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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Etrasimod Compared With Biologic Therapies for the Treatment of Patients with Moderately-to-Severely Active Ulcerative Colitis in Spain

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Abstract

Background Etrasimod (2 mg orally, once daily) is a novel advanced therapy (AT) for patients aged 16 years and older, with moderately-to-severely active ulcerative colitis (UC). This cost-effectiveness analysis compared etrasimod with biologics for the treatment of moderately-to-severely active UC within the Spanish healthcare system.

Methods A mixed model was used to estimate direct health-related costs (€, 2025) and outcomes (quality-adjusted life years [QALYs]) during the patient's lifetime (annual discount rate: 3%). The model simulated the course of UC, including induction and maintenance treatments, modeled by a decision tree and a Markov model. Model inputs were derived from scientific literature. All data were validated by a multidisciplinary panel of national experts. Etrasimod was compared against commonly used treatments in Spain in AT-naïve (vs adalimumab, golimumab, infliximab, intravenous vedolizumab [vedolizumab-IV], subcutaneous vedolizumab [vedolizumab-SC]) and AT-experienced patients (vs adalimumab, golimumab, infliximab, ustekinumab, vedolizumab-IV, vedolizumab-SC) by estimating incremental cost-effectiveness ratios.

Results Etrasimod yielded 19.505 QALYs and €600,289 per AT-naïve patient lifetime, being associated with more QALYs and cost savings than adalimumab (+0.042; −€35,084), golimumab (+0.107; −€39,424), infliximab (+0.039; −€49,514), vedolizumab-IV (+0.170; −€16,153) and vedolizumab-SC (+0.166; −€55,850). In AT-experienced patients, etrasimod produced 18.407 QALYs and €589,423/patient lifetime. In this population, etrasimod was also associated with more QALYs and cost-savings versus adalimumab (+0.013; −€20,850), ustekinumab (+0.018; −€39,354), vedolizumab-IV (+0.166; −€572) and vedolizumab-SC (+0.171; −€26,890). Etrasimod was dominant versus all biologic therapies. Deterministic and probabilistic sensitivity analyses varying all model inputs confirmed the robustness of the results (etrasimod dominancy).

Conclusions In AT-naïve and AT-experienced patients, etrasimod is a dominant therapy (cost savings, greater effectiveness) compared with commonly used ATs.

Key Points for Decision Makers

Etrasimod (2 mg orally, once daily) is a novel advanced therapy (AT) for patients aged 16 years and older with moderately-to-severely active ulcerative colitis (UC).

Under the perspective of the Spanish national health care system, etrasimod compared with currently used biologic therapies for UC represents a more effective alternative, producing cost savings (dominant) in both naïve patients and those previously treated with advanced therapies.

Extended author information available on the last page of the article

1 Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic conditions that lead to progressive inflammation and damage in the gastrointestinal tract [1, 2]. CD is associated with transmural lesions and involves any segment of the gastrointestinal tract, but the ileum remains as the most commonly affected part [1, 2], while UC shows inflammation in the mucosal and submucosal layer along the colon and rectum [1, 2]. Although UC-related symptoms depend on the location and severity of the inflammation, the most frequent gastrointestinal symptoms include diarrhea, abdominal pain, rectal bleeding, bowel urgency, tenesmus

or fecal incontinence [2, 3]. Additionally, patients might suffer from other extraintestinal manifestations that could be musculoskeletal, dermatological, oral, ocular and/or hepatobiliary, among others [2, 3].

Globally, Europe reports the highest prevalence rates of UC (505 cases/100,000 inhabitants in Norway, and >100 cases/100,000 inhabitants in many European countries) [4], followed by North America (286 cases/100,000 inhabitants in the United States) [4]. In Spain, the most recent epidemiological data suggest that 8.1 incident cases per 100,000 inhabitants are diagnosed every year [5, 6], leading to a prevalence ranging from 42 to 354 cases per 100,000 inhabitants [5].

In addition to the large population of patients with UC [4–7], the impact on patient health-related quality of life (HRQoL) caused by the symptoms [5, 8] and the economic burden of the disease poses additional challenges for healthcare systems [5, 9, 10]. Direct healthcare costs associated with IBD in Europe range from €4.6 billion to €5.6 billion per year [11]. Specifically in Spain, the annual direct and indirect costs per patient with UC were estimated to be €1754.1 and €399.3, respectively (2012 values) [10]. Nonetheless, more recent estimates suggest that indirect costs could rise to €2634–€11,109 in informal care, €3649–€5869 in absenteeism and €5600–13,624 in presenteeism, depending on whether the UC is active or remitted (€, 2019) [12].

Although there is no curative treatment currently available for UC, several interventions are effective in controlling the inflammatory process and preventing further relapses or complications [13]. Given the advances in therapeutics, the main cost drivers have shifted from surgery to pharmacotherapy, relying mainly on biologics or small molecules [13, 14].

Etrasimod is a sphingonsine-1-phosphate receptor (S1PR) modulator that reversibly reduces the egress of lymphocytes from the lymph nodes into the systemic circulation and, thus, controls the inflammatory response in the bowel [15]. This novel oral advanced therapy (AT) has proved to be effective and safe for controlling the symptoms of UC in the ELEVATE UC 12 and ELEVATE UC 52 trials (ClinicalTrials.gov identifier: NCT03950232) [16]. For this reason, different regulatory agencies worldwide have approved etrasimod for the treatment of patients aged 16 years and older with moderately-to-severely active UC [17–20].

Nonetheless, there is still limited evidence on the economic impact related to the use of etrasimod in UC and evaluation of whether it represents an efficient alternative for healthcare systems. Therefore, the aim of this project was to perform a cost-effectiveness analysis (CEA) of etrasimod compared with biologic therapies currently used in clinical practice for the treatment of patients with moderately-to-severely active UC in Spain.

2 Material and Methods

2.1 Model Overview

This CEA was conducted by adapting an analytic decision model previously designed in Microsoft Excel® to the Spanish setting [19]. The CEA was conducted based on the guidelines for economic evaluations [21, 22], including those recently published by the Spanish health institutions [23].

A hybrid model simulated the lifetime of patients with moderately-to-severely active UC. This model starts with a decision tree to capture the treatment induction phase, followed by a Markov model to simulate the evolution of the treatment maintenance phase (Fig. 1). According to the treatment response (efficacy), mortality and surgery frequency in the decision tree, the patients were distributed between several health conditions, coincident with the health states defined for the Markov model. The length of the induction treatment depended on the comparator's major dosing regimen: adalimumab (8 weeks) [24–29], golimumab (6 weeks) [30], infliximab (8 weeks) [31–35], ustekinumab (8 weeks) [36], and vedolizumab (6 weeks) [37, 38]. Those patients without response after the induction treatment moved to the 'Active UC' state, whereas those achieving response were distributed to 'Response without remission' or 'Remission', depending on whether or not the disease remits during the induction phase. Additionally, some patients were susceptible to receiving surgical treatment for UC, moving towards the 'Surgery' state. Finally, the decision tree accounted for those patients who die during this period.

Those patients located in 'Active UC' were modeled receiving a second-line therapy in perpetuity, which means that each patient not achieving treatment response would receive an additional treatment until transition to another health state or death. The patients could undergo surgical treatment and move to the health states of 'Surgery without complication' or 'Surgery with complications'. Between these health states, only transitions from 'Surgery without complications' to 'Surgery with complications' were allowed, aiming to reflect the occurrence of long-term complications related to colectomy. During the simulation, each patient had a risk of dying. All transitions between health states were produced in 8-week cycles. Given the relatively short cycle length, no half-cycle correction was applied. The model captured health outcomes and costs during the patients' lifetime (€, 2025), both of which were discounted by applying a 3% annual discount rate according to the recommendations in Spain [23].

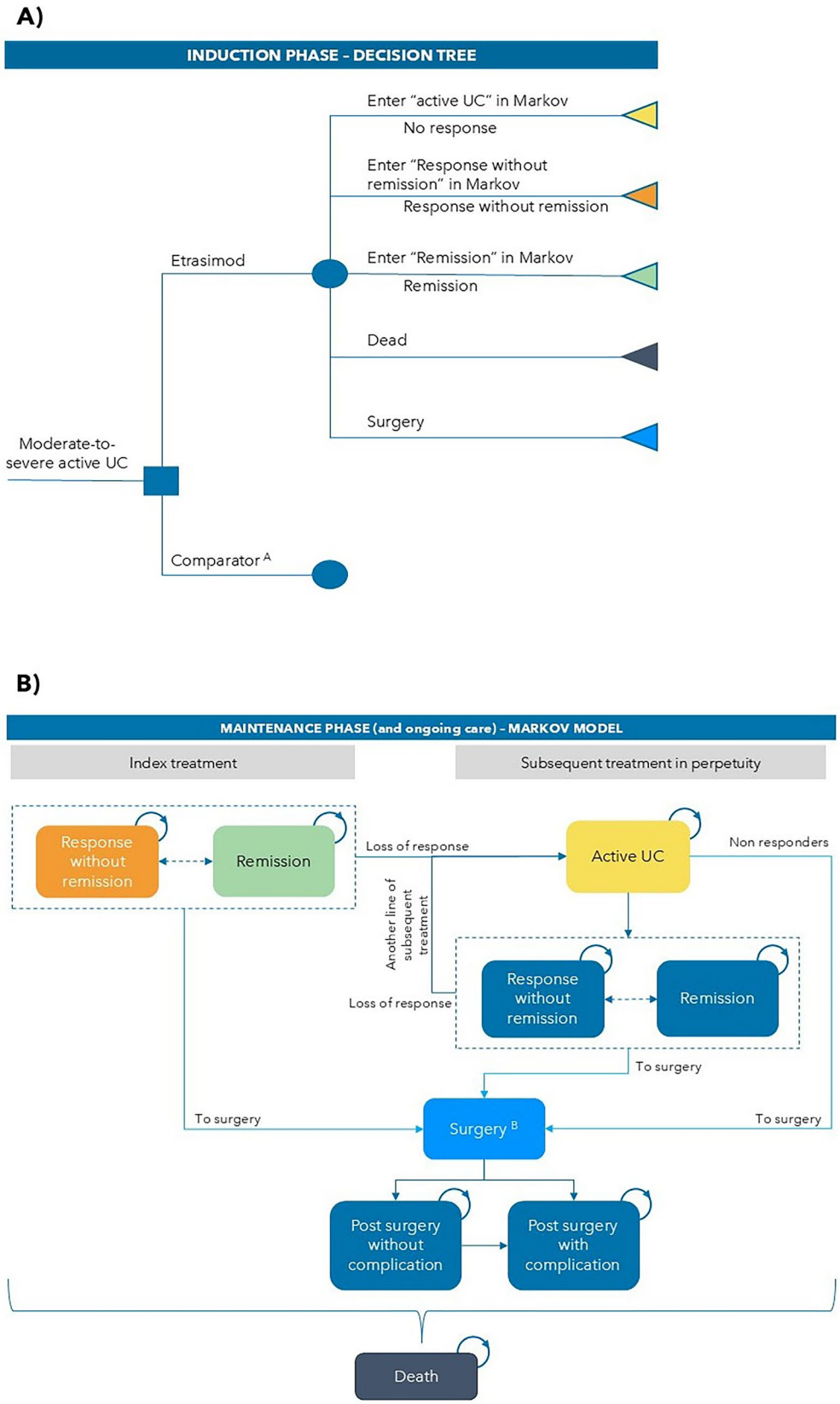


Fig. 1 Model structure. [A]The structure of the decision tree for the comparators remains equal to the structure for etrasimod. [B]Modeled as a transient state. Transitions represented with dashed lines are not modeled explicitly. All transitions in the Markov model were produced in 8-week cycles. *UC* ulcerative colitis

All model inputs and their sources were validated by a multidisciplinary panel including national experts in gastroenterology, pharmacy and health economics, representing different regions in Spain. For this purpose, the evidence regarding the model inputs was sourced from scientific literature and presented to the experts in a survey, which was completed individually. Subsequently, their responses were pooled together in a consensus meeting to agree and validate every single model input according to Spanish clinical practice.

