, 2.34)	ICER NMA

AE: adverse event, CI: confidence interval, CrI: credible interval, CD: Crohn's disease, NMA: network meta-analysis, RR: relative risk

*No data was available to inform the RR for discontinuation due to AEs during induction for infliximab. Results from the ICER NMA for adalimumab were used as a proxy given the similar mechanisms of action.

Mortality

The risk of death was based on general population age- and sex-adjusted mortality using United States (US) 2019 life tables and adjusted for an increased risk of death among patients with UC and CD in all alive health states.[143] Standardized mortality ratios (SMRs) for UC (1.19; 95% CI: 1.06 to 1.35) and CD (1.38; 95% CI: 1.23 to 1.55) were applied to general population mortality based on a meta-analysis of studies reporting all-cause mortality SMRs for UC and CD.[144] There was no evidence to suggest that mortality risk differs between health states, so the same SMR was applied to all health states. A one-time acute risk of death from colectomy (UC) and small bowel surgeries (CD) were also included based on data from a prospective surgical database in the US (American College of Surgeons National Surgical Quality Improvement Program [ACS-NSQIP]) and specifically for individuals ≥65 years of age.[136] Mortality inputs are outlined in Table E2.14 (UC) and Table E2.15 (CD). No direct effects of treatment on mortality were modeled.

Table E2.14. Mortality Inputs (UC)

Parameter	Value	Source	Notes
SMR, UC	1.19 (95% CI: 1.06, 1.35)	Bewtra 2013[144]	Lifetime risk
Acute Risk of Death, Colectomy	5.1%	Bollegala 2017[136]	One-time risk*

CI: confidence interval, SMR: standardized mortality ratio, UC: ulcerative colitis

*Based on a weighted average of the percentage of patients with open and laparoscopic procedures and total and partial colectomy.

Table E2.15. Mortality Inputs (CD)

Parameter	Value	Source	Notes
SMR, CD	1.38 (95% CI: 1.23, 1.55)	Bewtra 2013[144]	Lifetime risk
Acute Risk of Death, Small Bowel Resection	4.2%	Bollegala 2017[136]	One-time risk*

CD: Crohn's Disease, CI: confidence interval, SMR: standardized mortality ratio

*Based on a weighted average of the percentage of patients with open and laparoscopic procedures.

Adverse Events

The model included the costs and quality of life impacts associated with ongoing risk of treatment-related serious infections based on data from the ICER Clinical review for UC (Table E2.16) and CD (Table E2.17). Rates of serious infections for conventional therapy were derived from the pooled placebo arms of the ICER NMA for induction and from the published literature for maintenance and were assigned a one-time cost of $10,850 based on the cost of an inpatient visit for pneumonia given that it is a commonly reported serious infection. The cost was calculated using the weighted average cost per admission from the Healthcare Cost and Utilization Project National Inpatient

Sample (HCUP NIS) database of simple pneumonia and pleurisy with major complications or comorbidities, with complications or comorbidities, and without complications or comorbidities (Medicare Severity Diagnosis Related Group [MS-DRG] 193, 194, 195).[145] The weighted average of costs was based on the frequency of each case during the same time period (44% with major complications or comorbidities, 32% with complications or comorbidities, 24% with no complications or comorbidities). Hazard ratios for infliximab vs conventional therapy and Entyvio and ustekinumab versus infliximab were based on published literature (Table E2.16 and E2.17). There was no evidence to demonstrate a differential rate of thrombotic and hepatic events, or differential rates of treatment-related lymphomas between treatments, so these events were not included in the model.

Table E2.16. Adverse Events from Treatment (UC)

Treatment	Serious Infection	Source
	Per Cycle, %	
Conventional Therapy (Induction)	1.7% (95% CI: 0.9% to 3.0%)	ICER Clinical review (pooled placebo)
Conventional Therapy (Maintenance)	0.17% (95% CI: 0.25% to 0.55%)	Panes 2019[80]
	HR	
Infliximab vs. Conventional Therapy	1.98 (95% CI:: 1.34 to 2.91)	Panes 2019[80]
Entyvio vs. Infliximab	0.68 (95% CI: 0.56 to 0.83)	Solitano 2023[81]
Ustekinumab vs. Infliximab	0.72 (95% CI: 0.58 to 0.89)	Almasri 2025[78]
	Value*	
Disutility	-0.15	Mangen 2017[146]
Inpatient Hospitalization Costs	$10,850	AHRQ 2022[145]

AHRQ: Agency for Healthcare Research and Quality, HR: hazard ratio

*Assuming inpatient hospitalization for pneumonia and one-time disutility for one cycle.

Table E2.16. Adverse Events from Treatment (CD)

Treatment	Serious Infection	Source
	Per Cycle, %	
Conventional Therapy (Induction)	1.4% (95% CI: 0.8% to 2.2%)	ICER Clinical review (pooled placebo)
Conventional Therapy (Maintenance)	0.15% (95% CI: 0.12% to 0.18%)	Lichtenstein 2012[79]
	HR	
Infliximab vs. Conventional Therapy	1.43 (95% CI: 1.11 to 1.84)	Lichtenstein 2012[79]
Entyvio vs. Infliximab	1.03 (95% CI:, 0.78 to 1.35)	Solitano 2023[81]
Ustekinumab vs. Infliximab	0.49 (95% CI:, 0.25 to 0.93)	Solitano 2023[81]
	Value*	
Disutility	-0.15	Mangen 2017[146]
Inpatient Hospitalization Costs	$10,850	AHRQ 2022[145]

AHRQ: Agency for Healthcare Research and Quality, HR: hazard ratio

*Assuming inpatient hospitalization for pneumonia and one-time disutility for one cycle.

Utilities

Health state utilities were derived from publicly available literature, prior models, or manufacturer-submitted data and applied to health states. We used consistent health state utility values across treatments evaluated in the model. For the base case, we used utility estimates reported from a post-hoc analysis of EQ-5D data from GEMINI I (UC), Table E2.17, and GEMINI II/III (CD) trials, Table E2.18, conducted by the manufacturer. These estimates were reported in prior cost-effectiveness models including a company submission to the National Institute for Health and Care Excellence (NICE) in the UK,[147,148] and a peer-reviewed manuscript conducted by the manufacturer in the Canadian setting.[149] During the focused sessions with patients, we heard that there was variability in experiences while in remission, responding to treatment, and in active disease. As such, we also conducted a scenario analysis using alternative health state utility values from the literature. Please see details in the Scenario Analyses section.

Table E2.17. Health State Utilities (UC)

Health State	Value	Source
Moderately to Severely Active UC	0.68	GEMINI-I (based on NICE 2025)[147]
Clinical Response without Remission	0.80	GEMINI-I (based on NICE 2025)[147]
Clinical Response with Remission	0.86	GEMINI-I (based on NICE 2025)[147]
Post-Colectomy Remission* (No complications)	0.79	Brown 2015[150]
Post-Colectomy Remission* (With complications)	0.40	Arseneau 2006[139]

NICE: National Institute for Health and Care Excellence, UC: ulcerative colitis

*Note that patients post-colectomy were at risk of short term and long-term complications (chronic pouchitis) which were associated with additional decrements to quality of life as outlined in the Clinical Events section above.

Table E2.18. Health State Utilities (CD)

Health State	Value	Source*
Moderately to Severely Active CD	0.57	GEMINI-II/III (based on NICE 2025)[148] and Fischer 2025[149]
Clinical Response without Remission	0.73	GEMINI-II/III (based on NICE 2025)[148] and Fischer 2025[149]
Clinical Response with Remission	0.82	GEMINI-II/III (based on NICE 2025)[148] and Fischer 2025[149]

CD: Crohn's Disease, NICE: National Institute for Health and Care Excellence

*As reported in NICE 2015 review of Entyvio and Fischer 2025 (post-hoc analysis of EQ-5D data from the pivotal trials).

Drug Utilization

Table E2.19 outlines the recommended dosing for Entyvio, infliximab and ustekinumab as well as the availability of biosimilars for each. Where multiple biosimilars exist, specific brand names and manufacturers were not mentioned in Table E2.19, but were accounted for in the calculation of drug cost estimates. For the purposes of cost calculations, conventional therapy was modeled as an induction period of prednisone 40 mg orally once daily, followed by mercaptopurine 1-1.5 mg/kg per day or azathioprine 2-3 mg/kg per day.

