PharmacoEconomics - Open (2026) 10:557–566
https://doi.org/10.1007/s41669-026-00642-1

ORIGINAL RESEARCH ARTICLE

# Cost-Effectiveness Analysis of Sequential Treatment Strategies for Moderate to Severe Crohn's Disease in Spain: Where Should Biosimilar Ustekinumab Be Positioned?

**Iago Rodríguez-Lago[1,2,3] · José Ignacio Peinado-Fabregat[4] · Marcelo Guigini[4] · Mónica Cerezales[5] · Francisco Ibáñez[6] · Carlos Crespo[6,9] · Manuel Barreiro-de Acosta[7,8]**

Received: 8 July 2025 / Accepted: 16 February 2026 / Published online: 9 March 2026


## Abstract

**Background/Objective** Crohn's disease is associated with a high economic burden for the Spanish National Healthcare System, driven by pharmacological expenses. Following the recent incorporation of ustekinumab biosimilars into the market, this study aimed to evaluate the cost effectiveness of different treatment sequences, including biosimilar ustekinumab (bsUST), for moderate-to-severe Crohn's disease from the NHS perspective in Spain.

**Methods** Treatment sequences were defined according to clinical practice. A Markov model with 2-week cycles and a lifetime horizon was developed, including health states such as active disease, response, remission, surgery, and death. Funnel states simulated induction and treatment changes after loss of response, and surgery was considered only after four pharmacological lines. Efficacy data for biosimilar adalimumab (bsADA), biosimilar intravenous infliximab (bsIFX), biosimilar ustekinumab (bsUST) risankizumab (RIS), upadacitinib (UPA), vedolizumab (VDZ), and surgery (Q) were obtained through published literature, including network meta-analyses and clinical trials. Unitary costs were sourced from Spanish databases and literature. Pharmacological costs were ex-factory prices applying Royal Decree-Law (RDL) 8/2010 discount. For bsADA and bsIFX, average biosimilar market prices were used. A 30% discount was assumed for bsUST versus reference ustekinumab. Sequence 1 (bsADA-bsUST-UPA-RIS-Q) was set as the reference.

**Results** Alternative strategies provided QALY gains ranging from 0.06 to 0.34 compared with the reference. However, due to varying incremental costs, Sequence 2 (bsUST, bsADA, UPA, RIS, Q) emerged as the only cost-effective strategy at a willingness-to-pay threshold of €27,000/QALY, with an incremental cost-effectiveness ratio (ICER) of €8672.6/QALY. Conversely, all other sequences exceeded the threshold, with ICERs starting at €42,594/QALY. Probabilistic sensitivity analysis confirmed the robustness of these findings, identifying Sequence 2 as the cost-effective option in 98.03% of simulations.

**Conclusions** Positioning bsUST as a first line of treatment appears to be cost effective and an efficient alternative from the NHS perspective in Spain. Additionally, none of the alternative sequences proved to be cost effective compared with the sequence starting with bsADA-bsUST. bsUST may significantly impact Crohn's disease management in Spain, improving patient access due to its lower drug acquisition costs.

## 1 Introduction

Crohn's disease (CD) is one of the two main subtypes of inflammatory bowel disease (IBD); it is characterized by skip intestinal lesions in the gastrointestinal (GI) tract, mainly affecting the ileocecal region, with chronic, relapsing transmural inflammation that leads to chronic and disabling symptoms such as abdominal pain, diarrhoea, intestinal obstruction and/or perianal lesions [1]. It is a progressive disease with a relapsing and remitting course that greatly affects patients in aspects such as their quality of life (QoL), experiencing negative outcomes, requiring hospitalization and eventually surgery, with around 18% of patients requiring surgery in the 5 years following diagnosis [1, 2].

The incidence and prevalence of CD have been reported to increase in recent years, with the most recent incidence figure being 18/100,000 inhabitants and a prevalence of 191/100,000 inhabitants in Spain [3]. These patients also experience frequent comorbidities, leading to a significant impact on their health-related quality of life (HRQoL) [3]. Furthermore, due to associated comorbidities, complications, and disease management, these patients represent a

Extended author information available on the last page of the article

**Key Points for Decision Makers**

First-line biosimilar ustekinumab (bsUST) may represent a cost-effective strategy for moderate-to-severe Crohn's disease in Spain, offering a favorable balance between clinical outcomes and healthcare costs.

When compared with the reference treatment sequence, only the sequence beginning with biosimilar ustekinumab was found to be cost effective, as all other alternative sequences exceeded the cost-effectiveness threshold commonly used in the Spanish healthcare setting.

The introduction of bsUST could expand access to biologic therapies, driven by the foreseeable lower acquisition cost of the biosimilar, potentially alleviating the economic burden of this chronic condition on the Spanish National Healthcare System.

high economic burden for the national healthcare system (NHS) [3]. In a recent study, yearly costs for these patients ranged between 11,000€ and 18,000€, being those direct healthcare costs comparable among treatments and differences driven by pharmacological expenses [4]. CD also leads to numerous sick leave or disability pension days, with a reported mean of 13.2 sick leave days per year and 19.8 disability pension days [5].

Therapeutic goals in patients with CD have evolved in recent years towards targeting mucosal healing due to its association with improved outcomes, decreased risk of surgery, lower relapse rates, and improved QoL [1]. Disease activity is commonly measured through the Crohn's Disease Activity Index (CDAI), which accounts for eight items, and disease remission is defined by a score < 150 [6]. The current therapeutic armamentarium includes multiple biologic agents and small molecules. In 2020, ustekinumab (UST) was included as a therapy of choice for both induction and maintenance for patients with moderate-to-severe CD, in the ECCO Guidelines 2020 for patients who have not responded to conventional therapy and/or anti-TNFs [7], while the latest published guidelines in 2024 have positioned ustekinumab as first line for induction therapy in moderate-to-severe CD and as maintenance therapy [8]. Other biologic agents include anti-TNFs (adalimumab [ADA], or infliximab [IFX]), anti-IL23 (risankizumab [RIS]), anti-α4β7-integrin (vedolizumab [VDZ]), or Janus kinase (JAK) inhibitors (upadacitinib [UPA]) [8]. These biologics and small molecules have changed the paradigm of treatment and outcomes for these patients [1], although they are associated with notable costs [4].