The conceptualization of the present manuscript was based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist published by the International Society for Pharmacoeconomics & Outcomes Research (ISPOR) in 2022 (Table S1 in the electronic supplementary material [ESM]) [39]. No health economic analysis plan was published previously to the present report.

2.2 Study Population and Alternatives Compared

The population assessed in this CEA comprised patients aged 16 years and older with active moderately-to-severely active UC requiring AT. Independent analyses were conducted for two separate cohorts. This approach attempted to provide economic evidence for etrasimod used in those patients naïve to AT (AT-naïve) and those who have received previous AT (AT-experienced), as AT use is a prognostic variable and/or potential treatment effect modifier of etrasimod. The baseline clinical and demographic characteristics for both cohorts were sourced from an etrasimod clinical trial (ELEVATE UC 52) [16]. Although these baseline characteristics came from international cohorts, these were considered representative of the Spanish population according to the experts' criteria.

For the AT-naïve patient cohort, 51.57% were males (standard error [SE] 2.95%), the mean age was 39.63 years (SE 0.83) and mean weight was 73.31 kg (SE 1.05; weight distribution: <55 kg = 14.98%; 55–85 kg = 62.37%; >85 kg = 22.65%) [16]. Given that the alternatives evaluated for this cohort represented first-line treatment (after receiving conventional therapy), the comparators considered were adalimumab [24–29], golimumab [30], infliximab [31–35], and vedolizumab administered by both intravenous (IV) [37] and subcutaneous (SC) [38] routes. The model relies on evidence regarding the efficacy and safety of the comparators derived from a Bayesian network meta-analysis (NMA) [40, 41], which represents one of the most robust indirect treatment comparison (ITC) methods [42]. Given that ustekinumab was approved for naïve patients with moderately-to-severely active UC during 2023, which is after the date of completion of the NMA [40, 41], there was not enough robust evidence for ustekinumab to be included in the ITC. Although other approaches could have been used to include ustekinumab in this CEA, all of them would require conducting unanchored ITCs, which are subject to many biases and are thus not appropriate compared with Bayesian NMAs [42].

Regarding AT-experienced patients, 62.30% were males (SE 4.39%), with a mean age and weight of 42.92 years (SE 1.27) and 76.72 kg (SE 1.58; weight distribution: <55 kg = 13.11%; 55–85 kg = 55.74%; >85 kg = 31.15%), respectively [16]. In this case, adalimumab [24–29], ustekinumab [36], vedolizumab (IV) [37] and vedolizumab (SC) [38] were the comparators evaluated. These alternatives represented second-line treatments or further. Although adalimumab is frequently used as a first-line therapy, it was included as a comparator due to the evidence of its efficacy in patients previously treated with AT [40, 41], and available treatment patterns in Spain [13] and other settings [43–46]. Given that the phase III clinical trials of infliximab [47] and golimumab [48] only included naïve patients, these comparators were excluded for the AT-experienced group analyses.

In order to provide an accurate reflection of Spanish clinical practice, additional ATs were considered as part of the subsequent treatment in perpetuity. These alternatives included filgotinib [49], tofacitinib [50] and upadacitinib [51]. Nonetheless, only biologic therapies were considered as comparators of etrasimod in the present CEA. The rationale for the selection of these comparators was based on the treatment patterns and trends observed in the TRENDY study [13], which used data from ENEIDA, a Spanish prospectively maintained registry of patients with IBD. According to registered data specific to UC, anti-tumor necrosis factor (TNF) therapies were used in 67.6% of patients (infliximab: 32.3%; adalimumab: 31.8% and golimumab: 3.5%), followed by ustekinumab (16.8%) and vedolizumab (13.8%). The use of Janus kinase (JAK) inhibitors for UC remained low in the study period (2015–2021) [13].

2.3 Clinical Inputs

Given the absence of previously published direct comparisons between the interventions considered, the efficacy was sourced from a Bayesian NMA including all advanced therapies currently available in UC [40, 41]. This NMA provided data on the relative efficacy of the ATs compared with placebo (patients achieving clinical response and clinical remission, patients exhibiting loss of response, and safety) (Table 1). Previous economic evaluations of ustekinumab [52] and upadacitinib [53], conducted by the National Institute for Health and Care Excellence (NICE) in the United Kingdom, considered serious infections as the only adverse event. The rationale for this approach was based on the similar safety profile between therapies, serious infections being the adverse event producing the greatest costs and impairment of HRQoL [52, 53]. Thus, the present CEA was aligned with these approaches [52, 53].

Table 1 NMA results: efficacy, loss of response and safety data of the advanced therapies

Advanced therapies	Efficacy (induction phase)[a]				Efficacy (maintenance phase)[a]				Loss of response [%][b]				Safety (adverse events) [%][c]	
	AT-naïve		AT-experienced		AT-naïve		AT-experienced		AT-naïve		AT-experienced		Induction phase	Maintenance phase
	Response	Remission	Response	Remission	Response	Remission	Response	Remission	With remission	Without remission	With remission	Without remission		
Placebo	40.9% (37.6–44.3)	11.3% (9.5-13.1)	29.8% (28.1–31.4)	4.7% (3.9–5.4)	50.8% (30.4–71.5)	31.1% (14.8–51.8)	53.1% (47.4–59.0)	30.8% (25.4–36.7)						
Etrasimod	1.65 (1.46–1.84)	2.65 (2.04–3.36)	1.70 (1.27–2.15)	2.75 (1.57–4.63)	1.47 (1.18–2.04)	1.83 (1.29–2.85)	1.21 (0.71–1.60)	1.35 (0.61–2.20)	25	68	39	74	4.51	1.62
Adalimumab	1.36 (1.23–1.50)	1.77 (1.46–2.14)	1.24 (0.84–1.72)	1.49 (0.73–2.84)	1.15 (0.85–1.52)	1.24 (0.80–1.86)	1.45 (1.06–1.74)	1.83 (1.09–2.55)	42	69	26	80	1.60	5.32
Filgotinib	1.44 (1.20–1.65)	1.99 (1.41–2.65)	2.19 (1.83–2.54)	4.80 (3.23–6.98)	1.22 [d] (1.00–1.54)	1.35 [d] (1.00–1.89)	1.39 [d] (1.07–1.62)	1.70 [d] (1.12–2.24)	22	73	20	80	3.38	3.95
					1.54 [e] (1.25–2.07)	1.98 [e] (1.47–2.89)	1.57 [e] (1.33–1.79)	2.13 [e] (1.58–2.67)						
Golimumab	1.50 (1.33–1.70)	2.18 (1.70–2.81)			1.35 [d] (1.14–1.73)	1.58 [d] (1.23–2.20)			29	69			0.77	5.33
					1.42 [e] (1.19–1.83)	1.72 [e] (1.34–2.40)								
Infliximab	1.76 (1.62–1.91)	3.08 (2.57–3.66)			1.39 (1.08–1.85)	1.66 (1.13–2.46)			29	64			2.67	4.03
Tofacitinib	1.51 (1.26–1.74)	2.20 (1.53–2.96)	2.06 (1.73–2.39)	4.20 (2.88–5.94)	1.61 [d] (1.28–2.22)	2.12 [d] (1.54–3.19)	1.54 [d] (1.33–1.76)	2.05 [d] (1.58–2.59)	16	76	19	82	14.77	3.82
					1.71 [e] (1.32–2.46)	2.38 [e] (1.66–3.79)	1.67 [e] (1.49–1.86)	2.39 [e] (1.93–2.89)						
Upadacitinib	1.95 (1.77–2.13)	3.93 (3.11–4.80)	2.79 (2.54–3.03)	9.12 (7.02–11.65)	1.55 [d] (1.23–2.15)	2.00 [d] (1.41–3.12)	1.71 [d] (1.54–1.91)	2.52 [d] (2.10–3.07)	18	66	11	87	6.23	3.44
					1.65 [e] (1.29–2.32)	2.22 [e] (1.57–3.50)	1.77 [e] (1.60–1.97)	2.72 [e] (2.27–3.28)						
Ustekinumab			2.02 (1.69–2.35)	4.01 (2.72–5.70)			1.30 [d] (1.07–1.54)	1.52 [d] (1.11–2.03)	30	67	30	74	0.95	5.96
							1.45 [e] (1.24–1.67)	1.83 [e] (1.41–2.34)						
Vedolizumab (IV)	1.70 (1.50–1.89)	2.83 (2.17–3.59)	2.02 (1.33–2.63)	4.00 (1.70–7.78)	1.63 [d] (1.28–2.31)	2.17 [d] (1.55–3.42)	1.56 [d] (1.22–1.82)	2.10 [d] (1.35–2.74)	19	72	20	81	1.07	3.79
					1.58 [e] (1.25–2.20)	2.07 [e] (1.47–3.21)	1.60 [e] (1.28–1.85)	2.20 [e] (1.47–2.84)						

Table 1 (continued)

Advanced therapies	Efficacy (induction phase)[a]				Efficacy (maintenance phase)[a]				Loss of response [%][b]				Safety (adverse events) [%][c]	
	AT-naïve		AT-experienced		AT-naïve		AT-experienced		AT-naïve		AT-experienced		Induction phase	Maintenance phase
	Response	Remission	Response	Remission	Response	Remission	Response	Remission	With remission	Without remission	With remission	Without remission		
Vedolizumab (SC)	1.70 (1.50–1.89)	2.83 (2.17–3.59)	2.02 (1.33–2.63)	4.00 (1.70–7.78)	1.63 (1.28–2.31)	2.17 (1.55–3.42)	1.56 (1.22–1.82)	2.10 (1.35–2.74)	17	72	21	80	1.07	3.79

AT advanced therapy, *IV* intravenous, *NMA* network meta-analysis, *RR* relative risk, *SC* subcutaneous, *95% CIs* 95% confidence intervals

[a]Efficacy results in the NMA are measured as percentage of patients achieving response/remission with placebo, and RR of achieving response/remission with each advanced therapy vs placebo. All estimates include their respective 95% CIs

[b]Loss of response results in the NMA are measured as percentage of patients losing response

[c]Safety results in the NMA are measured as the percentage of adverse events for a specified time. The time for induction phase was the length of induction period for each advanced therapy. The time for maintenance phase was the cycle length (8 weeks)

[d]Regular dose for maintenance phase

[e]Intensified dose for maintenance phase

Regarding surgical treatment, the annual rate of surgical interventions for UC in Spain (0.34%) [54], which was converted to an 8-week rate, was sourced from a study analyzing data of 738 patients with UC retrieved from 55 hospitals in Catalonia [54]. The study assessed postoperative-related outcomes in those patients previously treated with biologics.

The surgeries performed were further distributed according to whether they were elective (61.8%) [55] or emergency (38.2%) [55], according to a retrospective study conducted with 68 Spanish participants with IBD followed for 9.9 years [55].