Table E2.19. Treatment Regimen Recommended Dosage (UC and CD)

Generic Name	Entyvio		Biosimilar Infliximab IV	Infliximab SC	Biosimilar Ustekinumab	
Biosimilars	No		Yes	No	Yes	Yes
Brand Name	Entyvio®		Multiple	Zymfentra®	Multiple	Multiple
Manufacturer	Takeda		Multiple	Celltrion	Multiple	Multiple
Route of Administration	IV	SC	IV	SC	IV	SC
Dosing	300 mg at 0, 2, 6 weeks then every 8 weeks	108 mg every 2 weeks after IV induction	5 mg/kg at 0, 2, 6 weeks, then every 8 weeks	120 mg every 2 weeks starting at week 10 after IV induction	390 mg dose at week 0 then SC every 8 weeks	90 mg every 8 weeks after IV induction

IV: intravenous, SC: subcutaneous

*Infliximab and ustekinumab dosing based on an average weight of 73.4 kg for UC and 70.0 kg for CD.

Economic Inputs

Drug costs for the model are outlined in Table E2.20 based on January 21, 2026 price estimates. For all drugs with subcutaneous modes of administration, we obtained net pricing estimates from RedBook and SSR Health, LLC. SSR Health combines data on unit sales with publicly disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, and this data was used to derive a net price. Drug costs were calculated assuming that patients received dosing as indicated in the FDA label and explored the impact of dose escalation in a scenario analysis.

For branded subcutaneous drugs (i.e., Entyvio and Zymfentra) we estimated net prices by comparing the four-quarter averages of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. We applied this average discount to the WAC from RedBook to arrive at an estimated net price per unit. Where discounts were not available from SSR Health, we used estimates from IPD Analytics. For biosimilar subcutaneous drugs (i.e., ustekinumab) we used the median WAC price across all available biosimilars (90 mg/1 mL and 45 mg/0.5 mL forms) assuming that there are no additional discounts and rebates beyond what was achieved from the reference product.

For all drugs with intravenous administration, we used Centers for Medicare and Medicaid Services Average Sales Prices (ASP) plus 8% for ustekinumab and infliximab (where the mark-up will be based on the originator products) and plus 6% for Entyvio (where there was no biosimilar available, so a standard mark-up was applied). Infliximab biosimilar doses, which are weight based, were rounded up to the nearest vial.

For drugs with both subcutaneous and intravenous administration, we assumed a weighted overall average cost based on current or anticipated use. For UC, first line market share for the SC version of Entyvio was found to be 11% in 2023 based on data from DataMonitor.[151] For CD, only forecasted estimates were available estimating SC use to be 5% In 2024 and 15% in 2025.[151] For the purposes of the analysis, we based pricing estimates using an assumed 10% of SC use for both UC and CD given that this approximates the most recent data available and aligns with estimates from clinical experts and payers.

Conventional therapy costs were based on an induction period of prednisone 40 mg orally once daily (for eight weeks), followed by mercaptopurine 1 to 1.5 mg/kg per day or azathioprine 2 to 3 mg/kg per day (assuming a 50:50 split between mercaptopurine and azathioprine).

Table E2.20. Drug Costs (UC and CD)

Drug	WAC Price Per Dose	Discount from WAC (if applicable)	Primary Source	Net Price Per Dose
Entyvio IV (Entyvio®)	Not Applicable	Not Applicable	ASP	$6,048
Entyvio SC (Entyvio®)	$3,639	29.23%*	REDBOOK	$2,575
Infliximab IV (Biosimilar)†	Not Applicable	Not Applicable	ASP	$833 (UC); $485 (CD)
Infliximab SC (Zymfentra®)	$3,343	10%‡	REDBOOK	$3,008
Ustekinumab IV (Biosimilar)§	Not Applicable	Not Applicable	ASP	$3,522
Ustekinumab SC (Biosimilar) (90 mg)	$4,176	Not Applicable	REDBOOK	$4,176
Prednisone (20 mg)	$0.18	Not Applicable	REDBOOK	$0.18
Mercaptopurine (50 mg)	$3.13	Not Applicable	REDBOOK	$3.13
Azathioprine (50 mg)	$0.34	Not Applicable	REDBOOK	$0.34

ASP: average sales price, IV: intravenous, SC: subcutaneous, WAC: wholesale acquisition cost

Note: Prices based on January 21, 2026 estimates.

*Discount from WAC sourced from SSR Health for the most recent four quarter moving average.

†Weight-based dosing assuming 73.4 kg for UC and 70.0 kg for CD.

‡Discount based on IPD Analytics Market and Financial Insights forecasted discount for 2025 for Zymfentra.[152]

§Ustekinumab IV only used during the induction phase

Table E2.21. Cost of Induction and Maintenance (UC and CD)

Drug	# of Induction Administr-ations	Net Cost of Induction	Induction Mark-up	# of Maintenance Administrations	Annual Net Cost of Maintenance	Maintenance Mark-up
Entyvio IV (Entyvio®)	3*	$18,145	$1,089	Every eight Weeks	$39,423	$2,365
Entyvio SC (Entyvio®)	0*	NA	NA	Every two weeks	$67,145	NA
Infliximab IV (Biosimilar)	3	$2,499 (UC); $2,355 (CD)	$200 (UC); $188 (CD)	Every eight weeks	$5,430 (UC); $5,116 (CD)	$434 (UC); $409 (CD)
Infliximab SC (Zymfentra®)	NA	NA	NA	Every two Weeks‡	$78,435	NA
Ustekinumab IV (Biosimilar)	1	$3,522	$361	NA	NA	NA
Ustekinumab SC (Biosimilar)	NA	NA	NA	Every eight weeks	$27,221	NA
Prednisone (20 mg)†	Daily	$20.16	NA	NA	NA	NA
Mercaptopurine†	NA	NA	NA	Daily	$2,547 (UC); $2,399 (CD)	NA
Azathioprine†	NA	NA	NA	Daily	$458 (UC); $431 (CD)	NA

CD: Crohn's disease, NA: Not applicable, IV: intravenous, SC: subcutaneous, UC: Ulcerative colitis

Note: Prices based on January 21, 2026 estimates.

*If patients switched to SC Entyvio, only two IV administrations were required for induction.
†Assuming 40 mg per day for prednisone induction, 2.5 mg/kg for azathioprine, and 1.5 mg/kg for mercaptopurine and a mean weight of 73.4 kg for UC and 70.0 kg for CD.
‡In the model, for the first cycle of the maintenance therapy, three SC administrations were included because maintenance therapy starts at week 10. For all subsequent maintenance therapy cycles, four SC administrations were included.

Administration Costs

Administration costs were included for IV formulations at a cost of $129.16 per infusion based on the Centers for Medicare and Medicaid Use Physician Fee Schedule average non-facility price for Medicare-specific CPT 96413 (Chemo iv infusion; initial, up to one hour).[153] The average non-facility price for Medicare-specific CPT 96415 (Chemo iv infusion additional hour) of $27.63 was included for infliximab for a second hour of infusion time as per product labeling.

Cost of Colectomy (UC)

The cost of colectomy was assumed to be $31,557 per procedure, calculated by the weighted average cost per admission from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) database of major small and large bowel procedures with major complications or comorbidities, with complications or comorbidities, and without complications or comorbidities (diagnostic related group [DRG] 329, 303, and 331).[145] A weighted average of costs was used based on the frequency of each procedure during the same time period (29% with major complications or comorbidities, 44% with complications or comorbidities, 27% with no complications or comorbidities). Additional costs related to chronic pouchitis were included and are outlined in the *Rate of Colectomy (Ulcerative Colitis)* section above. Costs were inflated to 2024 US dollars.

Cost of Surgeries (CD)

The cost of surgery for rectal resection was assumed to be $25,674 per procedure, calculated by the weighted average cost per admission from the HCUP NIS database of rectal resection with major complications or comorbidities, with complications or comorbidities, and without complications or comorbidities (DRG 332, 333, 334).[145] A weighted average of costs was used based on the frequency of each procedure during the same time period (11% with major complications or comorbidities, 45% with complications or comorbidities, 45% with no complications or comorbidities). Costs were inflated to 2024 US dollars.

Health State Costs

For non-intervention direct medical costs, we used estimates from Lichtenstein 2020 which was a study of commercial claims and encounters, and Medicare Supplemental databases between 2008

and 2015 for patients with UC and CD.[154] The study assessed retrospective medical and pharmacy claims data to estimate quarterly cost data for low, moderate, and high-cost individuals stratified by age groups including 65 to 69 years and 70+ years. Given the median starting age of the modeled population was 71 years, we used costs for the 70+ age group. We used prevalent population costs because it was expected that most Medicare beneficiaries had a longer-standing diagnosis of UC or CD. The matched UC and CD group was used to inform the costs for the remission health state, and an average of the Low-Moderate-cost group, and the Moderate-High-cost group data was used to inform the costs for clinical response without remission and moderate to severely active health states, respectively, for both UC and CD. Costs included emergency room, outpatient, and inpatient costs and were converted to annual costs (and eight-week cycle costs for the model). Pharmacy costs were removed given that they are captured separately in the model. Costs were inflated to 2024 US dollars.