In Spain, UST was initially approved in 2009 for moderate to severe plaque psoriasis and in 2016 for CD. Since then, several ustekinumab biosimilars (bsUST) have been incorporated into the Spanish market, with the first one commercially available in mid-2024. In light of this wide range of new treatment options for CD, which is a highly impactful disease for the public healthcare system, this study aimed to evaluate the cost effectiveness of different treatment sequences for patients with moderate-to-severe CD including bsUST from the NHS perspective in Spain.

## 2 Materials and Methods

### 2.1 Literature Review

A pragmatic literature review was carried out to identify relevant clinical studies. A PICO-S-T approach was followed:

- Population: adult patients with moderate-severe CD.
- Intervention: bsUST.
- Comparator: ADA, intravenous IFX, RIS, UST, UPA, VDZ.
- Outcome: clinical response, clinical remission, odds ratio (OR), relative risk (RR), number needed to treat (NNT), cost per responder, CDAI.
- Time frame: 2011–2024.
- Study type: systematic review, meta-analysis, network meta-analysis and real-world evidence (RWE) studies.

Clinical trials were identified by screening the references of the selected reviews.

### 2.2 Model and Scope

A model-based cost-effectiveness analysis was conducted through the development of a Markov model, based on a previous one [9], to evaluate, over a lifetime horizon, different treatment sequences in the management of patients with moderate-severe CD [9]. Sequences were defined according to common clinical practice in Spain by two expert gastroenterologists with experience in IBD (IRL and MBA) based on current standard of care according to clinical guidelines [7], their clinical expertise, reimbursed treatments in Spain, and potential shifts in practice following the availability of bsUST (Fig. 1).

The Markov model included a cycle length of 2 weeks (Fig. 2). All patients entered the model in the active disease health state and funnel health states were created to simulate induction times for each treatment. After induction, patients could achieve response, defined as a reduction of ≥100 points from basal CDAI or remission,

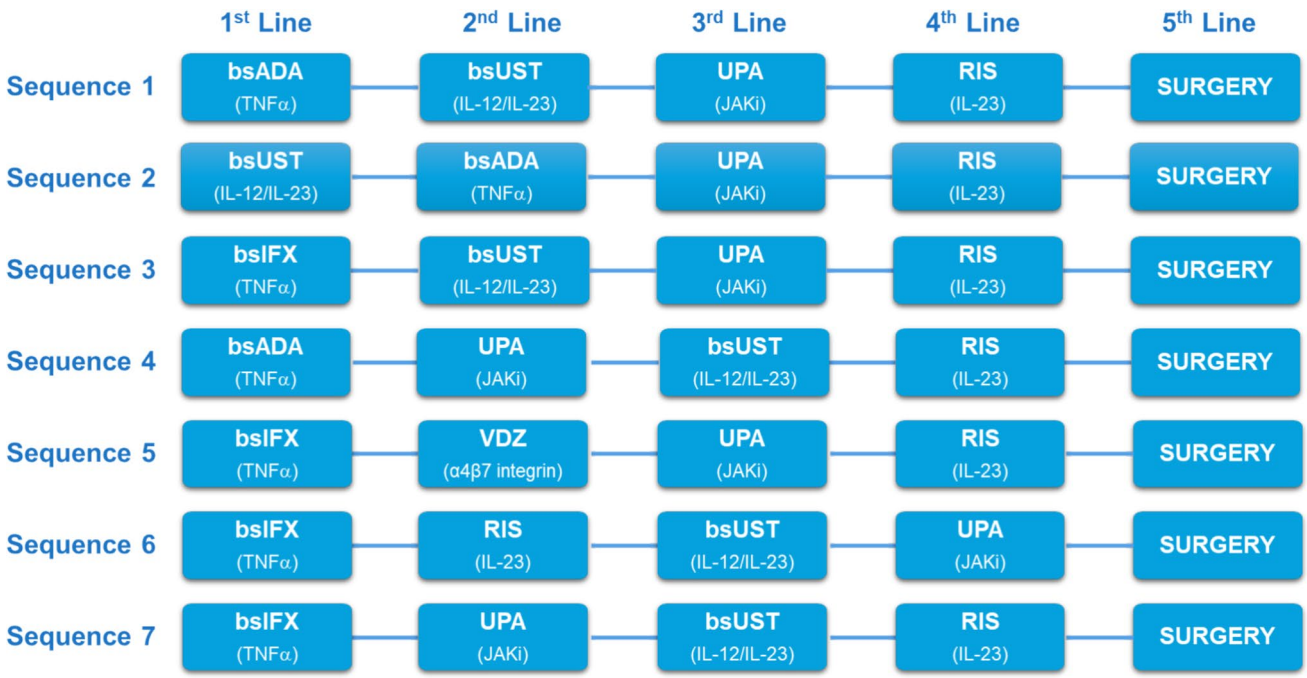


**Fig. 1** Treatment sequences for the management of Crohn's disease patients included in the model. *bsADA* biosimilar adalimumab, *bsIFX* biosimilar infliximab, *bsUST* biosimilar ustekinumab, *RIS* risankizumab, *UPA* upadacitinib, *VDZ* vedolizumar

the achievement of a CDAI < 150 points [10]. Patients responding to induction therapy were continued on the same maintenance treatment; patients not achieving any of these health states stayed in the active disease state and switched to the subsequent line of treatment. Those patients developing loss of response were transitioned to the next line of treatment 3 months after loss of response to reflect the potential clinical delay between the identification of treatment failure and the initiation of a new therapy. Patients failing the last line of treatment, after four lines of medical treatment, underwent surgery and could move to remission or active disease. Death was considered an absorbing health state and patients can enter it from any other health state. A discount of 3% was applied to both effects and costs.