In order to model the occurrence of surgical complications, previous work from the Spanish Working Group on Crohn's Disease and UC (GETECCU [*Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa*]) was considered as the most representative source of the frequency of post-surgery complications in Spain [56]. The study included data from patients with UC surgically treated during 2009–2019, split between those exposed to biological treatments (n = 711; incidence 18.7%) and those not exposed (n = 824; incidence 18.0%) [56]. The average incidence, estimated at 18.4%, was used to feed the CEA model.

In addition to complications that appear immediately after surgery, patients may develop long-term complications. Therefore, a rate of 46.0% (observed over a follow-up period of 6.5 years) [57] was considered. This data was observed in a prospective study including 182 patients with UC in Belgium [57].

Mortality was based on age-dependent risk of death published by the Spanish national statistics institute (INE [*Instituto Nacional de Estadística*]) [58]. The excess mortality associated with the surgical intervention was modeled by applying a relative risk (RR) comparing surgically treated patients with UC to the general population (RR = 1.3; 95% confidence interval [95% CI] 0.7 - 2.2) [59]. The input was estimated in a published meta-analysis including 10 studies [59], which was used by NICE in previous economic evaluations of therapies for UC [52, 53].

2.4 Health Resource Consumption and Costs

This CEA was conducted from the Spanish national health system (NHS) perspective; thus, only the following direct medical costs were included (Table 2): (1) treatment acquisition and administration; (2) concomitant treatments; (3) UC-related health state management; and (4) adverse events management.

In order to provide a precise estimate of the pharmaceutical costs derived from the AT, both induction and

Table 2 Summary of model inputs: Health resources consumption, unit costs (€, 2025) and health utility values

Characterization of the treatment with advanced therapies								
Advanced therapy	Posology				Authorized medicine			Price per package [b] [€, 2025]
	Induction dose (treatment length)	Maintenance standard dose	Maintenance intensified dose	Patients intensifying [%] [a]	Pharmaceutical form	Units	Dose per unit	
Etrasimod [15]	2 mg/day (12 weeks)	2 mg/day			Tablets (oral)	28	2 mg	776.88
Adalimumab [24–29]	Week 0: 160 mg / Week 2: 80 mg / Weeks 4: 40 mg / Week 6: 40 mg (8 weeks)	40 mg every 2 weeks	40 mg every week	60	Pre-filled pen (SC)	2	40 mg	874.05
Filgotinib [49]	200 mg/day (10 weeks)	200 mg/day			Tablets (oral)	30	100 mg	932.40
						30	200 mg	932.40
Golimumab [30]	Week 0: 200 mg / Week 2: 100 mg (6 weeks)	50 mg every 4 weeks (since the 6th week)	100 mg every 4 weeks (since the 6th week)	70	Pre-filled pen (SC)	1	100 mg / 1 mL	2066.45
						1	50 mg / 0.5 mL	1033.23
Infliximab [31–35]	5 mg/kg at weeks 0-2-6 (8 weeks)	5 mg/kg every 8 weeks	10 mg/kg every 8 weeks [c]	60	Solution for perfusion (IV)	1	100 mg	439.75
Tofacitinib [50]	20 mg/day (8 weeks)	10 mg/day	20 mg/day	50	Tablets (oral)	56	5 mg	762.20
						56	10 mg	1524.40
Upadacitinib [51]	45 mg/day (8 weeks)	15 mg/day	30 mg/day	60	Tablets (oral)	28	15 mg	870.24
						28	30 mg	1740.48
Ustekinumab [36]	Single dose – weight <55 kg: 260 mg / weight 55–85 kg: 390 mg / weight >85 kg: 520 mg (8 weeks)				Solution for perfusion (IV)	1	130 mg	2867.50
		90 mg every 8 weeks	90 mg every 4 weeks [c]	50	Pre-filled syringe (SC)	1	90 mg	2867.50
Vedolizumab [37, 38] [D]	Perfusion of 300 mg at weeks 0-2-6 for 30 min (6 weeks)	300 mg every 8 weeks [c]	300 mg every 4 weeks [c]	50	Solution for perfusion (IV)	1	300 mg	3206.05
		108 mg every 2 weeks			Pre-filled pen (SC)	1	108 mg	863.16

Distribution of patients between subsequent treatments (in perpetuity) [%]								
	To (subsequent treatment)…[e]							
From…	Etrasimod	Adalimumab	Filgotinib	Tofacitinib	Upadacitinib	Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC)
Etrasimod		20	10	20	10	20	10	10

Table 2 (continued)

Distribution of patients between subsequent treatments (in perpetuity) [%]

From…	To (subsequent treatment)…[e]							
	Etrasimod	Adalimumab	Filgotinib	Tofacitinib	Upadacitinib	Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC)
Adalimumab	12		0	35	6	12	24	12
Golimumab	12	0	0	35	6	12	24	12
Infliximab	10	0	5	20	10	25	20	10
Ustekinumab	17	11	6	11	11		33	11
Vedolizumab (IV)	17	11	6	11	11	44		0
Vedolizumab (SC)	17	11	6	11	11	44	0	

Concomitant treatments

Concomitant treatment	Usage (% of patients)		Posology	Authorized medicine		Price per package [b] [€, 2025]
	Etrasimod [f]	Other biologic therapies		Units	Dose per unit	
Azathioprine [63]	0	35	2.5 mg / kg per day	50 tablets	100 mg	13.32
Mercaptopurine [64]	0	15	1.5 mg / kg per day	25 tablets	50 mg	8.33
Methotrexate [65]	0	0	17 mg per week [g]	24 tablets	2.5 mg	1.22
Mesalazine (5-ASA) [66]	40	40	3000 mg per day [g]	100 tablets	400 mg	17.94
Prednisone [67]	20	20	50 mg per day (for 8 weeks) [g]	30 tablets	5 mg	2.41
Beclomethasone [68]	10	10	7.5 mg per day (for 8 weeks) [g]	30 tablets	5 mg	53.70

Annual health resources consumption and utility values associated with the health states

	Annual health resources consumption in each health state [units/patient] [70, 95]							Unit cost [€, 2025]
	Active UC	Response without remission	Remission	Post-surgery without complications	Post-surgery with complications	Emergency surgery	Elective surgery	
Health resources								
Visit to gastroenterologist	6.5	4.485	2.015	1.755	1.495	2.0[i]	2.0[i]	125.11[h]
Blood/biochemistry tests	6.5	3.9	3.25	3.25	1.495	0.0	0.0	108.41[h]
Emergency endoscopy	0.78	0.26	0.0	0.65	0.52	0.0	0.0.	381.77 [70]
Elective endoscopy	2.015	0.52	0.195	0.65	1.235	0.0	0.0	381.77 [70]
Hospital admission[i]	0.7	0.14	0.0	0.0	2.1	0.0	0.0	2575.50[h]
Day hospital	0.325	0.625	0.325	0.13	0.0	0.0	0.0	254.16[h]

Table 2 (continued)

Annual health resources consumption and utility values associated with the health states								
	Annual health resources consumption in each health state [units/patient] [70, 95]							Unit cost [€, 2025]
	Active UC	Response without remission	Remission	Post-surgery without complications	Post-surgery with complications	Emergency surgery	Elective surgery	
Stoma care (post-colectomy)[i]	0.0	0.0	0.0	0.0	0.0	4.5	4.5	932.77[h]
Surgical procedure	0.0	0.0	0.0	0.0	0.0	1.0	1.0	7233.59[h]
Utility value associated with health states [mean (SE)][j]	0.780 (0.030) [16][k]	0.820 (0.020) [16][k]	0.890 (0.010) [16][k]	0.900 (0.090) [72]	0.710 (0.071) [72]	0.740 (0.074) [72]	0.740 (0.074) [72]	

IV intravenous, *NICE* National Institute for Health and Care Excellence, *SC* subcutaneous, *SE* standard error, *UC* ulcerative colitis

[a]Percentage of patients intensifying the dose was provided by the experts based on their experience in clinical practice

[b]Notified ex-factory prices were sourced from the national database of pharmaceutical costs (BOTPlus) [60]. According to the Spanish legislation (Royal Decree 8/2010 of May 20, 2010) [61], a discount of 7.5% (etrasimod, filgotinib, golimumab, tofacitinib [constrained to subsequent treatment], upadacitinib [constrained to subsequent treatment], ustekinumab and vedolizumab) or 0% (adalimumab, infliximab, azathioprine, mercaptopurine, methotrexate, mesalazine [5-ASA], prednisone and beclomethasone) was applied to the laboratory selling price (price deductions updated in January 2025)

[c]The dose was determined based on the experience of the clinicians

[d]Two separate comparators were considered for vedolizumab depending on its administration pathway during maintenance treatment. Both IV and SC comparators required induction with vedolizumab administered by the IV route

[e]A subsequent treatment was considered when patients do not achieve response to the previous treatment. This subsequent treatment was modeled in perpetuity. Both golimumab and infliximab were discarded as a subsequent treatment as they are authorized for patients naïve to any previous advanced therapy [30–35]. The distribution was based on the clinicians' experience in their daily practice

[f]Aligned with the NICE approach [69], and according to the experts' criteria, it was considered that patients receiving etrasimod (S1PR agonist) are not susceptible to receiving any concomitant treatment with azathioprine, mercaptopurine and/or methotrexate

[g]The posology was determined by clinical experts as an average regimen based on clinical practice

[h]Unit cost estimated as an average of public published tariffs (Table S2, see ESM)

[i]Health resource consumption was determined by the clinical experts based on clinical practice

[j]Deviation measure estimated by considering a variability of 20%

[k]Patient-level data from ELEVATE UC 52

maintenance treatment phases were modeled based on the authorized posology for each one [15, 24–38, 49–51]. Those patients receiving maintenance treatment with adalimumab, golimumab, infliximab, tofacitinib (constrained to subsequent treatment), upadacitinib (constrained to subsequent treatment), ustekinumab and vedolizumab (IV) are susceptible to receive an intensified therapeutic regimen. Thus, a proportion of patients was modeled to receive an alternative posology for these comparators, which was established by the experts' experience in clinical practice. Additionally, a cost of €77.16 was associated with the administration of therapies by IV route at day hospital facilities, estimated as the average of the costs published in public tariffs (Table S2, see ESM). Those treatments received by oral or SC routes were considered not to incur additional costs. The notified ex-factory cost per package associated with the AT was derived from the database of drug prices in Spain (BOT-Plus), provided by the General Council of Official Colleges of Pharmacists (*Consejo General de Colegios Oficiales de Farmacéuticos* [CGCOF]) [60]. For those alternatives with a commercialized biosimilar (adalimumab and infliximab), the selected price was the lowest available. A discount on the price was applied when necessary, according to the Spanish legislation [61].

Regarding the management of adverse events, a cost of €5964.49 per serious infection was included. This cost was derived from data published by the Spanish Health Ministry [62], being an average estimated cost for the management of several infections including sepsis (€8000.04), pneumonia (€6443.83), urinary tract infection (€5067.20), respiratory infection (€4917.47) and bronchitis (€4497.22) [62].

In addition to the AT received, patients with UC might receive concomitant treatment with azathioprine [63], mercaptopurine [64], methotrexate [65], mesalazine (5-ASA) [66], prednisone [67] and/or beclomethasone [68] (Table 2). The percentage of patients receiving each concomitant therapy was based on expert consensus, which aligned with the previous NICE approaches for assessing therapies in UC [69]. The dosing regimen used for each drug in clinical practice [63–68], in addition to the notified ex-factory price per package [60], were considered to quantify the cost associated with the concomitant treatment. All treatments evaluated are currently reimbursed by the Spanish NHS.