Table E2.22. Health State Costs (UC) - Annual

Health State	Value	Source
Moderately to Severely Active	$80,603	Lichtenstein 2020[154]
Clinical Response without Remission	$16,481	Lichtenstein 2020[154]
Clinical Response with Remission	$3,400	Lichtenstein 2020[154]
Post-Colectomy (No Chronic Complications)	$3,400	Lichtenstein 2020[154]*Assumption
Post-Colectomy (With Chronic Complications)	$16,212	Lichtenstein 2020[154]*Assumption and Barnes 2022[138]

UC: ulcerative colitis

*Post-colectomy remission was assumed to incur the same annual costs as the response with remission health state, and post-colectomy with chronic complications were assumed to incur the same costs as the response with remission health state plus the annual costs associated with chronic pouchitis. Separate costs were included for colectomy (one-time).

Table E2.23. Health State Costs (CD) - Annual

Health State	Value	Source
Moderately to Severely Active	$97,240	Lichtenstein 2020[154]
Clinical Response without Remission	$21,960	Lichtenstein 2020[154]
Clinical Response with Remission	$3,435	Lichtenstein 2020[154]

CD: Crohn's disease

Productivity Costs

In the modified societal perspective, we included patient productivity costs for 18% of the population based on an OECD 2025 report suggesting that 59% of adults maintain continuous employment in their 50s, of whom, 31% were consistently employed in their 60s.[155] This is likely a conservative estimate (overestimate) of the percentage of working individuals given that the percentage of individuals employed is likely decline over time, and other research suggests that the

employment rate for people with a disability was 27% less than people without a disability.[156] Productivity costs were based on data from study of 281 working adults in the US with a diagnosis of UC or CD who completed the Work Productivity and Activity Impairment questionnaire (WPAI) with their gastroenterologist between 2014 to 2015 and 2017 to 2018. Results from the study were stratified by disease activity according to Mayo score for patients with UC and CDAI score for patients with CD.[157] Costs were inflated to 2024 US dollars.

Table E2.24. Patient Productivity Costs (UC) - Annual

Health State	Value	Source
Moderately to Severely Active	$33,542	Ding 2022[157]
Clinical Response without Remission	$20,653	Ding 2022[157]
Clinical Response with Remission	$8,145	Ding 2022[157]
Post-Colectomy (No Chronic Complications)	$8,145	*Assumption
Post-Colectomy (With Chronic Complications)	$38,840	*Assumption

*Post-colectomy remission is assumed to incur the same annual patient productivity costs as the response with remission health state. Post-colectomy with chronic complications was assumed to incur lost productivity costs using the ratio of post-colectomy with/without complications health care costs above (i.e., approximately five times the productivity costs as experienced with no complications). Separate productivity impacts were included for missed time from work due to colectomy.

Table E2.25. Patient Productivity Costs (CD) - Annual

Health State	Value	Source
Moderately to Severely Active	$24,283	Ding 2022[157]
Clinical Response without Remission	$11,423	Ding 2022[157]
Clinical Response with Remission	$4,348	Ding 2022[157]

We also included lost productivity costs related to IV treatment administration based on a study reporting indirect costs associated with seeking care using the American time use survey data from 2003 to 2010.[158] This study reported an average total time per visit of 121 minutes which includes time waiting for care, receiving care, and traveling to the clinic. An additional 60 minutes of time was added for infliximab IV infusion given the longer infusion time based on the product monograph. This time was valued for all patients at the post-tax wage rate plus fringe benefits $41.08).[159,160] We also heard during the focused sessions with patients that there was an impact on caregivers for patients receiving IV infliximab due to the inability to drive because of needing to take Benadryl and other medication on the day of the infusion. As a result, caregiver productivity loss was also included at the same value as patient productivity loss for IV infliximab infusion.

Additionally, missed time from work due to colectomy (for UC) was included based on a retrospective claims analysis of patients undergoing partial colectomy in the US between 2012 and 2016.[161] This study reported an average of 100 days of missed work for open partial colectomy procedures and was valued according to the marginal pre-tax wage rate plus fringe benefits ($48.05) for 18% of the population (i.e., individuals ≥65 years) assumed to be working in our

modeled population.[159,160] For CD, missed time from work for patients undergoing a bowel resection was based on a population-level cohort of patients from Sweden.[162] This study reported the mean number of days lost from work for patients who underwent intestinal surgery over one year post-surgery compared to six months prior to surgery. The mean number of lost days from work at months zero, three, six, nine, and 12 were used to calculate an average of 28.05 days lost from surgery over one year. This time was valued using the marginal pre-tax wage rate plus fringe benefits ($48.05) for 18% of the population (i.e., individuals ≥ 65 years) assumed to be working in our modeled population.[159,160]

E3. Results

Table E3.1. Lifetime Discounted Intervention Acquisition and Intervention Related Health Care Sector Costs for Entyvio versus infliximab and Entyvio vs Ustekinumab for UC

	First line Treatment Acquisition and Related Costs			Second line Treatment Acquisition and Related Costs			Conventional Therapy Acquisition Costs
Treatment	Acquisition Cost	Mark-Up Cost	Administration Cost	Acquisition Cost	Mark-Up Cost	Administration Cost	Acquisition Cost
Entyvio vs. Infliximab							
Entyvio	$68,180	$3,594	$1,279	$52,872	$586	$210	$10,423
Infliximab	$15,596	$608	$1,178	$53,455	$592	$212	$10,598
Incremental	$52,584	$2,986	$101	$(583)	$(6)	$(2)	$(174)
Entyvio vs. Ustekinumab							
Entyvio	$68,180	$3,594	$1,279	$14,648	$643	$1,246	$11,625
Ustekinumab	$58,348	$361	$129	$13,761	$605	$1,172	$10,598
Incremental	$9,831	$3,233	$1,150	$888	$38	$74	$1,027

Table E3.2. Lifetime Average Discounted Intervention Acquisition and Intervention Related Health Care Sector Costs for Entyvio versus infliximab and Entyvio versus Ustekinumab for CD

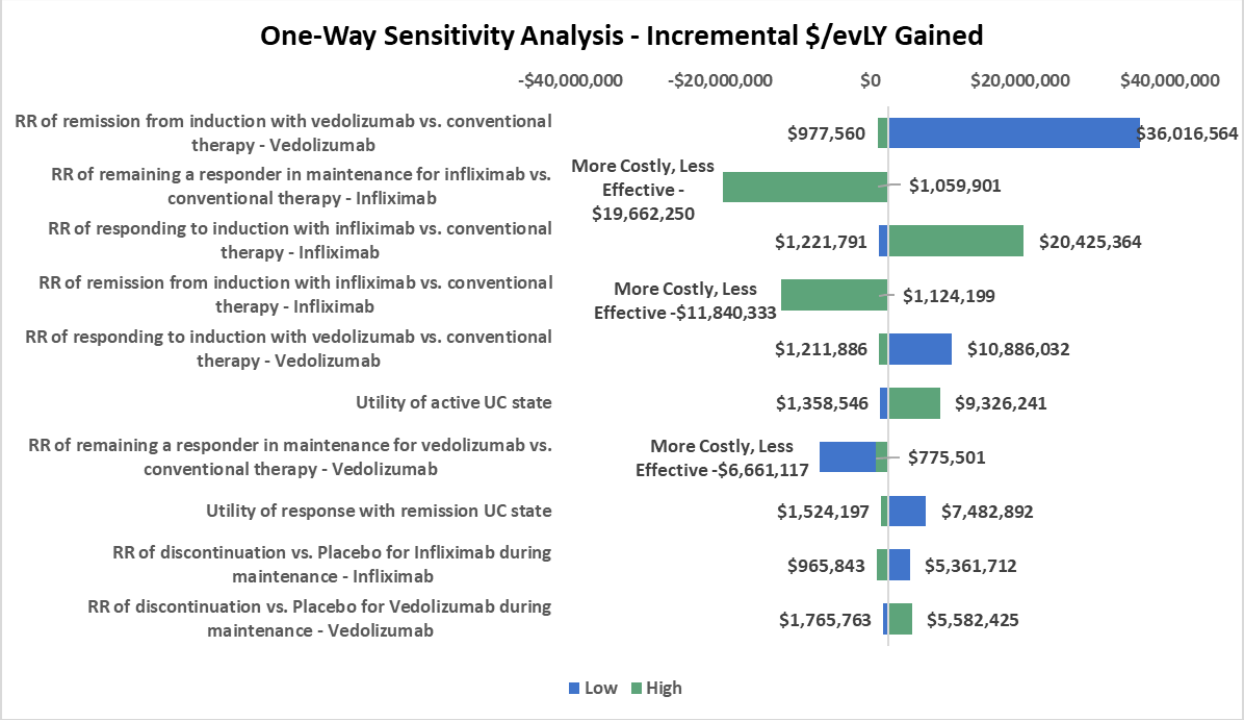
	First Line Treatment Acquisition And Related Costs			Second Line Treatment Acquisition And Related Costs			Third Line Conventional Therapy Acquisition Costs
Treatment	Acquisition Cost	Mark-Up Cost	Administration Cost	Acquisition Cost	Mark-Up Cost	Administratio-n Cost	Acquisition Cost
Entyvio vs. Infliximab							
Entyvio	$40,069	$2,176	$774	$25,068	$533	$191	$15,463
Infliximab	$14,966	$566	$1,165	$24,401	$519	$186	$14,812
Incremental	$25,103	$1,610	$(390)	$667	$14	$5	$650
Entyvio vs. Ustekinumab							
Entyvio	$40,069	$2,176	$774	$14,677	$615	$1,266	$15,211
Ustekinumab	$26,280	$361	$129	$14,429	$606	$1,246	$14,812
Incremental	$13,789	$1,815	$645	$248	$10	$20	$398

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we conducted one-way sensitivity analyses and probabilistic analyses. For the one-way sensitivity analyses, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional evLY. The probabilistic analyses were performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We also generated price thresholds and price premium thresholds for Entyvio versus therapeutic alternatives across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per evLY gained).