Upon initiation of each therapeutic line, patients entered a treatment-specific sequence of several tunnel sub-states through which patients must transit before their induction outcome was determined. This initial sequence of tunnel sub-states represented the treatment induction period. Following this induction phase, patients could progress to either a 'response' or 'remission' state. Patients who did not achieve either a response or remission state after the defined induction period transitioned to a state specifically designated as 'active disease'. In this model state, patients awaited the initiation of the next available line of treatment. After the induction period, patients were assigned for the first year to the remission or response state based on inputs from the maintenance treatment. Starting from the first year of treatment, annual discontinuation rates, specific to each therapy, were applied. These discontinuation rates were derived from RWE studies [9, 11–13]. Patients who did not maintain remission or response moved to the next line of treatment.

## 2.3 Base Case

Patient characteristics used in this model were based on the population included in the UNITI-2 [14], and included adult patients with a mean age of 39.2 years, 46.7% women, and a mean weight of 73.4 kg. This patient profile was validated against Spanish real-world data from the ENEIDA registry [15], showing clinical characteristics consistent with patients managed in local practice.

The following sequences were defined for the base case:

- Sequence 1: Adalimumab → Ustekinumab → Upadacitinib → Risankizumab → Surgery
- Sequence 2: Ustekinumab → Adalimumab → Upadacitinib → Risankizumab → Surgery
- Sequence 3: Infliximab → Ustekinumab → Upadacitinib → Risankizumab → Surgery
- Sequence 4: Adalimumab → Upadacitinib → Ustekinumab → Risankizumab → Surgery
- Sequence 5: Infliximab → Vedolizumab → Upadacitinib → Risankizumab → Surgery

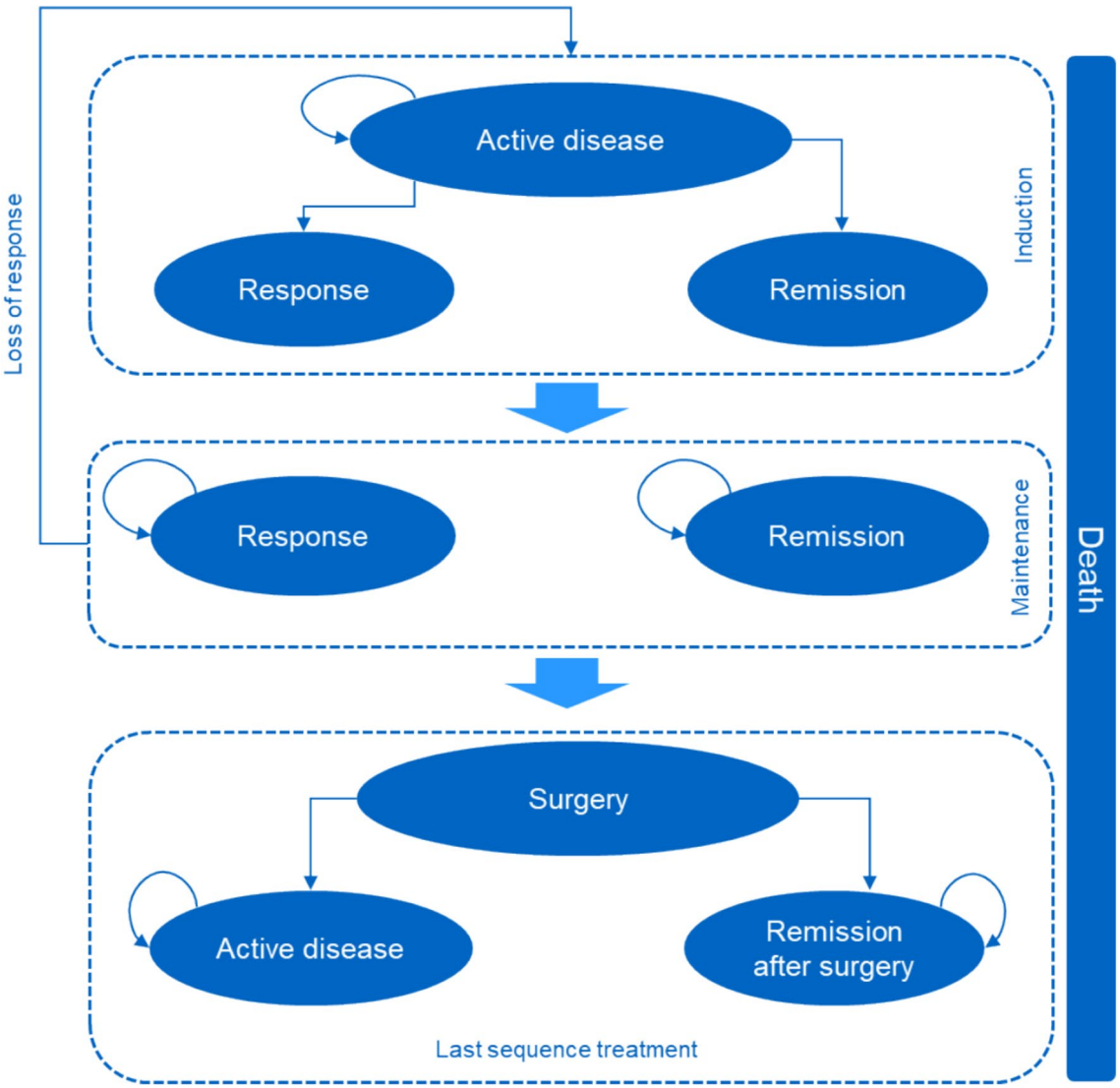


**Fig. 2** Markov model structure used for the cost-effectiveness evaluation of different treatment sequences for the treatment of moderate to severe Crohn's disease in Spain

- Sequence 6: Infliximab → Risankizumab → Ustekinumab → Upadacitinib → Surgery
- Sequence 7: Infliximab → Upadacitinib → Ustekinumab → Risankizumab → Surgery

## 2.4 Clinical Inputs

Clinical efficacy data was based on the results from the network meta-analysis published by Barberio et al. [16]. This NMA provided all induction and maintenance outcomes (remission and response) for the biologic-naïve population and the induction outcomes for the biologic-experienced population. For maintenance efficacy in biologic-experienced patients, data were extracted directly from the pivotal clinical trials for ADA [17], intravenous IFX [18], RIS [19], UST [14], UPA [20], and VDZ [21]. In the absence of data for infliximab in the biologic-experienced setting, its efficacy was assumed to be the lowest of all comparators.