Finally, the health resources consumption associated with the management of UC was used to estimate the cost associated with the modeled health states (micro-costing approach). The consumption was sourced from a previous CEA conducted in Spain [70] (Table 2).

All costs were included in euros (€), and inflated to 2025 according to variations in the consumer price index (CPI) published by the INE [71] when applicable.

2.5 Health Outcomes and Utility Values

Based on the clinical inputs described above, the model provided an estimation of life-years gained (LYGs) and quality-adjusted life years (QALYs) per patient over a lifetime. To account for the HRQoL, the QALYs were estimated by applying state-specific utility values (Table 2).

The health utilities associated with 'Active UC', 'Response without remission' and 'Remission' were sourced from the ELEVATE UC52 clinical trial [16]. In contrast, those utilities in the states related to surgery were sourced from a study conducted in the United Kingdom involving 202 patients with UC undergoing bowel surgery, of whom 58% were recruited after 1 year since the surgical procedure [72]. Both studies administered the EQ-5D to estimate these utility values [16, 72].

A disutility was applied to those patients who had adverse events (serious infections) derived from the AT (−0.156) [73]. The input was sourced from a systematic literature review including economic evaluations of biologic therapies in rheumatoid arthritis conducted by NICE [73]. Given the lack of evidence regarding the impact of serious infections in the HRQoL of patients with UC, the experts agreed on this disutility value due to the similarities between treatments (biologics) in the NICE review [73] and the present CEA.

2.6 Analyses

The base-case analysis consisted of a deterministic estimate of the average cost and health outcomes (LYGs and QALYs) per patient, both of which were used to provide the incremental cost-effectiveness ratio (ICER, in terms of €/QALY) for etrasimod versus each biologic therapy. Moreover, several sensitivity analyses evaluated the uncertainty and tested for the robustness of both model and results.

One-way sensitivity analyses (OWSAs) were conducted by varying every model input according to their respective published variability (95% CI or SE). Those inputs lacking published dispersion measures were varied by applying a variability of ±10%, which was assumed for the clinical parameters and utility values, and ±20% for the costs.

Two additional OWSAs were included to test for the sensitivity of the results when discounts of 50% were applied to the prices of adalimumab (€437.03) and infliximab (€219.88).

Additionally, a probabilistic sensitivity analysis (PSA) was conducted, which consisted of 1000 Monte Carlo simulations. All model inputs were varied in each simulation according to several probabilistic distributions including Normal, Log-Normal, Beta and Gamma (Table S3, see ESM).

3 Results

3.1 Base-Case Results

In the AT-naïve cohort, the model estimated that a patient receiving etrasimod was associated with 19.505 QALYs and a total cost of €600,289 during their lifetime. In contrast, treatment with biologic therapies yielded QALYs that ranged between 19.336 in the case of vedolizumab (IV) to 19.467 in the case of infliximab. The costs associated with biologic treatments exceeded the costs estimated with etrasimod in all cases. Among all biologic therapies, the treatment with vedolizumab (IV) achieved the lowest total cost over the patient's lifetime (€616,442). In contrast, vedolizumab (SC) was associated with €656,138, being the highest total cost.

Etrasimod achieved additional QALYs when compared with each of the biologic therapies, ranging from 0.039 (vs infliximab) to 0.170 (vs vedolizumab [IV]). Additionally, etrasimod produced cost savings over the patient's lifetime that ranged between €16,153 (vs vedolizumab [IV]) and €55,850 (vs vedolizumab [SC]), varying depending on the comparator. Consequently, etrasimod was identified as a dominant alternative in all the pairwise comparisons against the currently available biologic therapies in UC (Table 3).

Considering those AT-experienced patients, etrasimod yielded 18.407 QALYs and €589,423 per patient's lifetime. For those receiving biologic therapies, the QALYs achieved per patient's lifetime ranged between 18.236 and 18.394 with vedolizumab (SC) and adalimumab, respectively. In terms of costs, ustekinumab was associated with the highest total cost during a lifetime (€628,778) among all biologic therapies, and vedolizumab (IV) was associated with the lowest total cost (€589,995).

In this population, etrasimod yielded more QALYs (a minimum of 0.013 and a maximum of 0.171 when compared with adalimumab and vedolizumab [SC], respectively). Cost savings were observed when comparing etrasimod against all the biologic therapies, which ranged between €572, when compared with vedolizumab (IV), and €39,354 when compared with ustekinumab (Table 3).

3.2 OWSA Results

Etrasimod remained dominant in most of the OWSAs considering both AT-naïve and AT-experienced patients (Table 4). No important changes were observed for any variable in the AT-naïve cohort. In contrast, in AT-experienced patients, two parameters produced remarkable variations in the model estimates: discount rate and time horizon (Table 4).

Following the guidelines for economic evaluation [74], when the discount rate was set at 1%, the ICER of etrasimod compared with vedolizumab (IV) was estimated to be €76,644/QALY. Likewise, when comparing etrasimod with adalimumab, etrasimod was associated with fewer QALYs (−0.006) but cost savings (−€26,573), placing the ICER in the southwest quadrant of the cost-effectiveness plane.

Regarding the time horizon, when considering costs and results for 5 years, the ICER was estimated at €2770 per additional QALY with etrasimod compared with adalimumab.

Finally, etrasimod was found to be dominant compared with all biologics, even when remarkable discounts of 50% were applied to adalimumab and infliximab.

3.3 Results of Probabilistic Sensitivity Analyses

The average results of the 1000 Monte Carlo simulations in the PSA revealed that etrasimod was a dominant intervention compared with any of the other biologic therapies (achieves more QALYs and produces cost savings) in both AT-naïve and AT-experienced patients (Table 5).

Given that there is no official willingness-to-pay (WTP) threshold in Spain, several values have been proposed, ranging from €22,000 to €60,000 per additional QALY [75–77]. Considering the latest WTP threshold proposed and published (€27,000/QALY) [77], the probability of etrasimod being cost effective compared with the biologic therapies was over 90% in all comparisons.

Moreover, the results of the PSA were examined according to a dominance WTP threshold of etrasimod compared with the other biologic therapies (better effectiveness, cost savings). At this WTP threshold associated with the dominancy of etrasimod, the probability of etrasimod being dominant ranged from 84.1% (vs vedolizumab [IV] in AT-naïve patients) to 99.9% (vs infliximab in AT-naïve patients, and vs ustekinumab in AT-experienced patients).

4 Discussion

4.1 Interpretation of Results

The present CEA demonstrated that, compared with the other biologic agents currently available, etrasimod is a cost-effective or dominant alternative for AT-naïve and AT-experienced patients aged 16 years and older with moderately-to-severely active UC in Spain.

The ELEVATE UC 52 trial already proved that etrasimod, compared with placebo, represents an effective and safe alternative for patients with moderately-to-severely active UC (clinical remission at weeks 12 [27% vs 7%; $p < 0.0001$] and 52 [32% vs 7%; $p < 0.0001$]) [16], which

Table 3 Base-case results

	Etrasimod	Adalimumab	Golimumab	Infliximab	Ustekinumab[a]	Vedolizumab (IV)	Vedolizumab (SC)
AT-naïve							
Total LYG	24.319	24.318	24.329	24.318		24.329	24.329
Total QALYs	19.505	19.463	19.398	19.467		19.336	19.339
Total costs [€]	€600,289	€635,372	€639,713	€649,802		€616,442	€656,138
Index treatment							
Acquisition	€19,809	€19,824	€46,650	€34,779		€94,573	€139,653
Administration	€0	€0	€0	€1111		€2257	€231
Adverse events	€1331	€1913	€3656	€2896		€3253	€4294
Disease management	€2609	€1651	€2211	€2386		€2869	€3006
Subsequent treatments							
Acquisition	€508,167	€544,209	€522,077	€542,305		€447,810	€443,833
Administration	€2119	€4557	€4372	€3868		€439	€435
Adverse events	€32,881	€28,686	€27,520	€28,774		€30,057	€29,790
Disease management	€24,681	€25,575	€24,543	€24,990		€26,779	€26,543
Surgery/post-surgery	€8110	€8364	€8103	€8113		€7840	€7790
Incremental QALYs (etrasimod vs comparator)		+0.042	+0.107	+0.039		+0.170	+0.166
Incremental total costs [€] (etrasimod vs comparator)		−€35,084	−€39,424	−€49,514		−€16,153	−€55,850
ICER [€/QALY] (etrasimod vs comparator)		Etrasimod dominant [b]	Etrasimod dominant [b]	Etrasimod dominant [b]		Etrasimod dominant [b]	Etrasimod dominant [b]
AT-experienced							
Total LYG	23.209	23.207			23.207	23.195	23.195
Total QALYs	18.407	18.394			18.388	18.240	18.236
Total costs [€]	€589,423	€610,273			€628,778	€589,995	€616,314
Index treatment							
Acquisition	€10,783	€21,545			€47,956	€78,674	€103,700
Administration	€0	€0			€77	€1871	€231
Adverse events	€772	€2091			€2604	€2645	€3115
Disease management	€1895	€1614			€2027	€2438	€2365
Subsequent treatments							
Acquisition	€508,501	€520,919			€512,331	€440,778	€443,004
Administration	€2110	€4341			€5816	€430	€432
Adverse events	€32,694	€27,312			€25,583	€29,309	€29,457
Disease management	€24,578	€24,386			€24,436	€26,157	€26,288

Table 3 (continued)

	Etrasimod	Adalimumab	Golimumab	Infliximab	Ustekinumab[a]	Vedolizumab (IV)	Vedolizumab (SC)
Surgery/post-surgery	€7522	€7499			€7387	€7146	€7173
Incremental QALYs (etrasimod vs comparator)		+0.013			+0.018	+0.166	+0.171
Incremental total costs [€] (etrasimod vs comparator)		−€20,850			−€39,354	−€572	−€26,890
ICER [€/QALY] (etrasimod vs comparator)		Etrasimod dominant[b]			Etrasimod dominant[b]	Etrasimod dominant[b]	Etrasimod dominant[b]

AT advanced therapy, *ICER* incremental cost-effectiveness ratio, *IV* intravenous, *LYG* life year gained, *QALY* quality-adjusted life year, *SC* subcutaneous

[a]Ustekinumab was excluded in the AT-naïve population because the model was originally designed at the international level and does not allow the incorporation of this comparator

[b]Etrasimod is dominant (achieves better health outcomes and reduces total costs)

led to its approval by several regulatory agencies [17–20]. Moreover, according to the Bayesian NMA considered in this CEA, the efficacy of etrasimod compared with other ATs in naïve patients with UC, in terms of clinical remission and clinical response, was found to be similar to most comparators both in induction and maintenance phase [40, 41]. The results of this Bayesian NMA were consistent with other published ITC [78]. In this context, assessing the cost effectiveness of etrasimod in moderately-to-severely active UC is key to informing the decision making of both physicians and healthcare institutions.

Based on the decision analytic model, an AT-naïve patient would live 19.51 QALYs and accrue a total direct cost during their lifetime of €600,289. In this population, etrasimod represented the best alternative in terms of health outcomes (QALYs), followed by infliximab (19.47) and adalimumab (19.46). Likewise, the total cost associated with etrasimod was the lowest, followed by vedolizumab (IV) (€616,442) and adalimumab (€635,372). The main drivers of health outcomes associated with the alternatives assessed included their efficacy, speed with which they produce their therapeutic effect, loss of response, and safety. In addition, the profile of adverse events represented a key driver of costs.