Ulcerative Colitis

Figure E4.1. Tornado Diagram for Entyvio versus Infliximab for UC



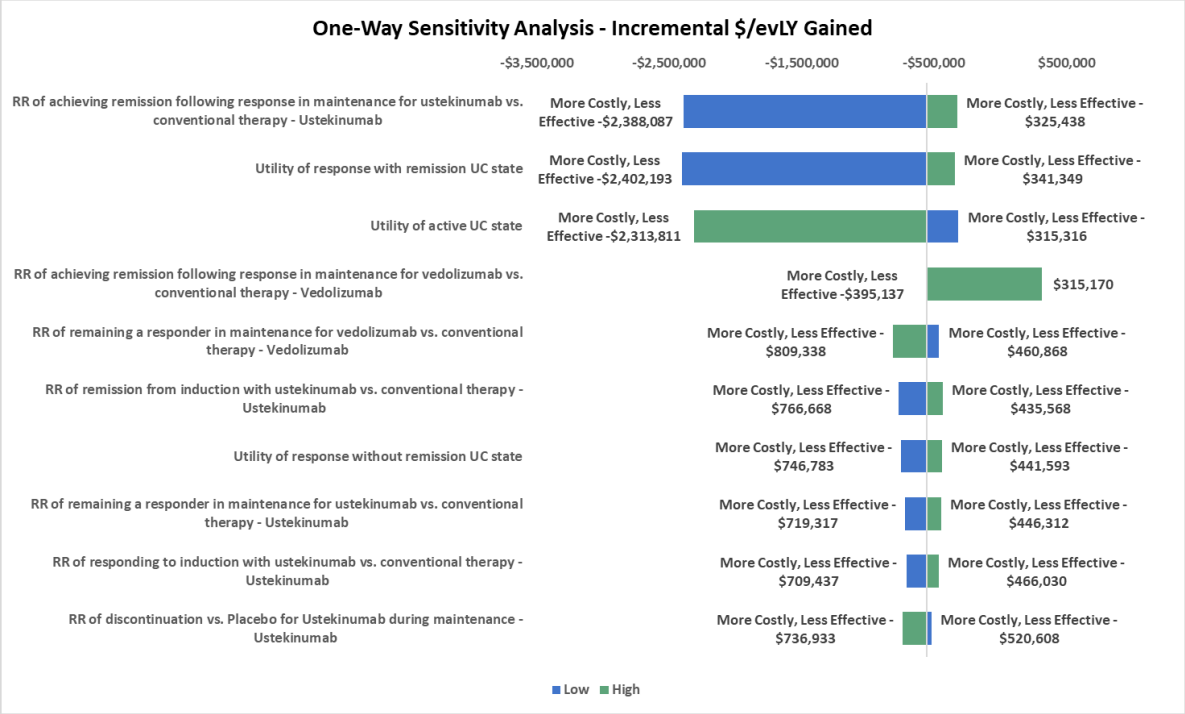
evLY: equal value of life years, RR: relative risk, UC: ulcerative colitis

Table E4.1. Tornado Diagram Inputs and Results for Entyvio versus Infliximab for UC

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
RR of Remission From Induction With Vedolizumab vs. Conventional Therapy - Vedolizumab	$36,016,564	$977,560	1.97	4.00
RR of Remaining A Responder In Maintenance For Infliximab vs. Conventional Therapy - Infliximab	$1,059,901	More Costly, Less Effective	1.11	2.16
RR of Responding To Induction With Infliximab vs. Conventional Therapy - Infliximab	$1,221,791	$20,425,364	1.38	2.09
RR of Remission From Induction With Infliximab vs. Conventional Therapy - Infliximab	$1,124,199	More Costly, Less Effective	1.76	3.82
RR of Responding To Induction With Vedolizumab vs. Conventional Therapy - Vedolizumab	$10,886,032	$1,211,886	1.46	2.14
Utility Of Active UC State	$1,358,546	$9,326,241	0.54	0.82
RR of Remaining A Responder In Maintenance For Vedolizumab vs. Conventional Therapy - Vedolizumab	More Costly, Less Effective	$775,501	1.02	2.33
Utility of Response With Remission UC State	$7,482,892	$1,524,197	0.69	1.00
RR of Discontinuation vs. Placebo For Infliximab During Maintenance - Infliximab	$5,361,712	$965,842	0.30	2.08
RR of Discontinuation vs. Placebo For Vedolizumab During Maintenance - Vedolizumab	$1,765,763	$5,582,425	0.21	0.95

evLY: equal value of life years, RR: relative risk, UC: ulcerative colitis *Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E4.2. Tornado Diagram for Entyvio versus Ustekinumab for UC



CE: cost-effectiveness, RR: relative risk, UC: ulcerative colitis

Table E4.2. Tornado Diagram Inputs and Results for Entyvio versus Ustekinumab for UC

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
RR of Achieving Remission Following Response In Maintenance For Ustekinumab vs. Conventional Therapy - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	1.80	3.42
Utility of Response With Remission UC State	More Costly, Less Effective	More Costly, Less Effective	0.69	1.00
Utility of Active UC State	More Costly, Less Effective	More Costly, Less Effective	0.54	0.82
RR of Achieving Remission Following Response In Maintenance For Vedolizumab vs. Conventional Therapy - Vedolizumab	More Costly, Less Effective	More Costly, Less Effective	1.03	3.40
RR of Remaining A Responder In Maintenance For Vedolizumab vs. Conventional Therapy - Vedolizumab	More Costly, Less Effective	More Costly, Less Effective	1.02	2.33
RR of Remission From Induction With Ustekinumab vs. Conventional Therapy - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	1.96	5.21
Utility of Response Without Remission UC State	More Costly, Less Effective	More Costly, Less Effective	0.64	0.96
RR of Remaining a Responder In Maintenance For Ustekinumab vs. Conventional Therapy - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	1.53	2.37
RR of Responding To Induction With Ustekinumab vs. Conventional Therapy - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	1.47	2.43
RR of Discontinuation vs. Placebo For Ustekinumab During Maintenance - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	0.05	0.94

CE: cost-effectiveness, RR: relative risk, UC: ulcerative colitis

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.3. Results of Probabilistic Sensitivity Analysis for Entyvio versus Infliximab and Ustekinumab for UC

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Entyvio vs. Infliximab	1.7%	3.8%	5.9%	7.7%
Entyvio vs. Ustekinumab	0.9%	1.9%	2.2%	2.7%

CE: cost-effectiveness, evLYs: equal-value life year

Table E4.4. Results of Probabilistic Sensitivity Analysis for Entyvio versus Infliximab for UC

	Entyvio Mean	Infliximab Mean	Incremental
Mean Costs	$725,447	$678,854	$46,593
Mean evLYs (95% CrI)	8.00 (2.50, 13.78)	7.98 (2.49, 13.75)	0.02 (-0.14, 0.29)
Incremental CE Ratio			$2,358,536