Discontinuation rates adjusted per cycle, for both naïve and biologic-experienced patients, were taken into account considering data from real-world practice, including ADA [9] 1.7% and 1.1%; IFX [9] 0.8% and 1.2%; UST [11] 0.8% and 0.8% for naïve and biologic-experienced, respectively. RIS [13], UPA [12], and VDZ [9] discontinuation was considered for biologic-experienced patients only, at 1.2%, 1.8%, and 1%, respectively.

Data from adverse events, specifically serious infections, was recorded from corresponding clinical trials (Online

Resource 1, see electronic supplementary material [ESM]) [14, 17–21].

In accordance with published literature that has not identified statistically significant differences in mortality between patients with CD and the general population [22], age- and sex-matched general population mortality rates were applied, sourced from the Spanish National Institute of Statistics (INE) [23].

All the dosing regimens were considered in accordance with approved indications in the corresponding technical sheets of the products, not taking into account intensification or optimization of the different dosing regimens.

The assessment of the HRQoL for this baseline case varies depending on the health status of the disease using the utility values 0.41, 0.87, 0.76, 0.41, 0.71, and 0.54 for active disease, remission, response, surgery, remission after surgery, and active disease, respectively; that were retrieved from a cost-effectiveness analysis of sequential biologic treatment for IBD [9]. The disutility value applied to serious infections was 0.07, applied per occurrence [9].

### 2.5 Economic Inputs

The analysis considered only direct healthcare costs, consistent with the perspective of the Spanish National Health System. All costs were inflation-adjusted to 2024 euros using the Spanish Consumer Price Index (CPI) [24].

Treatment dosing regimen was included according to the *Summary of Product Characteristics* data sheet and approved doses for CD both in the induction and maintenance phase [25–30]. Pharmacological costs were ex-factory prices retrieved from BotPlus [31], applying the deduction from 'Real Decreto Ley' (RDL) 8/2010; for comparators with available biosimilars, an average cost of the marketed biosimilar presentations for the indication was used. In the case of bsUST, a 30% price reduction compared with the reference biological was assumed. Vial sharing was considered for bsUST and IFX.

Yearly healthcare resource consumption for each health state was determined through a structured consensus between the clinical experts. An initial set of resource use estimates, derived from the literature and clinical guidelines, was presented to the experts and subsequently refined and validated during a consensus meeting to ensure the model accurately reflects current clinical practice in Spain.

Unitary costs for the use of resources in patient management (such as primary healthcare visits, specialist visits, hospital stay, emergency room visits, Online Resource 1, ESM), serious infections, and surgery (Online Resource 1, ESM) were obtained from the Ministry of Health database (RAE-CMBD) and published regional tariffs [32, 33].

### 2.6 Sensitivity Analysis

To assess the robustness of the Markov model results and address inherent parameter uncertainty, both deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were performed. One-way DSA involved individually varying key model parameters within a plausible range (± 20% of their base-case value or using 95% confidence intervals when available), while all other parameters were held at their base-case values. The impact of these variations on the incremental cost-effectiveness ratio (ICER) was examined using a tornado diagram to identify the parameters exerting the most significant influence on the model's conclusions. Additionally, a PSA was conducted to quantify the joint impact of uncertainty across all parameters simultaneously. In the PSA, appropriate probability distributions were assigned to the model parameters: beta distribution for transition probabilities and safety parameters, 1-gamma for utilities and disutilities, and log normal for costs. The model was then run for 10,000 iterations in a Monte Carlo simulation with parameter values randomly sampled from their respective distributions in each iteration. The PSA results were used to generate a scatter plot on the cost-effectiveness plane and a cost-effectiveness acceptability curve, which illustrates the probability of the intervention being cost effective at different willingness-to-pay (WTP) thresholds. A WTP threshold of €27,000 per quality-adjusted life year (QALY), commonly referenced in the Spanish context [34], was used to assess cost effectiveness.

### 2.7 Alternative Reference Analysis

In order to assess the cost effectiveness of bsUST as the first-line treatment, an alternative reference analysis, setting Sequence 2 as the reference, was performed.

This article has been written according to the ISPOR CHEERS checklist [35].

## 3 Results

### 3.1 Base Case

Sequence 1 was established as the reference comparator as it represented the strategy with the lowest total cost (€157,223.9). Comparison of alternative strategies against this reference revealed that, considering a WTP threshold of 27,000€/QALY, Sequence 2 was the only cost-effective option, with an ICER of 8672.6€/QALY, (Table 1). In contrast, all other alternatives exceeded this threshold. Sequence 4 presented an ICER of 60,901.3€/QALY. Sequences starting with bsIFX provided QALY gains (ranging from 0.06 to 0.34) compared with the reference and their incremental

**Table 1** Results of the cost-effectiveness analysis of seven treatment sequences for the management of moderate-to-severe Crohn's disease patients in Spain

| Therapeutic sequence (*by ascending cost/patient*) | Cost per patient | Δ Cost (vs Sequence 1) | QALYs per patient | Δ QALYs (vs Sequence 1) | ICER |
|---|---|---|---|---|---|
| Sequence 1 (bsADA, bsUST, UPA, RIS, Q) | 157,223.9€ | - | 11.78 | - | - |
| Sequence 4 (bsADA, UPA, bsUST, RIS, Q) | 158,194.8€ | 970.8€ | 11.79 | 0.02 | Sequence 4 not cost effective 60,901,3€/QALY |
| Sequence 2 (bsUST, bsADA, UPA, RIS, Q) | 160,303.8€ | 3079.8€ | 12.13 | 0.36 | Sequence 2 cost effective 8672.6€/QALY |
| Sequence 3 (bsIFX, bsUST, UPA, RIS, Q) | 170,665.7€ | 13,441.8€ | 12.05 | 0.27 | Sequence 3 not cost effective 49,093.6€/QALY |
| Sequence 7 (bsIFX, UPA, bsUST, RIS, Q) | 171,632.7€ | 14,408.7€ | 12.07 | 0.29 | Sequence 7 not cost effective 49,511.7€/QALY |
| Sequence 6 (bsIFX, RIS, bsUST, UPA, Q) | 171,694.9€ | 14,471€ | 12.12 | 0.34 | Sequence 6 not cost effective 42,594€/QALY |
| Sequence 5 (bsIFX, VDZ, UPA, RIS, Q) | 179,533.7€ | 22,309.7€ | 11.84 | 0.06 | Sequence 5 not cost effective 372,446€/QALY |