Regarding AT-experienced patients, etrasimod was associated with 18.41 QALYs and €589,423 during a lifetime. According to the health outcomes (QALYs), etrasimod was ranked first followed by adalimumab (18.39) and ustekinumab (18.39). In economic terms, etrasimod also produced the lowest direct total cost during the patient's lifetime (€589,423), followed by vedolizumab (IV) (€589,995) and adalimumab (€610,273).

According to the findings of this CEA, etrasimod would improve patients' lives, ensuring the sustainability of the Spanish healthcare system due to the potential reduction in total costs. In this context, further budget impact analyses would be key to informing the magnitude of these cost savings in a real-world setting, which is beyond the purpose of the present study.

However, the slight differences in terms of efficacy should be examined to ensure a proper interpretation of the CEA [40, 41]. Additionally, the dominance of etrasimod against biologics was consistent across the analyses conducted. In this setting, no priority groups to be treated with etrasimod were detected in sensitivity analyses, including previous treatment (AT-naïve or AT-experienced), sex or age groups. These findings were consistent with previous studies revealing that both the safety and efficacy of etrasimod was consistent regardless of the patient's age [79].

Within this context, differences at the regional level and between patients become increasingly important, highlighting the need for a personalized medicine which relies on clinical findings and economic evidence, as well as considering the patient's characteristics and preferences for treatment selection in clinical practice. Given the deterministic design of the analytic decision model, it was not feasible to capture the heterogeneity caused by regional or patient-related features. Thus, the findings of this CEA should be interpreted within the Spanish setting and extrapolation to other countries should be made with caution. Moreover, remission

Table 4 OWSA results for each comparator when varying key model inputs

	AT-naïve					AT-experienced			
	Adalimumab	Golimumab	Infliximab	Vedolizumab (IV)	Vedolizumab (SC)	Adalimumab	Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC)
Tornado graphs provided in ESM[a]	Fig. S1	Fig. S2	Fig. S3	Fig. S5	Fig. S6	Fig. S1	Fig. S4	Fig. S5	Fig. S6
Base-case results (ICER, €/QALY)	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
OWSA results (ICER, €/QALY)[b]									
Discount rate (base case: 3%)									
1%	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	€4,243,457 (SW) [C]	Etrasimod dominant	€74,014	Etrasimod dominant
5%	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
Time horizon (base case: lifetime)									
1 year	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
5 years	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	€2,770	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
Price of adalimumab (biosimilar)									
50% discount (€437.03)	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
Price of infliximab (biosimilar)									
50% discount (€219.88)	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
Remaining inputs[d]									
Lower limit	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
Upper limit	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant

AT advanced therapy, *ESM* electronic supplementary material, *ICER* incremental cost-effectiveness ratio, *INMB* incremental net monetary benefit, *IV* intravenous, *OWSA* one-way sensitivity analyses, *QALY* quality-adjusted life year, *RR* relative risk, *SC* subcutaneous, *SW* south-west, *WTP* willingness-to-pay

[a]The results of the OWSA represented in tornado graphs using INMB are provided in the ESM for the top 20 most influencing parameters

[b]OWSA were conducted by varying the base-case parameter by ±10% in clinical inputs and ±20% in costs, respectively

[c]ICER is located in the SW quadrant of the cost-effectiveness plane. This indicates that etrasimod achieves fewer QALYs, but produces cost savings vs comparator. In this setting, etrasimod should be considered cost effective when the value of the ICER is over the WTP threshold (€27,000/QALY)

[d]In all remaining OWSA, etrasimod was dominant vs all biologics in both AT-naïve and AT-experienced patients (Table S4 in the ESM)

and response rates are not unique drivers of the results. In contrast, the dominance of etrasimod versus biologics is caused by the convergence of various clinical parameters of the model (remission and response rates, loss of response, safety, etc.), utility values and costs.

For these reasons, sensitivity analyses are key to testing the robustness of the results, which remained consistent in most OWSAs. Moreover, it is noteworthy that the discount rate, time horizon, costs and utility values did not produce remarkable variations in the CEA estimates. Concerning the PSA, the average estimates of the 1000 Monte Carlo simulations revealed that etrasimod remained dominant in all the pairwise comparisons versus the other biologic therapies. When considering a WTP threshold reflecting the dominancy of etrasimod (€0/QALY), the probability of etrasimod being cost effective (dominant) was over 84% compared with all other comparators. This probability reached 99.9% when comparing etrasimod with infliximab or ustekinumab. The

Table 5 Summary of the PSA results

	AT-naïve					AT-experienced			
	Adalimumab	Golimumab	Infliximab	Vedolizumab (IV)	Vedolizumab (SC)	Adalimumab	Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC)
ΔQALY (etrasimod vs …)	+0.102	+0.166	+0.080	+0.175	+0.155	+0.062	+0.081	+0.160	+0.146
Δ Total cost (etrasimod vs …)	−€39,102	−€43,560	−€52,596	−€24,248	−€70,348	−€41,529	−€69,024	−€43,206	−€96,101
ICER [€/QALY]	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant	Etrasimod dominant
Probability of etrasimod being cost effective at WTP thresholds									
WTP threshold of dominancy of etrasimod	98.1%	98.3%	99.9%	84.1%	99.0%	93.8%	99.9%	85.6%	96.5%
WTP threshold									
€20,000/QALY	98.9%	99.5%	99.9%	89.6%	99.6%	94.3%	100.0%	91.5%	98.6%
€22,000/QALY	99.0%	99.5%	99.9%	90.1%	99.6%	94.3%	100.0%	92.0%	98.7%
€27,000/QALY	99.6%	99.8%	100.0%	91.1%	99.6%	94.3%	100.0%	93.8%	99.0%
€30,000/QALY	99.7%	99.8%	100.0%	92.1%	99.7%	94.3%	100.0%	64.4%	99.0%
€34,000/QALY	99.7%	99.8%	100.0%	92.7%	99.7%	94.4%	100.0%	95.1%	99.1%
€60,000/QALY	99.9%	100.0%	100.0%	96.7%	99.9%	94.4%	100.0%	98.4%	99.7%
Location of graphs in the ESM									
Cost-effectiveness plane	Fig. S7	Fig. S8	Fig. S9	Fig. S10	Fig. S11	Fig. S12	Fig. S13	Fig. S14	Fig. S15
Acceptability curve	Fig. S16	Fig. S17	Fig. S18	Fig. S19	Fig. S20	Fig. S21	Fig. S22	Fig. S23	Fig. S24

AT advanced therapy, *ESM* electronic supplementary material, *ICER* incremental cost-effectiveness ratio, *IV* intravenous, *PSA* probabilistic sensitivity analyses, *QALY* quality-adjusted life year, *SC* subcutaneous, *WTP* willingness-to-pay

sensitivity analyses demonstrated the robustness of the result and identified that data on efficacy and safety represented the most sensitive parameters.

Regarding efficacy, it was expected that modifying all parameters affecting the response and remission rates of etrasimod or its comparators would be highly sensitive. The Bayesian NMA from which these data were sourced found similar efficacy between all the therapies [40, 41], except for some pairwise comparisons in terms of clinical remission and response during the induction phase in AT-naïve patients, which revealed that etrasimod was significantly more effective than adalimumab administered in standard (RR for remission = 2.05 [95% CI 1.28–3.44]; RR for response = 1.43 [95% CI 1.13–1.89]) and intensified dose (RR for remission = 1.50 [95% CI 1.09–2.01; RR for response = 1.22 [95% CI 1.04–1.40]) [40, 41]. No statistical differences were found in terms of clinical response and remission when comparing the performance of etrasimod and biologic therapies during the maintenance phase [40, 41].

Given these similar remission and response rates [40, 41], several OWSAs were included by considering the lower and upper limits of the 95% CIs estimated by the NMA to test this source of uncertainty. Considering the induction phase in AT-naïve patients, the base-case NMA estimated an RR of response and remission versus placebo of 1.65 and 2.65, respectively. In this population, when considering the upper limit of the 95% CIs, the RR ranged from 1.70 (golimumab) to 1.91 (infliximab) for response, and between 2.59 (vedolizumab) and 3.66

(infliximab) for remission, both considering the induction phase. These trends in efficacy were observed for all comparators in both induction and maintenance phases, considering AT-naïve and experienced patients, except for adalimumab, which remained less effective than etrasimod in all OWSAs. Even when the comparators represented more effective alternatives compared with etrasimod in most OWSAs, etrasimod was cost effective in all these sensitivity analyses (Figs. S1–S6 in the ESM). Additionally, the tornado graphs provided as supplementary material revealed that when varying the efficacy inputs, the incremental net monetary benefit (INMB) remained positive in most cases, suggesting that etrasimod would still be a cost-effective alternative against the comparator.

The efficacy inputs considered in the CEA were consistent with a different NMA evaluating the efficacy and safety of several alternatives for UC during the maintenance phase [78]. In this ITC, the alternatives were split depending on whether those patients achieving response were re-randomized after the induction phase, or were kept in the same treatment group after induction regardless of response to induction therapy (treat-through). Etrasimod was included in the treat-through analysis, and was compared against adalimumab, vedolizumab, etrolizumab (currently not approved for UC) and infliximab. Etrasimod was ranked the best in those studies using a treat-through design according to its efficacy during the maintenance phase (surface under the cumulative ranking area [SUCRA] = 91.1%), and was found to be significantly more effective for achieving remission than adalimumab in standard dose (odds ratio [OR] 2.49 [95% CI 1.01–6.14]), etrolizumab (OR 3.06 [95% CI 1.09–8.56]) and placebo (OR 6.62 [95% CI 3.13–14.02]). No differences were found when comparing etrasimod with vedolizumab and different regimens of infliximab [78]. It should be noted that if the results of this NMA had been used as a source of efficacy [78], etrasimod would have achieved better results. Therefore, the base case can be considered as a conservative scenario.

Due to the similar efficacy of the alternatives, data regarding their safety could be a key driver for decision making. In relation to the approach for modeling adverse events, the model was constrained to consider serious infections exclusively [19], mainly because of the lack of comparative safety between etrasimod and biologic therapies. This design was aligned with previous assessments by NICE in the United Kingdom [52, 53] and, as observed in the base case and OWSAs, the impact on the results was low. Nonetheless, further studies will be needed to assess differences in these aspects.

Given that all the therapeutic alternatives considered in the CEA were associated with similar results in terms of survival (LYG), mainly because UC is not a lethal disease, the utility values represented additional key model inputs. Nonetheless, etrasimod remained dominant in all OWSAs varying utilities, considering all pairwise comparisons and both AT-naïve and AT-experienced cohorts. In addition, it could be argued that utility values for active UC (0.780), response without remission (0.820) and remission (0.890), derived from the ELEVATE UC 52 trial could be slightly favorable for etrasimod. In this regard, other sources can be considered for estimating QALYs ranging from 0.410 to 0.660 in active UC [80–82], 0.760–0.800 in response without remission [80–82], and 0.860–0.910 in remission [80–82]. All these sources were proposed to the experts, who agreed on using those values derived from ELEVATE UC 52 as being the most recent source. Moreover, the utility values provided by alternative sources presented wide differences between the states of active UC and remission (0.200–0.460) [80–82], active UC and response without remission (0.110–0.350) [80–82], and remission and response without remission (0.090–0.110) [80–82]. These remarkable differences between health state-specific utility values would lead to better outcomes associated with etrasimod.