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year

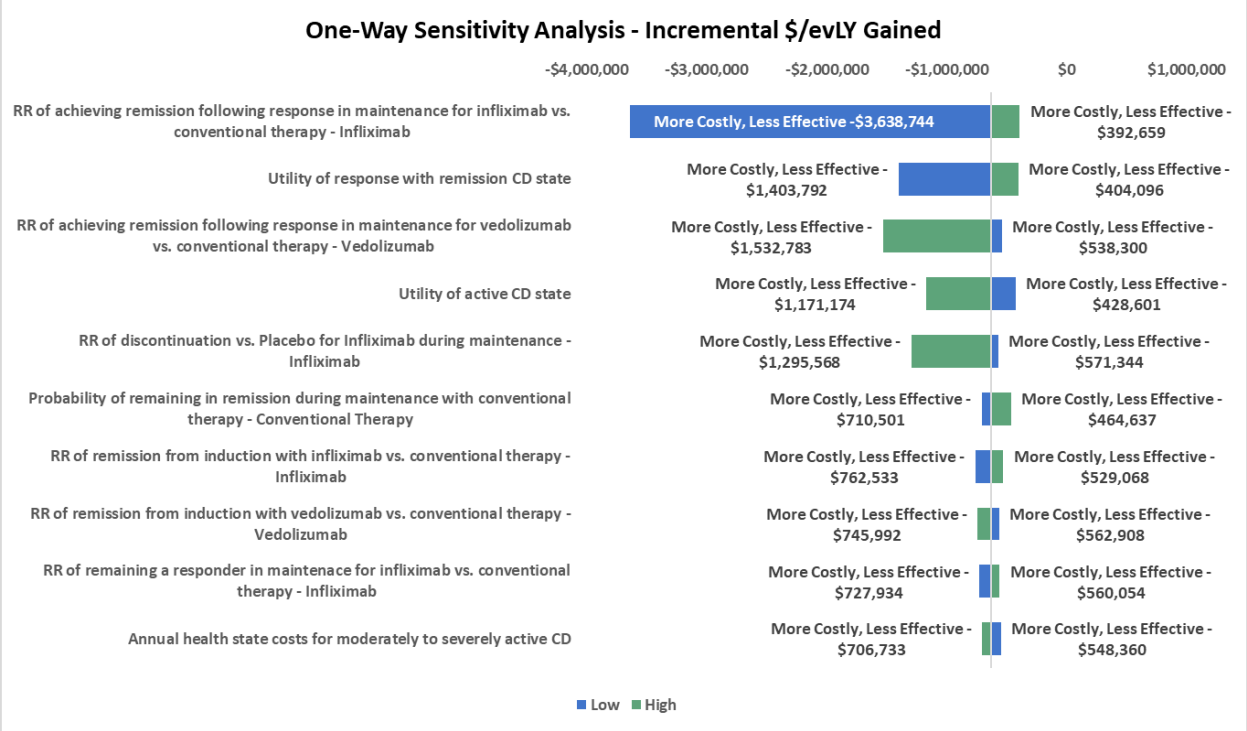
Table E4.5. Results of Probabilistic Sensitivity Analysis for Entyvio versus Ustekinumab for UC

	Entyvio Mean	Ustekinumab Mean	Incremental
Mean Costs	$731,660	$667,645	$64,016
Mean evLYs (95% CrI)	7.87 (2.29, 14.19)	7.98 (2.32, 14.47)	-0.11 (-0.62, 0.19)
Incremental CE Ratio			$(562,472), More Costly, Less Effective

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year

Crohn's Disease

Figure E4.3. Tornado Diagram for Entyvio versus Infliximab for CD



CD: Crohn's Disease, CE: cost-effectiveness, RR: relative risk

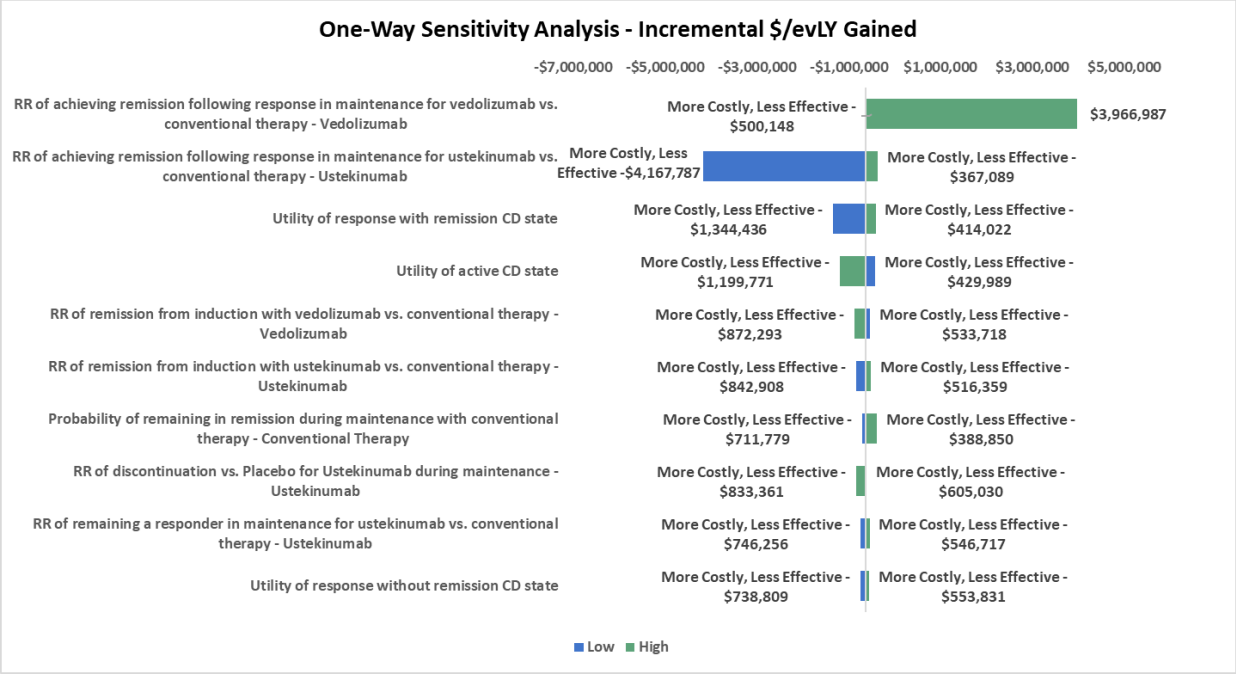
Table E4.6. Tornado Diagram Inputs and Results for Entyvio versus Infliximab for CD

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
RR Of Achieving Remission Following Response in Maintenance for Infliximab vs. Conventional Therapy - Infliximab	More Costly, Less Effective	More Costly, Less Effective	1.16	3.16
Utility Of Response with Remission CD State	More Costly, Less Effective	More Costly, Less Effective	0.66	0.98
RR Of Achieving Remission Following Response in Maintenance for Vedolizumab vs. Conventional Therapy - Vedolizumab	More Costly, Less Effective	More Costly, Less Effective	1.06	2.30
Utility Of Active CD State	More Costly, Less Effective	More Costly, Less Effective	0.46	0.68
RR Of Discontinuation vs. Placebo for Infliximab During Maintenance - Infliximab	More Costly, Less Effective	More Costly, Less Effective	0.13	3.36
Probability Of Remaining in Remission During Maintenance with Conventional Therapy - Conventional Therapy	More Costly, Less Effective	More Costly, Less Effective	0.19	0.45
RR Of Remission from Induction with Infliximab vs. Conventional Therapy - Infliximab	More Costly, Less Effective	More Costly, Less Effective	1.66	3.15
RR Of Remission from Induction with Vedolizumab vs. Conventional Therapy - Vedolizumab	More Costly, Less Effective	More Costly, Less Effective	1.21	2.31
RR Of Remaining a Responder in Maintenance For Infliximab vs. Conventional Therapy - Infliximab	More Costly, Less Effective	More Costly, Less Effective	1.14	2.63
Annual Health State Costs for Moderately To Severely Active CD	More Costly, Less Effective	More Costly, Less Effective	$77,792	$116,688

CD: Crohn's Disease, CE: cost-effectiveness, RR: relative risk

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E4.4. Tornado Diagram for Entyvio versus Ustekinumab for CD



CD: Crohn's Disease, CE: cost-effectiveness, RR: relative risk

Table E4.7. Tornado Diagram Inputs and Results for Entyvio versus Ustekinumab for CD

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
RR Of Achieving Remission Following Response in Maintenance for Vedolizumab vs. Conventional Therapy - Vedolizumab	More Costly, Less Effective	$3,966,987	1.06	2.30
RR Of Achieving Remission Following Response in Maintenance for Ustekinumab vs. Conventional Therapy - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	1.13	2.59
Utility Of Response with Remission CD State	More Costly, Less Effective	More Costly, Less Effective	0.66	0.98
Utility Of Active CD State	More Costly, Less Effective	More Costly, Less Effective	0.46	0.68
RR Of Remission from Induction with Vedolizumab vs. Conventional Therapy - Vedolizumab	More Costly, Less Effective	More Costly, Less Effective	1.21	2.31
RR Of Remission from Induction with Ustekinumab vs. Conventional Therapy - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	1.68	2.80
Probability Of Remaining in Remission During Maintenance with Conventional Therapy - Conventional Therapy	More Costly, Less Effective	More Costly, Less Effective	0.19	0.45
RR Of Discontinuation vs. Placebo for Ustekinumab During Maintenance - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	0.04	1.20
RR Of Remaining a Responder in Maintenance For Ustekinumab vs. Conventional Therapy - Ustekinumab	More Costly, Less Effective	More Costly, Less Effective	1.11	2.24
Utility Of Response Without Remission CD State	More Costly, Less Effective	More Costly, Less Effective	0.58	0.88