*bsADA* biosimilar adalimumab, *bsIFX* biosimilar infliximab, *bsUST* biosimilar ustekinumab, *ICER* incremental cost effectiveness ratio, *Q* surgery, *QALY* quality-adjusted life year, *RIS* risankizumab, *UPA* upadacitinib, *VDZ* vedolizumab

costs resulted in ICERs ranging from 42,594€/QALY to 372,446€/QALY.

In the base case, the first line of treatment in Sequence 2 had a duration of 3.9 years while the other sequences ranged between 2.2 and 3.3 years, and time to surgery ranged between 7.9 years for Sequences 2 and 4, and 9 years in Sequences 6 and 7.

### 3.2 Sensitivity Analysis

To assess the robustness of our base-case cost-effectiveness findings, both deterministic and probabilistic sensitivity analyses were conducted. Deterministic sensitivity analysis, conducted as one-way sensitivity analyses varying each parameter across its plausible range, revealed that the ICER was most sensitive to variations in the parameters related to the first line of treatment used in each sequence. Specifically, the most impactful variables were patient weight (which directly influences dosing for certain agents), the pharmacological costs of the first-line biologics, and the probability of achieving remission during the maintenance phase. (Online Resources 2–7, see ESM). The probabilistic sensitivity analysis, based on 10,000 Monte Carlo simulations, showed that at a WTP threshold of €27,000 per QALY, the probability of each sequence being cost effective compared with Sequence 1 was 98.03% for Sequence 2, 25.21% for Sequence 3, 54.96% for Sequence 4, 36.65% for sequence 5, 25.47% for Sequence 6, and 21.70% for Sequence 7. The results of the PSA are further illustrated by the cost-effectiveness acceptability curves (CEACs) presented in Fig. 3. A scatter plot is presented in Fig. 4, with confidence ellipses encompassing the data points for the 95% of each point cloud. For a detailed view, individual scatter plots showing the point cloud for each comparison between the different sequences and Sequence 1 have been included in Online Resources 8–13 (see ESM).

Results of the alternative reference analysis, with Sequence 2 as the reference, can be seen in Online Resource 14 (ESM). In this analysis, Sequences 3, 5, 6 and 7 were considered dominated. While Sequences 1 and 4 resulted in lower total costs (savings of €3079.8 and €2109.0, respectively), they were also associated with a loss in QALYs (−0.36 and −0.34). Therefore, Sequence 2 remains the preferred option as the incremental cost to gain these additional QALYs falls within the cost-effectiveness threshold.

## 4 Discussion

CD is a disease that imposes a significant burden on patients regarding HRQoL and results in high resource consumption for healthcare systems since it is a chronic disease affecting mostly young people [3]. Biologic treatments, in spite of their high costs, have reduced the overall cost of patient management by reducing the need for hospitalizations and surgery [36, 37]. Currently, a wide range of therapeutic options is available for these patients, and appropriate sequencing is necessary, considering patient-specific characteristics and careful evaluation by a multidisciplinary team engaged in shared decision making [8]. Most patients will require switching between therapies as loss of response is relatively frequent as the disease