4.2 Additional Implications for Clinical Practice

In addition to improving the patients' HRQoL, other unmet needs for those patients with UC that belong to specific subgroups should be considered. This is the case for patients with isolated proctitis, which is associated with extended affectation of the UC and produces a remarkable impact on HRQoL [83, 84]. In contrast to other clinical trials in UC excluding these patients with isolated proctitis, the ELEVATE UC clinical program considered this subgroup [85]. A total of 64 participants with isolated proctitis were enrolled, of whom 42 received etrasimod. At week 12, more patients with isolated proctitis achieved clinical remission (43% vs 14%), endoscopic improvement (52% vs 23%), symptomatic remission (52% vs 23%), endoscopic improvement—histological remission (EIHR) (38% vs 14%) and clinical response (71% vs 41%) with etrasimod compared with placebo, all results being statistically significant ($p < 0.05$) [83, 85]. The efficacy of etrasimod in this patient subgroup remained at week 56, in terms of clinical (44% vs 11%) and symptomatic (56% vs 11%) remissions [83, 85].

Other advantages of etrasimod compared with biologics should be considered. First, the daily 2-mg oral administration could represent a convenient posology compared with the IV or SC administrations for some patients, as it avoids needlesticks and hospital visits. The IV drug administration incurred additional out-of-pocket costs for patients, which produced a remarkable impact associated with the route of administration from a societal perspective. In this CEA, the perspective of the Spanish NHS was chosen to align with national recommendations [23], and because indirect costs could be a significant source of uncertainty.

In addition to its oral route of administration, etrasimod is associated with a fixed dose for the entirety the treatment. In contrast, biologic treatments require dose intensification in some patients. In comparison with the biologics in which dose regimens are susceptible to increase during treatment, the fixed dose of etrasimod led to a predictable economic impact per treated patient. However, future research could test the actual impact of the convenience of etrasimod's posology, based on patient preferences.

4.3 Comparison with Other Cost-Effectiveness Analyses

To the best of our knowledge, this is the first manuscript describing a CEA evaluating etrasimod in UC. Nonetheless, previous studies have already assessed the cost effectiveness of ATs in moderately-to-severely active UC at a national level [70, 86, 87]. Among those, the first CEA was conducted by developing a Markov model which simulated the progression of patients with UC, treated with infliximab, adalimumab, golimumab or vedolizumab, for a 10-year time horizon [70]. The model estimated total costs ranging from €62,767 (adalimumab) to €146,985 (vedolizumab) (€, 2017), and the QALYs associated with each intervention ranged between 5.070 (adalimumab) and 6.000 (vedolizumab). Compared with adalimumab, none of the biologics were cost effective at the WTP of €30,000/QALY considered by the authors (ICERs = €45,582 [vs infliximab] to €2,175,999 [vs golimumab]) [70].

In 2020, the authors of the previous CEA updated the analysis and included tofacitinib as a new comparator [86]. The estimated costs during the 10-year period were €66,030 for golimumab, €72,671 for adalimumab, €91,604 for infliximab, €134,073 for tofacitinib and €147,642 for vedolizumab (€, 2018). Moreover, these ATs were associated with a QALY gain ranging from 5.46 (golimumab) to 6.74 (vedolizumab). None of these alternatives were cost effective versus infliximab (ICERs = €31,340 [golimumab] to €270,503 [vedolizumab]) [86].

The most recent CEA compared tofacitinib with vedolizumab via a Markov model, considering two different cohorts of AT-naïve and AT-experienced patients [87]. During the patients' lifetime, tofacitinib produced costs of €181,584 (AT-naïve) and €160,907 (AT-experienced), which were associated with cost savings in both cohorts compared with vedolizumab (AT-naïve: €205,400; AT-experienced: €172,345) (€, 2019). Compared with the biologic, tofacitinib represented a dominant alternative that yielded 0.00014 and 0.042 additional QALYs in AT-naïve and AT-experienced patients, respectively [87].

Although comparison of the results between the present CEA and those previously published studies should be made with caution, some similar trends can be observed. First, adalimumab and infliximab were found to be the biologics associated with the lowest costs [70, 86]. In contrast, vedolizumab produced the greatest costs [70, 86]. Second, small molecules could be an efficient alternative when compared with vedolizumab [87]. Third, modeling AT-naïve patients separately from those previously treated with ATs is important, as their results present important differences in terms of costs and health outcomes [87]. Finally, the effectiveness of the ATs in UC is similar, producing slight differences in terms of quality of life (incremental QALYs), but their impact on survival is minimal due to the low mortality of the disease [70, 86, 87].

4.4 Strengths and Limitations

This CEA is not exempt from some limitations but is also linked to strengths that need to be critically addressed. The use of efficacy and safety data estimated by an NMA could be considered the main constraint of the analysis. However, it should be noted that there are limited head-to-head comparisons between the targeted alternatives. Given the lack of direct comparisons, ITCs are considered an acceptable source of evidence [88, 89]. Moreover, Bayesian NMAs represent updated and evolved methods for conducting these ITCs [88, 89]. In contrast to frequentist NMAs, the Bayesian models can account for the uncertainty inherent to health-related data [88, 89]. In any case, further research would be needed to assess these gaps.

The present CEA used notified ex-factory prices [60], applying the mandatory deduction when applicable [61]. However, in the Spanish setting the pharmaceutical companies, health institutions and hospitals agree on discounts on the notified prices of the commercialized medicines. Thus, the prices considered in this CEA may not present a faithful reflection of the real-world costs. Given that these discounts are not publicly available, the approach considered in the present CEA represented the most adequate method to estimate pharmaceutical costs, and additionally, the lowest published price was selected when biosimilars are available. Nonetheless, the potential impact of this issue could be considered low as the discounts mentioned are applied to both etrasimod and its comparators. In addition, those sensitivity analyses conducted by applying a 50% discount to the prices of adalimumab and infliximab both revealed that etrasimod would still be a dominant alternative compared with all biologics. In this context, the extended use of biosimilars of ustekinumab in the next few years could modify the results obtained.

The population baseline characteristics were derived from the ELEVATE UC 52 trial [16], which involved patients from several countries worldwide, including Spain. When comparing the study cohorts of the ELEVATE UC 52 trial

and the Spanish population with moderately-to-severely active UC, some differences could be expected regarding demographics and clinical characteristics. However, it was not feasible to gather regional and/or national specific data for these inputs, mainly due to the lack of the patients' distribution by weight, which was used to estimate the costs related to the acquisition of ustekinumab and infliximab. In any case, the modeled baseline characteristics (AT-naïve: 51.57% males, mean age = 39.63 years, mean weight = 73.31 kg; AT-experienced: 62.30% males, mean age = 42.92 years, mean weight = 76.72 kg) [16], and those demographics available from large Spanish UC registries including ENEIDA (N = 7089; 52% male, mean age = 43 years [SD 16]) [13] or EpidemIBD (N = 3611 [1807 patients with UC]; 53% male, median age = 42 years [interquartile range 30–55]) [6], are relatively similar. Moreover, for all parameters where possible, Spanish-specific sources were selected over international data (e.g. surgery rates, surgical complications, etc.).

Another potential limitation to discuss was the use of different sources for modeling the evolution of UC, in addition to the assumptions considered mainly in relation to subsequent treatments. Although both of these aspects represent a frequent practice in economic evaluations, in the present CEA an expert panel was consulted to agree on these parameters and validate assumptions. In any case, the sensitivity analyses revealed that the results can be considered robust.

Two novel biologics have been recently reimbursed while this CEA was being conducted. For this reason, mirikizumab and risankizumab were not included in the present analysis. Additionally, JAK inhibitors were not included as comparators because their use for the treatment of UC in Spain remained low during the time horizon of the TRENDY study [13]. Although international treatment patterns suggest a potential increase in the usage of tofacitinib and upadacitinib for the management of UC in future years [90–93], the prescription trends for JAK inhibitors remain unclear. A recent survey conducted in the United Kingdom, France, Germany, Italy and Spain revealed that the use of JAK inhibitors ranged between 1% (France and Italy) and 3% (Germany) of patients, while biologics were used in 33% (Germany) to 48% (Italy) [94]. In any case, there is an opportunity to conduct further CEAs providing complementary evidence to the present analysis.

The close collaboration with a multidisciplinary panel of experts highly experienced in the management of patients with UC represents one of the main strengths of the CEA. Moreover, the evaluation of the cost effectiveness of etrasimod in both patients who have previously received any AT and those who have not is an additional strength that should be highlighted.

Finally, in Spain, each AT currently available has a different recommended posology, which determines the time spent by the patients in an induction phase with adalimumab (8 weeks) [24–29], golimumab (6 weeks) [30], infliximab (8 weeks) [31–35], ustekinumab (8 weeks) [36] and vedolizumab (6 weeks) [37, 38]. Although it is common to use extended induction with some ATs, the strength of the model used to conduct the present CEA relied on the fact that it allowed the use of different time horizons for the induction phase, providing a more accurate reflection of clinical practice in this regard. Previous models used to evaluate interventions in UC considered fixed time horizons for the induction treatment and lacked decision trees [70, 86, 87]. This poses a potential bias due to the assumption that the efficacy of the comparators is independent of the time spent in this phase.

5 Conclusions

Based on the inputs and assumptions previously described, etrasimod is a dominant therapy, which would yield more QALYs and produce cost savings from the Spanish NHS perspective, compared with biologic therapies available for UC, in patients aged 16 years and older, both with and without experience of previous ATs. This CEA represents the first economic evaluation comparing etrasimod versus the biologic therapies available for the management of moderately-to-severely active UC conducted in Spain.

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Declarations

Contributors ALJ and AC participated in the project conceptualization and definition of model inputs. ADC and IO participated in the conceptualization, definition of model inputs, model adaptation, data analyses and first draft of the manuscript. IRL, FMN, AJL and EMB validated the model structure and the inputs and provided information about management of patients with ulcerative colitis in Spain. All the authors contributed to interpretation of the results, reviewed, edited and approved the final version of the manuscript and consented to its publication.

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Data Availability All the data used to conduct the present study are publicly available and/or presented in the manuscript or its supplementary materials.

Code Availability The economic model used to develop this project is owned by Pfizer and is not publicly available.

Patient and Public Involvement Not applicable to the present study.

Patient Consent for Publication Not applicable to the present study.

Ethics Approval Not applicable to the present study.