CD: Crohn's Disease, CE: cost-effectiveness, RR: relative risk

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.8. Results of Probabilistic Sensitivity Analysis for Entyvio versus Infliximab and Ustekinumab for CD

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Entyvio vs. Infliximab	0.10%	0.10%	0.20%	0.20%
Entyvio vs. Ustekinumab	0.10%	0.20%	0.20%	0.40%

CE: cost-effectiveness, evLYs: equal-value life year

Table E4.9. Results of Probabilistic Sensitivity Analysis for Entyvio versus Infliximab for CD

	Entyvio Mean	Infliximab Mean	Incremental
Mean Costs	$1,155,626	$1,079,332	$76,294
Mean evLYs (95% CrI)	7.76 (1.89, 13.82)	7.87 (2.04, 13.97)	-0.11 (-0.66, 0.02)
Incremental CE Ratio	$ (706,641), More Costly, Less Effective		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year

Table E4.10. Results of Probabilistic Sensitivity Analysis for Entyvio versus Ustekinumab for CD

	Entyvio Mean	Ustekinumab Mean	Incremental
Mean Costs	$1,105,998	$1,062,938	$43,061
Mean evLYs (95% CrI)	7.80 (1.6, 13.71)	7.86 (1.65, 13.74)	-0.06 (-0.32, 0.02)
Incremental CE Ratio	$(662,808), More Costly, Less Effective		

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year

E5. Scenario Analyses

The following scenario analyses were conducted for both the UC and CD models:

1. **Modified societal perspective** that included patient and caregiver productivity impacts.

2. **Alternative health state utility values**: As part of the focused discussion with patients, we heard about the variability in health-related quality of life for patients within each health state included in the model and between health states and have included alternative sources for utility values in the tables below.

Table E5.1. Health State Utilities (UC)

Health State	Base Case	Scenario Analysis	Alternative Source for Scenario Analysis
Moderately to Severely Active UC	0.68	0.41	Woehl 2008[163]
Clinical Response without Remission	0.80	0.76	Woehl 2008[163]
Clinical Response with Remission	0.86	0.87	Woehl 2008[163]
Post-Colectomy Remission*	0.79	0.71	Woehl 2008[163]

UC: ulcerative colitis

*Note that patients post-colectomy are at risk of short term and long term complications (chronic pouchitis) which are associated with decrements to quality of life as outlined in the Clinical Events section above.

Table E5.2. Health State Utilities (CD)

Health State	Base Case	Scenario Analysis	Alternative Source for Scenario Analysis
Moderately to Severely Active CD	0.57	0.64	Woehl 2008 [164]
Clinical Response without Remission	0.73	0.79	Versteegh 2025[31]
Clinical Response with Remission	0.82	0.90	Woehl 2008 [164]

CD: Crohn's Disease

3. **Exclusion of unrelated (non-drug) health care costs** that are not related to the condition of interest (i.e., UC or CD).

4. **Alternative assumption for conventional therapy costs:** In the base case, conventional therapy costs are included in the model as an induction period of prednisone followed by mercaptopurine or azathioprine and are assumed to apply for all patients reaching this line of therapy. Outcomes for conventional therapy are based on the placebo arms of the included clinical trials, where some patients were on no active therapy. In this scenario analysis, we adjusted the cost of conventional therapy to reflect the percentage of patients on active therapy based on the trial data.

5. **Medicare population who are 65 years and older:** The overall Medicare population was used in the base case (mean age of 71 years (UC) and 65 years (CD)). In this scenario analysis, we used the mean age for the Medicare population who are 65 years and older (74 years for UC and CD).[133]

6. **Dose escalation**: In the base case, intervention and comparator costs were calculated based on the dosing recommended in the FDA label. In this scenario analysis, we adjusted the cost of intervention and comparator drugs to account for the potential for dose escalation. No adjustments were made to treatment effectiveness estimates. The prevalence and magnitude of dose escalation for each intervention and comparator are reported in Table E5.3 and were based on prescription claims data for commercially insured patients in the US newly initiating therapy for UC or CD.[165]

Table E5.3. Prevalence and Magnitude of Dose Escalation

Intervention or Comparator	Percentage of Patients with Dose Escalation	Percentage Increase in Dose Among Those Who Had Dose Escalation	Source
Entyvio	23%	62%	Ehrenberg 2020[165]
Infliximab	39%	70%	Ehrenberg 2020[165]
Ustekinumab	22%	131%	Ehrenberg 2020[165]

For the CD model only, we also conducted the following scenario analysis:

7. **Inclusion of new-onset EIMs for patients with active CD:** We captured the additional pharmacy costs associated with treating the most common type of extra-intestinal manifestations which has been reported to be peripheral arthritis.[142] We assumed that patients remain on their current treatment and additional quality of life impacts and costs (except for anticipated pharmacy costs) were not be included as they were assumed to be captured in the health state cost and utility values.

Table E5.4. Scenario Analysis Results (Incremental Cost-Effectiveness Ratios, Cost per evLY Gained) for Entyvio versus Therapeutic Alternatives for UC and CD

	Ulcerative Colitis		Crohn's Disease	
	vs. Infliximab	vs. Ustekinumab	vs. Infliximab	vs. Ustekinumab
Base Case	**$2,371,620**	**More Costly, Less Effective**	**More Costly, Less Effective**	**More Costly, Less Effective**
Scenario 1 (Modified Societal Perspective)	$2,340,403	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Scenario 2 (Alternative Health State Utility Values)	$959,831	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Scenario 3 (Exclusion of Unrelated Health Care Costs)	$2,434,867	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Scenario 4 (Alternative Assumption for Conventional therapy Costs)	$2,375,150	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Scenario 5 (Medicare Population who are ≥65 years)	$2,491,791	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Scenario 6 (Dose Escalation)	$2,702,254	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Scenario 7 (Inclusion of new-onset EIMs for Active CD)	NA	NA	More Costly, Less Effective	More Costly, Less Effective

CD: Crohn's Disease, EIM: extraintestinal manifestations, evLY: equal value of life year, NA: not applicable (CD model only)

Scenario Analysis 1

Modified Societal Perspective

Ulcerative Colitis

Table E5.5. Lifetime Discounted Patient and Caregiver Productivity Costs for Entyvio versus Infliximab for UC

	Patient Productivity Loss			Caregiver Productivity Loss
Treatment	**Due To Management of Condition**	**Due To IV Infusions**	**Due To Colectomy**	**Due To Support for Infliximab IV Infusions**
Entyvio	$51,141	$140	$349	$0
Infliximab	$51,556	$179	$355	$157
Incremental	-$415	-$39	-$6	-$157

IV: intravenous

*Negative values for costs represent cost savings for Entyvio vs. comparator.

Table E5.6. Lifetime Discounted Patient and Caregiver Productivity Costs for Entyvio versus Ustekinumab for UC

	Patient Productivity Loss			Caregiver Productivity Loss
Treatment	**Due To Management of Condition**	**Due To IV Infusions**	**Due To Colectomy**	**Due To Support for Infliximab IV Infusions**
Entyvio	$54,047	$262	$390	$144
Ustekinumab	$51,495	$325	$355	$135
Incremental	$2,551	-$63	$35	$9

IV: intravenous

*Negative values for costs represent cost savings for Entyvio vs. comparator.

Crohn's Disease

Table E5.7. Lifetime Discounted Patient and Caregiver Productivity Costs for Entyvio versus Infliximab for CD

	Patient Productivity Loss			Caregiver Productivity Loss
Treatment	**Due To Management of Condition**	**Due To IV Infusions**	**Due To Surgery**	**Due To Support for Infliximab IV Infusions**
Entyvio	$49,505	$79	$496	$0
Infliximab	$48,037	$174	$474	$154
Incremental	$1,468	-$94	$22	-$154

IV: intravenous

*Negative values for costs represent cost savings for Entyvio vs. comparator.

Table E5.8. Lifetime Discounted Patient and Caregiver Productivity Costs for Entyvio versus Ustekinumab for CD

	Patient Productivity Loss			Caregiver Productivity Loss
Treatment	**Due To Management of Condition**	**Due To IV Infusions**	**Due To Surgery**	**Due To Support for Infliximab IV Infusions**
Entyvio	$48,926	$209	$488	$149
Ustekinumab	$48,044	$233	$474	$147
Incremental	$882	-$25	$13	$2

IV: intravenous

*Negative values for costs represent cost savings for Entyvio vs. therapeutic alternative.