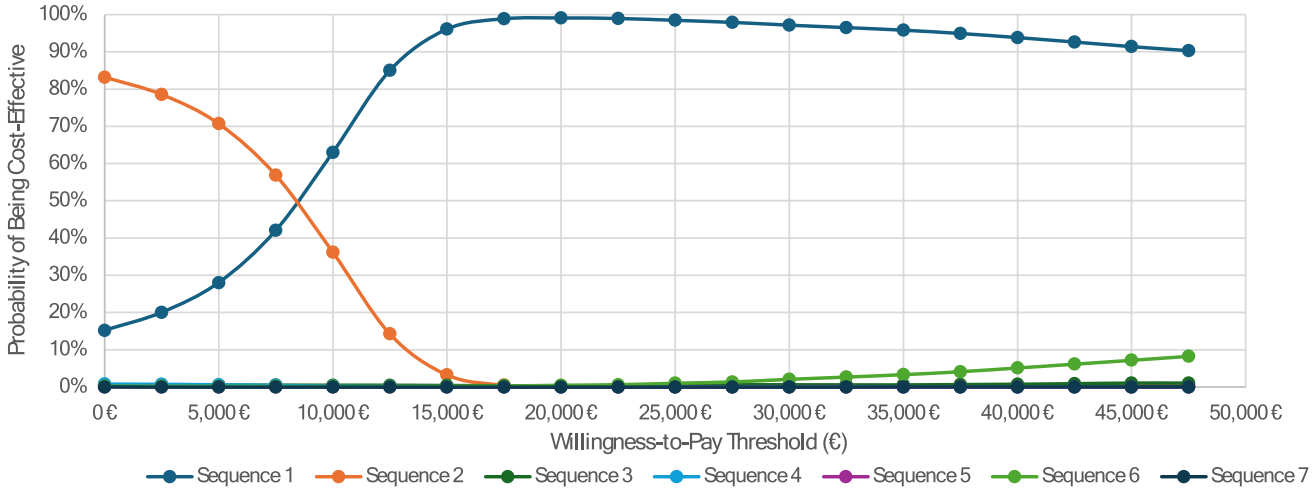


**Fig. 3** Cost-effectiveness acceptability curves; all sequences

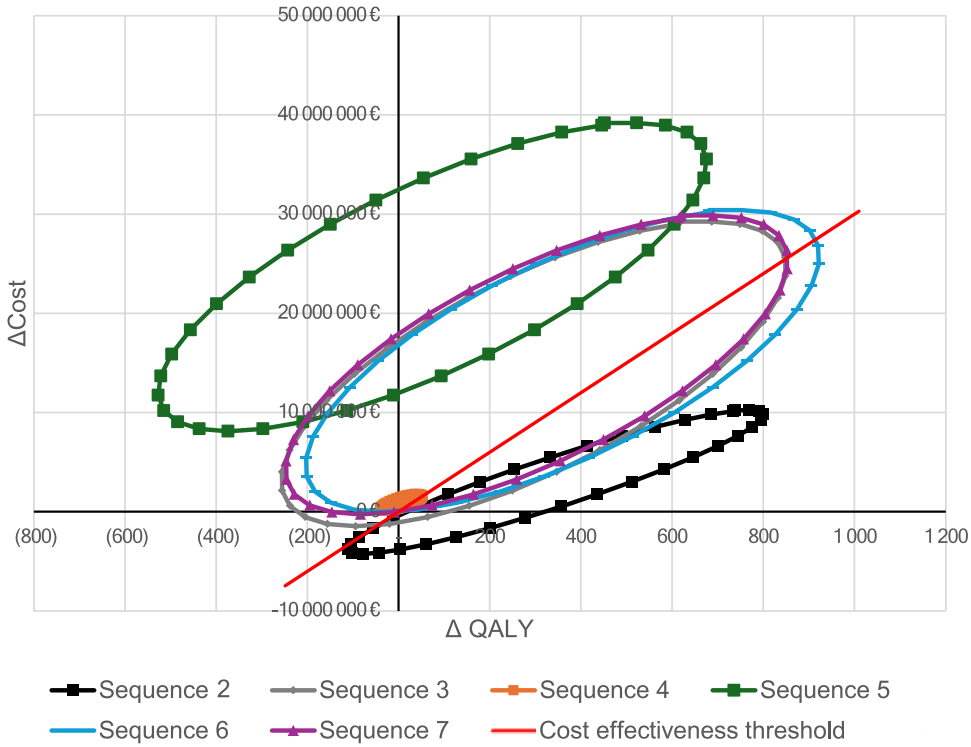


**Fig. 4** Cost-effectiveness plane with confidence ellipses of probabilistic sensitivity analysis (versus sequence 1). *QALY* quality-adjusted life year

progresses over time, and the more recent evidence supports very early initiation of effective treatment as this clearly improves clinical outcomes [8, 38]. However, due to the lack of head-to-head comparisons and published evidence, it is essential to develop in-silico analyses to assist decision makers and healthcare providers. Thus, this analysis incorporated evidence from a prior meta-analysis as the primary source of evidence for the effectiveness data for treatments [16] that was further reinforced with specific data from clinical trials.

Results from our study show that sequences positioning drugs with a good efficacy and safety profile such as bsUST in first lines of treatment not only contribute to better clinical results but also reduce costs for the healthcare system as has been demonstrated in previous studies [39]. UST as the first therapy of choice always yielded the highest effectiveness (measured in QALYs) [39]. This QALY advantage arises within the model because the efficacy and discontinuation data [17] translate into patients on UST spending a longer duration in the more favorable 'remission' and 'response' health states before switching to the next line of treatment

[16]. A previous cost-effectiveness analysis of treatments for CD in Spain reported the absence of effectiveness differences between drugs [40]. However, reference UST was the second most costly alternative, which could change with the introduction of biosimilars and their associated discount on pharmacological price [41], as it is considered in this work, highlighting the potential to improve clinical outcomes for patients while reducing costs.

This pharmacoeconomic evaluation, while employing a sequence-based Markov model validated by clinical experts and populated with data from the published literature, is subject to several inherent limitations. Firstly, in Markov models, future transitions depend solely on the current health state, potentially overlooking the influence of prior patient history or the sequence of events, which can be a simplification of complex disease pathways. The model also relies on discrete time cycles and assumes homogeneity within health states and constant transition probabilities over time, which may not fully capture the real-world disease progression or treatment effects. Secondly, the reliance on literature-derived data introduces uncertainties related to the generalizability of findings from diverse study populations and settings to the specific context of this evaluation. Parameters sourced from multiple studies may carry inherent heterogeneity, and the data may not always perfectly reflect current clinical practice or the specific characteristics of the drug under assessment. For instance, efficacy for third and fourth-line treatments was based on a conservative carry-forward of second-line efficacy (derived from bio-experienced patients) due to the unavailability of specific data. While we acknowledge this as a limitation, this approach was considered more robust than estimating efficacy from scarce or non-existent data. Additionally, the number of analyzed sequences is limited and even though they were designed and validated to represent most of the clinical practice in Spain, there might be other relevant sequences that are not considered in this model. Finally, while clinical expert validation enhances the model's face validity and relevance, it does not entirely mitigate the aforementioned limitations and can introduce subjective biases, particularly where empirical data are scarce or ambiguous. Therefore, the model's outcomes should be interpreted with consideration of these structural and data-related constraints. Additionally to these clinical and methodological limitations, the existence of a dual pricing system for pharmaceutical products at the national level (meaning that there is an official list price for private purchases and a negotiated confidential reimbursement price) could interfere in the conclusions, as final costs per sequence could suffer modifications in the real setting due to these discounts that we could not account for.

## 5 Conclusion

This study suggests that, from the perspective of the Spanish NHS, positioning bsUST as a first line of therapy for moderate-to-severe CD patients may lead to a cost-effective sequence of treatments, providing an efficient alternative that can potentially facilitate access to these therapies driven by its lower drug acquisition costs, thus contributing to healthcare resource optimization.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s41669-026-00642-1.

**Funding** This work was funded by Fresenius Kabi España, S.A.U. The funder was involved in the review and validation of the final results and manuscript. IRL is supported by a research grant from Gobierno Vasco-Eusko Jaurlaritza [Grant No 2020111061 and 2023222006].