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References

1. Dolinger M, Torres J, Vermeire S. Crohn's disease. Lancet. 2024;403:1177–91. https://doi.org/10.1016/S0140-6736(23)02586-2.
2. Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU), Hinojosa del Val JE, Nos Mateu P. Manual práctico: Conductas de actuación en la enfermedad inflamatoria crónica intestinal. 8ª. Madrid: GETECCU;
3. Gros B, Kaplan GG. Ulcerative colitis in adults: a review. JAMA. 2023;330:951–65. https://doi.org/10.1001/jama.2023.15389.
4. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769–78. https://doi.org/10.1016/S0140-6736(17)32448-0.
5. Barreiro-de Acosta M, Molero A, Artime E, Díaz-Cerezo S, Lizán L, de Paz HD, et al. Epidemiological, clinical, patient-reported and economic burden of inflammatory bowel disease (ulcerative colitis and Crohn's disease) in Spain: a systematic review. Adv Ther. 2023;40:1975–2014. https://doi.org/10.1007/s12325-023-02473-6.
6. Chaparro M, Garre A, Núñez Ortiz A, Diz-Lois Palomares MT, Rodríguez C, Riestra S, et al. Incidence, clinical characteristics and management of inflammatory bowel disease in Spain: large-scale epidemiological study. J Clin Med. 2021;10:2885. https://doi.org/10.3390/jcm10132885.
7. Hracs L, Windsor JW, Gorospe J, Cummings M, Coward S, Buie MJ, et al. Global evolution of inflammatory bowel disease across epidemiologic stages. Nature. 2025;642:458–66. https://doi.org/10.1038/s41586-025-08940-0.
8. Yarlas A, Rubin DT, Panés J, Lindsay JO, Vermeire S, Bayliss M, et al. Burden of ulcerative colitis on functioning and well-being: a systematic literature review of the SF-36® health survey. J Crohns Colitis. 2018;12:600–9. https://doi.org/10.1093/ecco-jcc/jjy024.
9. Burisch J, Vardi H, Schwartz D, Friger M, Kiudelis G, Kupčinskas J, et al. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: a population-based study. Lancet Gastroenterol Hepatol. 2020;5:454–64. https://doi.org/10.1016/S2468-1253(20)30012-1.
10. Aldeguer X, Sicras-Mainar A. Costs of ulcerative colitis from a societal perspective in a regional health care area in Spain: a database study. Gastroenterol Hepatol. 2016;39:9–19. https://doi.org/10.1016/j.gastrohep.2015.04.007.
11. Burisch J, Jess T, Martinato M, Lakatos PL. The burden of inflammatory bowel disease in Europe. J Crohns Colitis. 2013;7:322–37. https://doi.org/10.1016/j.crohns.2013.01.010.
12. Holko P, Kawalec P, Sajak-Szczerba M, Avedano L, Mossakowska M. Indirect costs of inflammatory bowel diseases: a comparison of patient-reported outcomes across 12 European countries. Inflamm Bowel Dis. 2022;29:752–62. https://doi.org/10.1093/ibd/izac144.
13. Gómez-Labrador C, Ricart E, Iborra M, Iglesias E, Martín-Arranz MD, De Castro L, et al. Trends in targeted therapy usage in inflammatory bowel disease: TRENDY study of ENEIDA. Pharmaceutics. 2024;16:629. https://doi.org/10.3390/pharmaceutics16050629.
14. Sedano R, Almradi A, Ma C, Jairath V, Feagan BG. Novel therapeutics for the treatment of IBD: current status and future directions. Curr Treat Options Gastroenterol. 2020;18:442–61. https://doi.org/10.1007/s11938-020-00299-7.
15. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Velsipity. Madrid: AEMPS; 2024. https://www.ema.europa.eu/en/documents/product-information/velsipity-epar-product-information_en.pdf. Accessed 17 Jan 2025
16. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, Dubinsky MC, Panes J, Yarur A, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet. 2023;401:1159–71. https://doi.org/10.1016/S0140-6736(23)00061-2.
17. European Medicines Agency (EMA). Velsipity. Amsterdam: EMA; 2024 Feb. https://www.ema.europa.eu/en/medicines/human/EPAR/velsipity. Accessed 5 Feb 2025
18. Center for Drug Evaluation and Research. Novel drug approvals for 2023. New Hampshire: Food and Drug Administration (FDA); 2025. https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2023. Accessed 7 Feb 2025
19. Canada's Drug Agency – L'Agence des Médicaments du Canada (CDA-AMC). Reimbursement Review - Etrasimod (Velsipity). Canadian Journal of Health Technologies. 2024;4. https://www.cda-amc.ca/sites/default/files/DRR/2024/SR0795_Velsipity_Combined_Review.pdf. Accessed 6 Feb 2025
20. National Institute for Health and Care Excellence (NICE). Etrasimod for treating moderately to severely active ulcerative colitis in people aged 16 and over. London: NICE; 2024. https://

www.nice.org.uk/guidance/ta956/resources/etrasimod-for-treating-moderately-to-severely-active-ulcerative-colitis-in-people-aged-16-and-over-pdf-82615732361413. Accessed 7 Feb 2025
21. Ortega EA. Guía de evaluación económica e impacto presupuestario en los informes de evaluación de medicamentos. Madrid: SEFH, Sociedad Española de Farmacia Hospitalaria; 2017.
22. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Londres: NICE; 2013. https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed 2 Jan 2023
23. Trapero-Bertran M, Oliva J, Catalá-López F, García-Pérez L, Segú L, Alegre-del-Rey EJ, et al. Guideline for the economic evaluation of medicines: a proposal by the Spanish National Health System's Advisory Committee for Pharmaceutical Financing. Gac Sanit. 2025;39:102448. https://doi.org/10.1016/j.gaceta.2025.102448.
24. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Humira. Madrid: AEMPS; 2008. https://cima.aemps.es/cima/dochtml/ft/103256021/FT_103256021.html
25. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Yuflyma. Madrid: AEMPS; 2021. https://cima.aemps.es/cima/pdfs/es/p/1201513015/1201513015_p.pdf
26. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Hulio. Madrid: AEMPS; 2018. https://cima.aemps.es/cima/dochtml/ft/1181319005/FT_1181319005.html
27. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Imraldi. Madrid: AEMPS; 2022. https://cima.aemps.es/cima/dochtml/ft/1171216010/FT_1171216010.html
28. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Hyrimoz. Madrid: AEMPS; 2018. https://cima.aemps.es/cima/dochtml/ft/1181286004/FT_1181286004.html
29. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Amgevita. Madrid: AEMPS; 2017. https://cima.aemps.es/cima/dochtml/ft/1161164002/FT_1161164002.html
30. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Simponi. Madrid: AEMPS; 2014. https://cima.aemps.es/cima/dochtml/ft/109546005/FT_109546005.html
31. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Dicha Técnica de Remicade. Madrid: AEMPS; 1999. https://cima.aemps.es/cima/pdfs/ft/99116001/FT_99116001.pdf
32. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Inflectra. Madrid: AEMPS; 2018. https://cima.aemps.es/cima/dochtml/ft/113854001/FT_113854001.html
33. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Remsima. Madrid: AEMPS; 2019. https://cima.aemps.es/cima/dochtml/ft/1130853006/FT_1130853006.html
34. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Zessly. Madrid: AEMPS; 2022. https://cima.aemps.es/cima/dochtml/ft/1181280001/FT_1181280001.html
35. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Flixabi. Madrid: AEMPS; 2022. https://cima.aemps.es/cima/dochtml/ft/1161106001/FT_1161106001.html
36. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Stelara. Madrid: AEMPS; 2021. https://cima.aemps.es/cima/dochtml/ft/08494003/FT_08494003.html
37. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Entyvio en polvo para concentrado para perfusión. Madrid: AEMPS; 2018. https://cima.aemps.es/cima/dochtml/ft/114923001/FT_114923001.html
38. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Entyvio en solución inyectable en jeringa precargada. Madrid: AEMPS; 2020. https://cima.aemps.es/cima/dochtml/p/114923002/P_114923002.html
39. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated health economic evaluation reporting standards (CHEERS) 2022 explanation and elaboration: a report of the ISPOR CHEERS II good practices task force. Value Health. 2022;25:10–31. https://doi.org/10.1016/j.jval.2021.10.008.
40. Jairath V, Leahy TP, Potluri R, Wosik K, Gruben D, Cappelleri JC, et al. Bayesian network meta-analysis of the efficacy of advanced therapies for patients with moderately to severely active ulcerative colitis naïve to advanced therapy. Sweden: 19th Congress of European Crohn's and Colitis Organisation (ECCO); 2024. https://scientificpubs.congressposter.com/p/k0b1nw0im7astcj2. Accessed 5 Feb 2025
41. Jairath V, Raine T, Leahy TP, Potluri R, Wosik K, Gruben D, et al. Efficacy and safety of advanced therapies for moderately to severely active ulcerative colitis in induction and maintenance: systematic literature review and Bayesian network meta-analysis. J Comp Eff Res. 2025;14:e240225. https://doi.org/10.57264/cer-2024-0225.
42. Guo JD, Gehchan A, Hartzema A. Selection of indirect treatment comparisons for health technology assessments: a practical guide for health economics and outcomes research scientists and clinicians. BMJ Open. 2025;15:e091961. https://doi.org/10.1136/bmjopen-2024-091961.
43. Jung YS, Han M, Park S, Cheon JH. Biologic use patterns and predictors for non-persistence and switching of biologics in patients with inflammatory bowel disease: a nationwide population-based study. Dig Dis Sci. 2020;65:1436–44. https://doi.org/10.1007/s10620-019-05867-1.
44. Jensen KJ, Jensen CB, Wennerström C, Burisch J, Petersen J. Drug utilization of biologic therapy in Crohn's disease and ulcerative colitis: a population-based Danish cohort study 2015–2020. Scand J Gastroenterol. 2023;58:726–36. https://doi.org/10.1080/00365521.2023.2173988.
45. Krugliak Cleveland N, Ghosh S, Chastek B, Bancroft T, Candela N, Fan T, et al. Real-world persistence of successive biologics in patients with inflammatory bowel disease: findings from ROTARY. Inflamm Bowel Dis. 2023;30:1776–87. https://doi.org/10.1093/ibd/izad245.
46. Markopoulos P, Gaki A, Kokkotis G, Chalakatevaki K, Kioulos N, Kitsou V, et al. Temporal trends in the use of biological agents in patients with inflammatory bowel disease: real-world data from a tertiary inflammatory bowel disease Greek center during a 5-year period. J Clin Med. 2025;14:1357. https://doi.org/10.3390/jcm14041357.
47. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76. https://doi.org/10.1056/NEJMoa050516.
48. Rutgeerts P, Feagan BG, Marano CW, Padgett L, Strauss R, Johanns J, et al. Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. Aliment Pharmacol Ther. 2015;42:504–14. https://doi.org/10.1111/apt.13291.
49. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Jyseleca. Madrid: AEMPS; 2020.