Scenario Analysis 2

Alternative Health State Utility Values

Ulcerative Colitis

Table E5.9. Lifetime Discounted Health Outcomes for Entyvio versus Infliximab for UC

Treatment	Years in Remission	Number of Colectomies	Life Years	evLYs
Entyvio	1.965	0.062	10.898	6.112
Infliximab	1.887	0.063	10.897	6.063
Incremental	0.0785	-0.0011	0.0005	0.0488

evLY: equal value of life years

Table E5.10. Lifetime Discounted Health Outcomes for Entyvio versus Ustekinumab for UC

Treatment	Years in Remission	Number of Colectomies	Life Years	evLYs
Entyvio	1.396	0.069	10.895	5.782
Ustekinumab	1.904	0.063	10.898	6.069
Incremental	-0.509	0.006	-0.003	-0.287

evLY: equal value of life years

Crohn's Disease

Table E5.11. Lifetime Discounted Health Outcomes for Entyvio versus Infliximab for CD

Treatment	Years in Remission	Number of Surgeries	Life Years	evLYs
Entyvio	1.26	0.31	12.82	8.66
Infliximab	1.63	0.30	12.83	8.77
Incremental	-0.364	0.014	-0.007	-0.111

evLY: equal value of life years

Table E5.12. Lifetime Discounted Health Outcomes for Entyvio versus Ustekinumab for CD

Treatment	Years in Remission	Number of Surgeries	Life Years	evLYs
Entyvio	1.42	0.31	12.82	8.70
Ustekinumab	1.63	0.30	12.82	8.77
Incremental	-0.210	0.008	-0.004	-0.067

evLY: equal value of life years

Scenario Analysis 3

Exclusion of Unrelated (Non-Drug) Health Care Costs

Ulcerative Colitis

Table E5.13. Lifetime Discounted Costs for Entyvio versus Infliximab for UC

Treatment	Cost of AEs	Health State Costs	Colectomy Costs	Non-Intervention Health Care Sector Costs
Entyvio	$1,146	$451,743	$1,960	$454,849
Infliximab	$1,322	$458,338	$1,994	$461,654
Incremental	-$176	-$6,594	-$34	-$6,805

AE: adverse event

Table E5.14. Lifetime Discounted Costs for Entyvio versus Ustekinumab for UC

Treatment	Cost of AEs	Health State Costs	Colectomy Costs	Non-Intervention Health Care Sector Costs
Entyvio	$1,181	$496,998	$2,190	$500,369
Ustekinumab	$1,303	$457,650	$1,993	$460,945
Incremental	-$122	$39,348	$197	$39,423

AE: adverse event

Crohn's Disease

Table E5.15. Lifetime Discounted Costs for Entyvio versus Infliximab for CD

Treatment	Cost of AEs	Health State Costs	Surgery Costs	Non-Intervention Health Care Sector Costs
Entyvio	$739	$678,280	$8,010	$687,029
Infliximab	$687	$651,595	$7,660	$659,942
Incremental	$52	$26,685	$349	$27,087

AE: adverse event

Table E5.16. Lifetime Discounted Costs for Entyvio versus Ustekinumab for CD

Treatment	Cost of AEs	Health State Costs	Surgery Costs	Non-Intervention Health Care Sector Costs
Entyvio	$517	$667,904	$7,879	$676,299
Ustekinumab	$586	$651,701	$7,661	$659,948
Incremental	-$70	$16,203	$218	$16,351

AE: adverse event

Scenario Analysis 4

Alternative Assumption for Conventional Therapy Costs

Ulcerative Colitis

Table E5.17. Lifetime Discounted Costs for Entyvio versus Infliximab for UC

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$127,306	$5,670	$581,505
Infliximab	$75,409	$2,591	$589,559
Incremental	$51,896	$3,079	-$8,054

Table E5.18. Lifetime Discounted Costs for Entyvio versus Ustekinumab for UC

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$89,803	$6,762	$635,634
Ustekinumab	$78,468	$2,267	$588,710
Incremental	$11,335	$4,495	$46,924

Crohn's Disease

Table E5.19. Lifetime Discounted Costs for Entyvio versus Infliximab for CD

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$74,414	$3,674	$1,071,995
Infliximab	$48,254	$2,436	$1,031,899
Incremental	$26,160	$1,238	$40,097

Table E5.20. Lifetime Discounted Costs for Entyvio versus Ustekinumab for CD

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$63,872	$4,832	$1,056,166
Ustekinumab	$49,597	$2,341	$1,031,961
Incremental	$14,276	$2,491	$24,204

Scenario Analysis 5

Medicare Population 65 Years and Older

Ulcerative Colitis

Table E5.21. Lifetime Discounted Health Outcomes and Costs for Entyvio versus Infliximab for UC

Treatment	Years in Remission	Number of Colectomies	LYs	evLYs	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	1.873	0.052	9.606	7.087	$126,991	$5,606	$498,451
Infliximab	1.799	0.053	9.605	7.068	$75,833	$2,565	$506,173
Incremental	0.0745	-0.0010	0.0004	0.0187	$51,158	$3,041	-$7,722

evLY: equal value of life years, LY: life years

Table E5.22. Lifetime Discounted Health Outcomes and Costs for Entyvio versus Ustekinumab for UC

Treatment	Years in Remission	Number of Colectomies	LYs	evLYs	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	1.336	0.059	9.603	6.963	$91,608	$6,668	$550,051
Ustekinumab	1.819	0.053	9.605	7.071	$79,183	$2,213	$505,206
Incremental	-0.483	0.006	-0.002	-0.108	$12,425	$4,455	$44,845

evLY: equal value of life years, LY: life years

Crohn's Disease

Table E5.23. Lifetime Discounted Health Outcomes and Costs for Entyvio versus Infliximab for CD

Treatment	Years in Remission	Number of Surgeries	LYs	evLYs	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	1.12	0.21	9.06	5.56	$73,690	$3,624	$727,006
Infliximab	1.46	0.19	9.07	5.66	$47,093	$2,370	$690,080
Incremental	-0.334	0.012	-0.004	-0.098	$26,597	$1,254	$36,926

evLY: equal value of life years, LY: life years

Table E5.24. Lifetime Discounted Health Outcomes and Costs for Entyvio versus Ustekinumab for CD

Treatment	Years in Remission	Number of Surgeries	LYs	evLYs	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	1.26	0.20	9.07	5.60	$63,446	$4,718	$712,676
Ustekinumab	1.45	0.19	9.07	5.66	$48,757	$2,254	$690,217
Incremental	-0.193	0.008	-0.003	-0.059	$14,689	$2,464	$22,460

evLY: equal value of life years, LY: life years

Scenario Analysis 6

Dose Escalation

Ulcerative Colitis

Table E5.25. Lifetime Discounted Costs for Entyvio versus Infliximab for UC

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$157,281	$6,396	$581,505
Infliximab	$99,312	$2,927	$589,559
Incremental	$57,969	$3,469	-$8,054

Table E5.26. Lifetime Discounted Costs for Entyvio versus Ustekinumab for UC

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$109,020	$7,495	$635,634
Ustekinumab	$103,279	$2,536	$588,710
Incremental	$5,741	$4,959	$46,924

Crohn's Disease

Table E5.27. Lifetime Discounted Costs for Entyvio versus Infliximab for CD

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$94,035	$4,164	$1,071,995
Infliximab	$65,297	$2,740	$1,031,899
Incremental	$28,738	$1,424	$40,097

Table E5.28. Lifetime Discounted Costs for Entyvio versus Ustekinumab for CD

Treatment	Intervention Acquisition Costs	Intervention Related Costs	Non-Intervention Health Care Sector Costs
Entyvio	$80,174	$5,337	$1,056,166
Ustekinumab	$67,035	$2,610	$1,031,961
Incremental	$13,139	$2,727	$24,204

Scenario Analysis 7

Inclusion of New-Onset EIMs for Patients with Active CD

Crohn's Disease

Table E5.29. Lifetime Discounted Costs for Entyvio versus Infliximab for CD

Treatment	Cost of AEs	Health State Costs	Surgery Costs	Cost Of EIMs	Non-Intervention Health Care Sector Costs
Entyvio	$739	$1,063,246	$8,010	$28,877	$1,100,873
Infliximab	$687	$1,023,551	$7,660	$27,691	$1,059,589
Incremental	$52	$39,695	$349	$1,187	$41,284

AE: adverse event, EIM: extraintestinal manifestation

Table E5.30. Lifetime Discounted Costs for Entyvio versus Ustekinumab for CD

Treatment	Cost of AEs	Health State Costs	Surgery Costs	Cost Of EIMs	Non-Intervention Health Care Sector Costs
Entyvio	$517	$1,047,770	$7,879	$28,421	$1,084,587
Ustekinumab	$586	$1,023,714	$7,661	$27,695	$1,059,656
Incremental	-$70	$24,056	$218	$727	$24,931

AE: adverse event, EIM: extraintestinal manifestation

Threshold Analysis

Threshold analyses assuming infliximab pricing are reported in Table E5.31. This calculation approach differs from the 30-day threshold price premiums that are presented in the main report which do not rely on assumed infliximab pricing in the calculation.