## Declarations

**Authors' Contributions** Study concept and design: JIPF, MG, MC, CC. Statistical analysis: FI, CC. Data interpretation: MC, FI, CC. Drafting of the manuscript: MC, FI. Critical revision of the manuscript for important intellectual content: IRL, JIPF, MG, CC, MBA. Study supervision: JIPF, MG, CC.

**Data Availability** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Conflict of Interest** IRL has received financial support for traveling and educational activities from or has served as an advisory board member for Abbvie, Adacyte, Alfasigma, Biogen, Chiesi, Faes Farma, Ferring, Fresenius Kabi, Galapagos, Johnson & Johnson, Eli Lilly, Mirum Pharmaceuticals, Merck, Pfizer, Roche, Takeda, and Tillotts Pharma. Research support from AbbVie. MBA has been speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Alphasigma, Lilly, Pfizer, Sandoz, Biocon, Abivax, Fresenius, Faes Farma, Ferring, Tillots, Chiesi, Adacyte, Diasorin, Oncostellae and SunRock. JIPF and MG are employees of Fresenius Kabi España. MC, FI, and CC are employees of Axentiva Solutions S.L., a consultancy firm that works for several pharmaceutical and medical devices companies.

**Ethics Approval** Not applicable.

**Code Availability** The model code is proprietary and subject to intellectual property restrictions; therefore, it is not available for public distribution. Access was provided to the editors and reviewers solely for the peer-review process.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

## References


1. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, et al. Crohn's disease. Nat Rev Dis Primers. 2020;6(1):1–19. https://doi.org/10.1038/s41572-020-0156-2.
2. Tsai L, Ma C, Dulai PS, Prokop LJ, Eisenstein S, Ramamoorthy SL, et al. Contemporary risk of surgery in patients with ulcerative colitis and Crohn's disease: a meta-analysis of population-based cohorts. Clin Gastroenterol Hepatol Internet. 2020;19:2031. https://doi.org/10.1016/J.CGH.2020.10.039.
3. 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 [Internet]. 2023;40:1975–2014. https://doi.org/10.1007/S12325-023-02473-6/TABLES/7.
4. Degli Esposti L, Daperno M, Dovizio M, Franchi A, Sangiorgi D, Savarino EV, et al. A retrospective analysis of treatment patterns, drug discontinuation and healthcare costs in Crohn's disease patients treated with biologics. Dig Liver Dis. 2023;55:1214–20. https://doi.org/10.1016/J.DLD.2023.04.010.
5. Everhov ÅH, Söderling J, Befrits G, Khalili H, Bröms G, Neovius M, et al. Increasing healthcare costs in inflammatory bowel disease 2007–2020 in Sweden. Aliment Pharmacol Ther. 2023;58:692–703. https://doi.org/10.1111/APT.17675.
6. Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn's Disease Activity Index: National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70:439–44. https://doi.org/10.1016/S0016-5085(76)80163-1.
7. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis. 2020;14(1):4–22. https://doi.org/10.1093/ECCO-JCC/JJZ180.
8. Gordon H, Minozzi S, Kopylov U, Verstockt B, Chaparro M, Buskens C, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis. 2024;18:1531–55. https://doi.org/10.1093/ECCO-JCC/JJAE091.
9. Bouhnik Y, Atreya R, Casey D, Górecki M, Baik D, Yoon SW, et al. Cost-effectiveness analysis of subcutaneous infliximab for inflammatory bowel diseases in sequential biologic treatment. Inflamm Bowel Dis. 2023;29:898–913. https://doi.org/10.1093/IBD/IZAC160.
10. Best W, Becktel J, Singleton J, Kern JF. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70:439–44.
11. 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 [Internet]. 2021;10:2885. https://doi.org/10.3390/JCM10132885/S1.
12. García MJ, Brenes Y, Vicuña M, Bermejo F, Sierra-Ausín M, Polo Cuadro C, et al. P569 persistence and safety of upadacitinib in Crohn's disease and ulcerative colitis in real life: results from a Spanish nationwide study. J Crohns Colitis. 2024;18:i1112–3. https://doi.org/10.1093/ECCO-JCC/JJAD212.0699.
13. Fumery M, Caron B, Hébuterne X, Altwegg R, Roblin X, Stefanescu C, et al. Long-term outcome of risankizumab in Crohn's disease: a real-world GETAID study. Clin Gastroenterol Hepatol. 2024. https://doi.org/10.1016/J.CGH.2024.04.016.
14. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med [Internet]. 2016;375:1946–60. https://doi.org/10.1056/NEJMOA1602773/SUPPL_FILE/NEJMOA1602773_DISCLOSURES.PDF.
15. Iborra M, Beltrán B, Fernández-Clotet A, Iglesias-Flores E, Navarro P, Rivero M, et al. Real-world long-term effectiveness of ustekinumab in Crohn's disease: results from the ENEIDA registry. Aliment Pharmacol Ther. 2020;52(6):1017–30. https://doi.org/10.1111/APT.15958.
16. Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut. 2023;72(2):264–74. https://doi.org/10.1136/GUTJNL-2022-328052.
17. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52–65. https://doi.org/10.1053/J.GASTRO.2006.11.041.
18. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359:1541–9. https://doi.org/10.1016/S0140-6736(02)08512-4.
19. Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet. 2022;399:2031–46. https://doi.org/10.1016/S0140-6736(22)00466-4.
20. Loftus EV, Panés J, Lacerda AP, Peyrin-Biroulet L, D'Haens G, Panaccione R, et al. Upadacitinib induction and maintenance therapy for Crohn's disease. N Engl J Med. 2023;388:1966–80. https://doi.org/10.1056/NEJMOA2212728/SUPPL_FILE/NEJMOA2212728_DATA-SHARING.PDF.
21. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel J-F, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711–21. https://doi.org/10.1056/NEJMOA1215739.
22. Follin-Arbelet B, Cvancarova Småstuen M, Hovde Ø, Jelsness-Jørgensen LP, Moum B. Mortality in patients with inflammatory bowel disease: results from 30 years of follow-up in a Norwegian inception cohort (the IBSEN study). J Crohns Colitis. 2022;17:497. https://doi.org/10.1093/ECCO-JCC/JJAC156.
23. Tablas de mortalidad. Resultados nacionales, por comunidades autónomas y provincias. [Internet]. Madrid; 2024. https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736177004&menu=resultados&idp=1254735573002. Accessed 14 Jan 2026
24. Instituto Nacional de Estadística. Cálculo de variaciones del Índice de Precios de Consumo (IPC) [Internet]. 2024 [cited 2024 Feb 2]. https://www.ine.es/calcula/. Accessed 2 Feb 2024
25. European Medicines Agency. Skyrizi (risankizumab): EPAR-Product Information. Annex I: summary of product characteristics [Internet]. Amsterdam; 2024. https://www.ema.europa.eu/en/documents/product-information/skyrizi-epar-product-information_es.pdf. Accessed 7 Jan 2025
26. European Medicines Agency. Stelara (ustekinumab): EPAR-Product Information. Annex I: summary of product characteristics [Internet]. Amsterdam; 2024. https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_es.pdf. Accessed 7 Jan 2025
27. European Medicines Agency. Rinvoq (upadacitinib): EPAR-Product Information. Annex I: summary of product characteristics