https://cima.aemps.es/cima/dochtml/ft/1201480003/FT_120148003.html
50. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Xeljanz. Madrid: AEMPS; 2022. https://cima.aemps.es/cima/dochtml/ft/1171178003/FT_1171178003.html
51. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Rinvoq. Madrid: AEMPS; 2019. https://cima.aemps.es/cima/dochtml/ft/1191404001/FT_1191404001.html
52. National Institute for Health and Care Excellence (NICE). Ustekinumab for moderately to severely active ulcerative colitis (TA633). Londres: NICE; 2020. https://www.nice.org.uk/guidance/ta633. Accessed 4 Sep 2023
53. National Institute for Health and Care Excellence (NICE). Upadacitinib for moderately to severely active ulcerative colitis (TA856). Londres: NICE; 2023. https://www.nice.org.uk/guidance/ta856. Accessed 4 Sept 2023
54. Guasch M, Vela E, Mañosa M, Clèries M, Cañete F, Parés D, et al. Postoperative mortality after surgery for inflammatory bowel disease in the era of biological agents: a population-based study in Southern Europe. Dig Liver Dis. 2021;53:54–60. https://doi.org/10.1016/j.dld.2020.09.026.
55. Núñez L, Mesonero F, Rodríguez de Santiago E, Die J, Albillos A, López-Sanromán A. High incidence of surgery and initiation of medical therapies after colectomy for ulcerative colitis or inflammatory bowel disease unclassified. Gastroenterol Hepatol. 2023;46:369–75. https://doi.org/10.1016/j.gastrohep.2022.08.010.
56. García MJ, Rivero M, Miranda-Bautista J, Bastón-Rey I, Mesonero F, Leo-Carnerero E, et al. Impact of biological agents on postsurgical complications in inflammatory bowel disease: a multicentre study of Geteccu. J Clin Med. 2021;10:4402. https://doi.org/10.3390/jcm10194402.
57. Ferrante M, Declerck S, De Hertogh G, Van Assche G, Geboes K, Rutgeerts P, et al. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. Inflamm Bowel Dis. 2008;14:20–8. https://doi.org/10.1002/ibd.20278.
58. Instituto Nacional de Estadística (INE). Demografía y población: Fenómenos demográficos - Tablas de mortalidad. Madrid: INE; https://ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736177004&menu=ultiDatos&idp=1254735573002. Accessed 19 June 2024
59. Jess T, Gamborg M, Munkholm P, Sørensen TIA. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. Am J Gastroenterol. 2007;102:609–17. https://doi.org/10.1111/j.1572-0241.2006.01000.x.
60. Consejo General de Colegios Oficiales de Farmacéuticos (CGCOF). BOTPlus. Madrid: CGCOF; 2023. https://botplusweb.farmaceuticos.com/. Accessed 21 Aug 2023
61. Jefatura del Estado. Real Decreto-ley 8/2010, de 20 de mayo, por el que se adoptan medidas extraordinarias para la reducción del déficit público. S ect. 1, Real Decreto-ley 8/2010 May 24, 2010 p. 45070–128. https://www.boe.es/eli/es/rdl/2010/05/20/8. Accessed 23 May 2024
62. Ministerio de Sanidad. Portal Estadístico: Área de Inteligencia de Gestión. Madrid: Ministerio de Sanidad; 2023. https://pestadistico.inteligenciadegestion.sanidad.gob.es/publicoSNS/N/rae-cmbd/rae-cmbd/grupos-relacionados-por-el-diagnostico-grd. Accessed 8 Nov 2023
63. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Immufalk. Madrid: AEMPS; 2024. https://cima.aemps.es/cima/pdfs/es/ft/78164/FT_78164.html.pdf. Accessed 20 Jan 2025
64. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Mercaptopurina Aspen. Madrid: AEMPS; 2022. https://cima.aemps.es/cima/dochtml/ft/34565/FT_34565.html
65. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Metotrexato semanal Cipla. Madrid: AEMPS; 2023. https://cima.aemps.es/cima/dochtml/ft/79758/FichaTecnica_79758.html
66. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Asacol. Madrid: AEMPS; 2008. https://cima.aemps.es/cima/dochtml/ft/57726/FT_57726.html. Accessed 5 Sept 2023
67. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Prednisona Cinfa EFG. Madrid: AEMPS; 2020. https://cima.aemps.es/cima/dochtml/ft/75649/FT_75649.html. Accessed 5 Sept 2023
68. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Ficha Técnica de Clipper. Madrid: AEMPS; 2019. https://cima.aemps.es/cima/pdfs/es/ft/66706/FT_66706.html.pdf. Accessed 20 Jan 2025
69. National Institute for Health and Care Excellence (NICE). Ozanimod for moderately to severely active ulcerative colitis (TA828). Londres: NICE; 2022. https://www.nice.org.uk/guidance/ta828. Accessed 4 Sep 2023
70. Trigo-Vicente C, Gimeno-Ballester V, Montoiro-Allué R, López-Del Val A. Cost-effectiveness analysis of infliximab, adalimumab, golimumab and vedolizumab for moderate to severe ulcerative colitis in Spain. Expert Rev Pharmacoecon Outcomes Res. 2018;18:321–9. https://doi.org/10.1080/14737167.2018.1411193.
71. Instituto Nacional de Estadística (INE). Índice de precios de consumo. Madrid: INE; https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176802&menu=ultiDatos&idp=1254735976607. Accessed 5 Dec 2024
72. Kosmas C, Kerr C, Marsh S, Gentile B, Doll H, Finney-Hayward T. Health related quality of life (Hrqol) in patients who have undergone colectomy for ulcerative colitis: impacts of complications post-surgery. Value Health. 2015;18:A630. https://doi.org/10.1016/j.jval.2015.09.2224.
73. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess. 2016;20:1–610. https://doi.org/10.3310/hta20350.
74. Comité Asesor para la Financiación de la prestación Farmacéutica del SNS. Guía de Evaluación Económica de Medicamentos. Madrid: Ministerio de Sanidad; 2024. https://www.sanidad.gob.es/areas/farmacia/comitesAdscritos/prestacionFarmaceutica/docs/20240227_CAPF_Guia_EE_definitiva.pdf. Accessed 13 Sep 2024
75. Vallejo-Torres L, García-Lorenzo B, Rivero-Arias O, Pinto-Prades J, Serrano-Aguilar P. Disposición a pagar de la sociedad española por un Año de Vida Ajustado por Calidad. Canarias: Servicio de Evaluación del Servicio Canario de Salud (SESCS); 2016. https://www3.gobiernodecanarias.org/sanidad/scs/content/c6b59111-420f-11e7-952b-a987475f03d3/SESCS_2016_DAP_AVAC.pdf. Accessed 28 Sep 2023
76. Sacristán JA, Oliva J, Campillo-Artero C, Puig-Junoy J, Pinto-Prades JL, Dilla T, et al. Qué es una intervención sanitaria eficiente en España en 2020? Gac Sanit. 2020;34:189–93. https://doi.org/10.1016/j.gaceta.2019.06.007.
77. Vallejo-Torres L. Estimating the incremental cost per QALY produced by the Spanish NHS: a fixed-effect econometric approach. Pharmacoeconomics. 2024. https://doi.org/10.1007/s40273-024-01441-4.
78. Rokkas T, Gisbert JP, Ekmektzoglou K, Dassopoulos T, Niv Y, O'Morain C. Comparative maintenance performance of all

biologic agents and small molecules in ulcerative colitis: a network meta-analysis. Eur J Gastroenterol Hepatol. 2024;36:520–33. https://doi.org/10.1097/MEG.0000000000002751.
79. Lichtenstein GR, Allegretti JR, Loftus EV, Irving PM, Banerjee R, Charabaty A, et al. Assessment and impact of age on the safety and efficacy of etrasimod in patients with ulcerative colitis: a post hoc analysis of data from the ELEVATE UC clinical program. Inflamm Bowel Dis. 2025. https://doi.org/10.1093/ibd/izae308.
80. Woehl A, Hawthorne A, McEwan P. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis. Gut. 2008.
81. Swinburn P, Elwick H, Bean K, Curry A, Patel S, Bodger K, et al. PTU-127 The impact of surgery on health related quality of life in ulcerative colitis: abstract PTU-127 figure 1. Gut. 2012;61:A237.2-A237. https://doi.org/10.1136/gutjnl-2012-302514c.127.
82. Vaizey CJ, Gibson PR, Black CM, Nicholls RJ, Weston AR, Gaya DR, et al. Disease status, patient quality of life and healthcare resource use for ulcerative colitis in the UK: an observational study. Frontline Gastroenterol. 2014;5:183–9. https://doi.org/10.1136/flgastro-2013-100409.
83. Gisbert JP, Chaparro M. Etrasimod: review of the efficacy and therapeutic prospects of a new oral therapy for the treatment of ulcerative colitis. Gastroenterol Hepatol. 2025;48:502363. https://doi.org/10.1016/j.gastrohep.2025.502363.
84. Ferreiro-Iglesias R, Porto Silva S, Marín S, Casanova MJ, Mañosa M, González-Muñoza C, et al. Need for therapeutic escalation in patients with refractory ulcerative proctitis: results from the PROCU study of the ENEIDA registry. Aliment Pharmacol Ther. 2024;60:604–12. https://doi.org/10.1111/apt.18133.
85. Peyrin-Biroulet L, Dubinsky MC, Sands BE, Panés J, Schreiber S, Reinisch W, et al. Efficacy and safety of etrasimod in patients with moderately to severely active isolated proctitis: results from the phase 3 ELEVATE UC clinical programme. J Crohns Colitis. 2024;18:1270–82. https://doi.org/10.1093/ecco-jcc/jjae038.
86. Trigo-Vicente C, Gimeno-Ballester V, Val AL-D. Cost-effectiveness analysis of infliximab, adalimumab, golimumab, vedolizumab and tofacitinib for moderate to severe ulcerative colitis in Spain. Eur J Hosp Pharm. British Medical Journal Publishing Group; 2020;27:355–60. https://doi.org/10.1136/ejhpharm-2018-001833
87. Taxonera C, De Andrés-Nogales F, García-López S, Sánchez-Guerrero A, Menchén B, Peral C, et al. Cost-effectiveness analysis of using innovative therapies for the management of moderate-to-severe ulcerative colitis in Spain. Expert Rev Pharmacoecon Outcomes Res. 2022;22:73–83. https://doi.org/10.1080/14737167.2021.1880324.
88. Member State Coordination Group on Health Technology Assessment. Methodological guideline for quantitative evidence synthesis: direct and indirect comparisons. Bruselas: Comisión Europea; 2024. https://health.ec.europa.eu/document/download/4ec8288e-6d15-49c5-a490-d8ad7748578f_en?filename=hta_methodological-guideline_direct-indirect-comparisons_en.pdf&prefLang=el. Accessed 10 Sep 2024
89. Member State Coordination Group on Health Technology Assessment. Practical guideline for quantitative evidence synthesis: direct and indirect comparisons. Bruselas: Comisión Europea; 2024. https://health.ec.europa.eu/document/download/1f6b8a70-5ce0-404e-9066-120dc9a8df75_en?filename=hta_practical-guideline_direct-and-indirect-comparisons_en.pdf. Accessed 10 Sep 2024
90. Brady JE, Stott-Miller M, Mu G, Perera S. Treatment patterns and sequencing in patients with inflammatory bowel disease. Clin Ther. 2018;40:1509-1521.e5. https://doi.org/10.1016/j.clinthera.2018.07.013.
91. Buisson A, Serrero M, Altwegg R, Guilmoteau T, Bouguen G, Nachury M, et al. Real-world comparison of the effectiveness of tofacitinib and ustekinumab in patients with ulcerative colitis: the TORUS study. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2025. https://doi.org/10.1016/j.cgh.2025.07.044.
92. Imbrizi M, Azevedo MFC, Baima JP, Queiroz NSF, Parra RS, Ferreira SDC, et al. Positioning and sequencing of advanced therapies in inflammatory bowel disease: a guide for clinical practice. World J Gastroenterol. 2025;31:107745. https://doi.org/10.3748/wjg.v31.i29.107745.
93. Gisbert JP, Chaparro M. Combination therapy with biologics and/or small molecules in inflammatory bowel disease: a comprehensive review. J Crohns Colitis. 2025. https://doi.org/10.1093/ecco-jcc/jjaf161.
94. Gisbert JP, Schreiber S, Siegel CA, Magro F, Jus A, Whichello C, et al. Benefit-risk trade-offs and patient preferences for therapy selection in ulcerative colitis: a multicountry preference study. Inflamm Bowel Dis. 2025;31:1281–94. https://doi.org/10.1093/ibd/izae162.
95. Xie F, Blackhouse G, Assasi N, Gaebel K, Robertson D, Goeree R. Cost-utility analysis of infliximab and adalimumab for refractory ulcerative colitis. Cost Eff Resour Alloc. 2009;7:20. https://doi.org/10.1186/1478-7547-7-20.

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