Table E5.31. Estimated 30-Day Threshold Prices for Entyvio versus Therapeutic Alternatives and Across a Range of Cost-Effectiveness Benchmarks

	30-Day Threshold Prices for Entyvio			
	$50,000/evLY	**$100,000/evLY**	**$150,000/evLY**	**$200,000/evLY**
Ulcerative Colitis				
vs. Infliximab	$1,120	$1,170	$1,210	$1,250
vs. Ustekinumab	Not calculated*	Not calculated*	Not calculated*	Not calculated*
Crohn's Disease	Not calculated*	Not calculated*	Not calculated*	Not calculated*
vs. Infliximab	Not calculated*	Not calculated*	Not calculated*	Not calculated*
vs. Ustekinumab	Not calculated*	Not calculated*	Not calculated*	Not calculated*
Multi-indication Price†				
vs. Infliximab	$510	$520	$540	$560
vs. Ustekinumab	Not calculated*	Not calculated*	Not calculated*	Not calculated*

evLYs: equal-value life years

Note: 30-day prices are rounded to the nearest $10

*Threshold prices were not calculated because Entyvio resulted in fewer evLYs gained relative to therapeutic alternatives.

†Weighted assuming 55% of Entyvio use is for CD and 45% for UC.

Thirty-day threshold price premiums for Entyvio were calculated assuming that 55% of the Medicare population is using Entyvio to treat CD and 10% of patents are using the SC form of administration. If the distribution of use for CD versus UC changes, threshold price premiums would change, ranging from $460 with no patients receiving Entyvio to treat CD to $0 when 100% use comes from CD based on a cost-effectiveness threshold of $100,000 per evLY. Similarly, a change in the percentage of patients assumed to take the SC form of administration would result in changes to the threshold price premiums ranging from $225 with no SC use (0%) to $100 with 100% SC use based on a cost-effectiveness threshold of $100,000 per evLY.

E6. Heterogeneity and Subgroups

Subgroups of interest included individuals with disabilities, the elderly, children, end-stage renal disease (ESRD), terminal illness, and prior biologic use. There were no data available for differential effects between treatments across all subgroups of interest except for prior biologic use. We determined that the relevance of this analysis is unlikely to be meaningful given that the ICER NMA accounted for differences between these subgroups in their analysis and because we are looking to inform CMS with a single price for Entyvio regardless of prior biologic use.

E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

Ulcerative Colitis

Our cost-effectiveness analysis was primarily informed by a prior 2020 ICER assessment of targeted immune modulators for UC, including Entyvio and other biologic therapies (i.e., adalimumab, golimumab, infliximab, tofacitinib, ustekinumab) compared to conventional treatment and infliximab. Our UC model followed similar methods using the same model structure consisting of health states for active UC, response without remission, response with remission, colectomy, and death, and included one subsequent line of biologic treatment, followed by conventional therapy. Both our model and the prior ICER model included a lifetime time horizon, an 8-week cycle length, and a 3% discount rate for costs and health outcomes. Our model also used results from an ICER conducted NMA; however, the results for our model were based on a pooled analysis and not evaluated separately for biologic naïve and biologic experienced populations as was done in the prior ICER NMA.

Our analysis was meant to inform a Medicare-specific population, and as such, we used baseline patient characteristics (e.g., mean age 71 years vs. 40 years in the prior ICER UC review), cost inputs, and risk of death from colectomy reflective of that context where possible. Consequently, it is not surprising that health outcomes reported from our analysis for Entyvio (LYs, evLYs) were lower than those reported in the prior model and cost outcomes higher (health state costs) than the prior model. However, if the starting age of 40 years was used in our model, we find that treatment with Entyvio resulted in an average of 22 life years, which is in line with the prior ICER assessment. Compared to infliximab in the biologic naïve population, in the prior ICER assessment, Entyvio resulted in higher cost and fewer LYs and evLYs; however, there was no data to assess Entyvio vs infliximab in a biologic experienced population. Incrementally, based on a naïve comparison between treatments, the incremental evLYs between treatments were small for both the biologic naïve and experienced populations (i.e., <0.1) and favored infliximab (biologic naïve) and ustekinumab (biologic naïve and experienced) on an absolute basis compared to Entyvio. These

results are similar to what we found in our analysis with the exception of Entyvio vs. infliximab which showed slightly more favorable health outcomes (incremental evLYs 0.02).

Other US-based UC models include an assessment of adalimumab, infliximab or Entyvio using a one year decision-tree,[166] an assessment of Entyvio vs adalimumab using a two year decision-tree,[167] and two studies assessing the optimal treatment sequence for biologic therapies including a one year Markov model,[168] and a lifetime Markov model which was a published extension of the ICER 2020 review.[169] Cost-effectiveness analyses for Entyvio in UC were also reviewed by CDA (2015 and 2020) and NICE (2015). Given the differences in methods, for example, the shorter time horizon, irrelevant therapeutic alternatives, and focus on treatment sequences, comparisons of our results to these analyses are challenging.

Crohn's Disease

Our cost-effectiveness analysis of Entyvio for CD followed similar methods to the UC model using the same model structure consisting of health states for active CD, response without remission, response with remission, and death. Surgery was considered a short-term occurrence and did not have a separate health state as was used for colectomy in UC. Similar to the UC model, subsequent therapy included one subsequent line of biologic treatment, followed by conventional therapy.

A 2025 published analysis[149] by the manufacturer of Entyvio assessed the cost-effectiveness of sequencing Entyvio before versus after anti-TNF therapy. The model was conducted using a Markov model with 1 year cycle lengths and from a Canadian public health care payer perspective. The time horizon was five years and used a 1.5% discount rate for both costs and health outcomes. In CD, Entyvio as a first line biologic was not found to be cost-effective compared to use in second line. Similar to our model, patients could discontinue treatment due to lack of treatment effectiveness or due to AEs, and generally had a similar model structure with health states for active CD, response with remission, and response without remission. However, in contrast to our analysis, Fischer 2025 included a health state for surgery and did not model lack of treatment effectiveness during induction. Effectiveness outcomes were derived from a real-world study that generated relative effect estimates showing that Entyvio had a higher probability of remission and response compared to anti-TNF in first line, but not in second line. Model inputs for serious infection and treatment discontinuation were lower for Entyvio compared to anti-TNF. This was different from our NMA findings which found that Entyvio had a lower probability of response and remission compared to anti-TNFs (infliximab and adalimumab). The difference in effectiveness estimates used between analyses is likely a key driver of the differences in results.

There were a limited number of other US-based models assessing Entyvio for CD. Vasudevan 2020[170] was primarily intended to assess the cost-effectiveness of infliximab, azathioprine and combination therapy as first line with Entyvio considered as a subsequent treatment option. When considered a first line option in the model, Entyvio was dominated by combination infliximab therapy, which was not a relevant therapeutic alternative in our assessment. Zhou 2021[171] assessed the cost-effectiveness of Entyvio compared to conventional therapy, which included corticosteroids, immunosuppressants, and aminosalicylates, and found that Entyvio to be a cost-effective strategy. Conventional therapy was not a relevant therapeutic alternative in our model.

Versteegh 2025[31] conducted a patient-level state transition model that assessed the cost-effectiveness of 156 different treatment sequences for moderate-to-severe CD from the Dutch societal perspective. The Markov state structure was different from the structure used in our model as it did not contain a health state for response. Versteegh 2025 also included a separate health state for remission due to surgery, whereas our model assumed that patients who had surgery remained in the same health state with no change in treatment. Versteegh included up to five lines of subsequent treatment and included combination therapies, which is different from our model where the focus was on standalone treatment options.

Cost-effectiveness analyses for Entyvio in UC and CD were also reviewed by CDA (2016 and 2021) and NICE (2015).[148] For patients with prior anti-TNF exposure, the company submission to NICE found that Entyvio was slightly more effective than adalimumab and slightly less effective than infliximab. Compared to conventional therapy, Entyvio generated greater costs and health outcomes compared to conventional therapy. For the CDA review in 2016, the manufacturer submitted a cost comparison of Entyvio to infliximab and adalimumab under the assumption of clinical similarity between drugs. Rationale for clinical similarity was based on a manufacturer-funded indirect treatment comparison.