[Internet]. Amsterdam; 2024. https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_es.pdf. Accessed 7 Jan 2025
28. European Medicines Agency. Entyvio (vedolizumab): EPAR-Product Information. Annex I: summary of product characteristics [Internet]. Amsterdam; 2018. https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_es.pdf. Accessed 7 Jan 2025.
29. European Medicines Agency. Remicade (infliximab): EPAR-Product Information. Annex I: summary of product characteristics [Internet]. Amsterdam; 2024. https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_es.pdf. Accessed 7 Jan 2025.
30. European Medicines Agency. Humira (adalimumab): EPAR-Product Information. Annex I: summary of product characteristics [Internet]. Amsterdam; 2024. https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_es.pdf. Accessed 7 Jan 2025.
31. Consejo General de Colegios Oficiales de Farmacéuticos. Bot PLUS Web (Base de datos de medicamentos) [Internet]. 2024 [cited 2024 Oct 7]. https://botplusweb.portalfarma.com/. Accessed 7 Oct 2024.
32. Valcárcel-Nazco C, Rodriguez-Díaz B, Guirado-Fuentes C, García-Pérez L, stupiñan-Romero F. CONCEPT-COSTS. Compendium of Healthcare Costs in Spain (CONCEPT-COSTS Database) [Internet]. 2024 [cited 2024 Nov 8]. https://zenodo.org/records/11387757. Accessed 8 Nov 2024.
33. Ministerio de Sanidad. Registro de Actividad de Atención Especializada (RAE-CMBD) [Internet]. Portal Estadístico del SNS. 2024 [cited 2024 Nov 5]. https://www.sanidad.gob.es/estadEstudios/estadisticas/cmbd.htm. Accessed 5 Nov 2024.
34. Vallejo-Torres L. Estimating the incremental cost per QALY produced by the Spanish NHS: a fixed-effect econometric approach. Pharmacoeconomics. 2025;43(1):109–22. https://doi.org/10.1007/S40273-024-01441-4.
35. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. Value Health. 2022;25:3–9. https://doi.org/10.1016/J.JVAL.2021.11.1351.
36. Perera S, Yang S, Stott-Miller M, Brady J. Analysis of healthcare resource utilization and costs after the initiation of biologic treatment in patients with ulcerative colitis and Crohn's disease. J Health Econ Outcomes Res. 2018;6(1):96–112. https://doi.org/10.36469/9791.
37. Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 2017;45(1):3–13. https://doi.org/10.1111/APT.13847.
38. Noor NM, Lee JC, Bond S, Dowling F, Brezina B, Patel KV, et al. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. Lancet Gastroenterol Hepatol. 2024;9(5):415–27. https://doi.org/10.1016/S2468-1253(24)00034-7.
39. Scott FI, Hans AK, Gerich ME, Fennimore B, Mamtani R, Vajravelu RK, et al. Identification of the most effective position for ustekinumab in treatment algorithms for Crohn's disease. Clin Gastroenterol Hepatol. 2021;19:2082-2092.e10. https://doi.org/10.1016/j.cgh.2020.08.021.
40. Martínez-Sesmero JM, Crespo-Diz C, Cerezales M, Crespo C, Guigini MA, Schoenenberger-Arnaiz JA. Cost-effectiveness analysis of adalimumab in patients with immune-mediated inflammatory diseases in Spain. OFIL ILAPHAR [Internet]. 2023; First online. https://www.ilaphar.org/cost-effectiveness-analysis-of-adalimumab-in-patients-with-immunemediated-inflammatory-diseases-in-spain/.
41. Kim H, Alten R, Avedano L, Dignass A, Gomollón F, Greveson K, et al. The future of biosimilars: maximizing benefits across immune-mediated inflammatory diseases. Drugs. 2020;80:99–113. https://doi.org/10.1007/s40265-020-01256-5.

## Authors and Affiliations

**Iago Rodríguez-Lago[1,2,3] · José Ignacio Peinado-Fabregat[4] · Marcelo Guigini[4] · Mónica Cerezales[5] · Francisco Ibáñez[6] · Carlos Crespo[6,9] · Manuel Barreiro-de Acosta[7,8]**

✉ Francisco Ibáñez
fibanez@axentiva.com

1 Gastroenterology Department, Hospital Universitario de Galdakao, Galdakao, Spain

2 Biobizkaia Health Research Institute, Barakaldo, Spain

3 Faculty of Health Sciences, Deusto University, Bilbao, Spain

4 Fresenius Kabi España, S.A.U., Barcelona, Spain

5 Axentiva Solutions S.L., Oviedo, Spain

6 Axentiva Solutions S.L., C/ Muntaner 200, 4º 5º, 08036 Barcelona, Spain

7 Gastroenterology Department, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain

8 Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), A Coruña, Spain

9 Department of G.M. Statistics, University of Barcelona, Barcelona, Spain