Annals of Gastroenterology (2025) **38,** 661-666

Darvadstrocel: real-world clinical outcomes and economic impact in the Spanish national health system

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Abstract

Background Complex perianal fistulas in Crohn's disease (CD) represent a therapeutic challenge. Darvadstrocel has demonstrated efficacy in clinical trials, but evidence from real-life clinical practice is limited. This study evaluated the effectiveness and safety of darvadstrocel in real-life clinical practice, and assessed the economic impact associated with the outcome-based payment model (OBPM) linked to its funding within the Spanish National Health System.

Methods An observational, descriptive, retrospective study was conducted on patients treated with darvadstrocel in the Servizo Galego de Saúde (SERGAS) between December 2019 and December 2024. Data were collected from the Therapeutic Value of Medicines Information System (VALTERMED), including demographic, clinical, safety and effectiveness variables at 6 and 12 months post-treatment. Descriptive statistics and Fisher's exact test were used for subgroup analyses.

Results A total of 26 patients were included (50.0% female; median age: 38.4 years). Combined remission was achieved in 69.2% (n=18) at 6 months and 57.7% (n=15) at 12 months. No significant differences were observed among subgroups. No treatment-related adverse events were reported. Regarding sustainability, the OBPM resulted in SERGAS covering 81.5% of the total treatment costs, as the second payment installment was not made for non-responders.

Conclusions Darvadstrocel demonstrated high effectiveness and safety in real-world clinical practice for patients with CD and complex perianal fistulas, with remission rates consistent with previous studies. The implementation of the OBPM linked to health outcomes proved to be a valuable tool for funding innovative therapies.

Keywords Darvadstrocel, mesenchymal stem cells, Crohn's disease, remission induction, safety

Ann Gastroenterol 2025; 38 (6): 661-666

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Conflict of Interest: None

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Received 5 May 2025; accepted 5 August 2025;
published online 26 September 2025

DOI: https://doi.org/10.20524/aog.2025.1007

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disorder characterized by transmural inflammation of the gastrointestinal tract. One of its most severe and disabling complications is the development of perianal fistulas, which affect approximately 15-50% of patients, particularly those with colonic and rectal involvement [1-3].

Perianal fistulas are classified as either simple or complex. Complex fistulas, which represent the majority of cases, are typically high or transsphincteric, with multiple external openings, abscesses, anal stenosis, or communication with adjacent organs [1,4,5]. These fistulas, especially the complex forms, have a substantial impact on patients' quality of life, due to pain, purulent discharge and recurrent infections. They are also associated with high hospitalization rates and frequent surgical interventions [6,7]. Management requires a multidisciplinary approach that combines pharmacological

and surgical therapies, along with magnetic resonance imaging (MRI) monitoring [1,5].

Until recently, the standard treatment included immunosuppressive agents and biologics such as tumor necrosis factor (TNF)-α inhibitors. However, these therapeutic approaches are associated with notable limitations, particularly the challenge of attaining sustained long-term response rates and the high risk of recurrence after treatment discontinuation [5,6]. In this context, darvadstrocel—an orphan drug consisting of allogeneic adipose-derived mesenchymal stem cells—was introduced as the first advanced therapy offering an innovative option for the treatment of complex perianal fistulas refractory to conventional therapy [1].

Darvadstrocel is administered as a single dose of 120 million cells, distributed across 4 vials. Intralesional administration is carried out in the operating room under anesthesia, following a preparatory phase of fistula conditioning that includes curettage and closure of the external fistulous openings [1,8]. The mechanism of action of darvadstrocel involves immunomodulatory and anti-inflammatory properties, reducing infiltration of activated lymphocytes and promoting tissue healing. The efficacy of darvadstrocel in patients with CD and complex perianal fistulas was evaluated in the ADMIRE-CD trial, which showed that 53% of treated patients achieved combined remission at 24 weeks, a modest but significantly higher proportion than the 36% observed in the placebo group (P=0.024) [3]. Moreover, the safety profile was favorable, with lower rates of complications such as abscesses [1,3]. Based on these results, darvadstrocel was approved by the European Medicines Agency in 2018, with the requirement to conduct additional post-authorization studies to gather more data on its efficacy and safety [9].

Advanced therapy medicinal products are innovative medications with a high clinical and economic impact. On the one hand, the complexity of clinical management and the need for tight coordination in their preparation and administration are highlighted in the risk management plan, which identifies inadequate conditioning of the fistulous tract as a potential medication error that may affect product viability. Therefore, as stipulated in the product information, administration must be carried out exclusively by specialists with experience in diagnosing and treating complex fistulas, who must perform a detailed clinical evaluation supported by MRI and strictly follow the preparation and administration protocol [1,8].

On the other hand, given the high economic impact of this therapy and the uncertainty regarding its effectiveness in real-world clinical practice, in September 2019 the Interministerial Pricing Committee for Medicines—responsible for pricing decisions on drugs funded by the Spanish National Health System (SNS)—established the maximum industrial price, along with specific reimbursement conditions for darvadstrocel, including an outcome-based payment model (OBPM) [10]. This agreement involves a 2-instalment payment: the initial payment is made upon administration of the drug, while the second is conditional upon patients achieving combined remission at 6 months.

To ensure standardized treatment assessment across the national territory, the General Directorate for the Basic Services Portfolio of the SNS issued in December 2019 a binding pharmacoclinical protocol titled *"Pharmacoclinical Protocol for the Use of Darvadstrocel in the Treatment of Complex Perianal Fistulas in Crohn's Disease in the National Health System."* This protocol defines initiation and follow-up criteria, as well as the variables necessary for evaluating clinical outcomes [11]. All parameters must be recorded individually for each patient using the VALTERMED platform (Therapeutic Value of Medicines Information System), a centralized information system developed by the Spanish Ministry of Health to determine the real-world therapeutic value of medicines [12]. The funding resolution for darvadstrocel established that compliance with the OBPM conditions would be verified by a monitoring committee in each autonomous community, composed of health administration representatives and the Marketing Authorization Holder (MAH).

In January 2025, the MAH voluntarily withdrew darvadstrocel's marketing authorization after the phase III ADMIRE-CD-II trial—larger than the pivotal ADMIRE-CD trial—failed to demonstrate a statistically significant superiority in combined remission at 24 weeks compared to placebo [13,14]. The aim of this study was to evaluate the effectiveness and safety of darvadstrocel in real-world clinical practice among Galician patients with CD and complex perianal fistulas at 6 and 12 months, based on data collected in VALTERMED, and to assess the economic impact associated with the OBPM.

Patients and methods

Study setting and population

An observational, descriptive, and retrospective study was conducted in the autonomous community of Galicia with the aim of assessing the real-world clinical effectiveness and safety of darvadstrocel for the treatment of complex perianal fistulas associated with CD. The study included data from patients treated with darvadstrocel within the Galician Health Service (Servizo Galego de Saúde - SERGAS) between December 2019 and December 2024, and who were registered in the VALTERMED platform since the implementation of the pharmacoclinical protocol.

Patients were excluded from the analysis if they had not completed a 6-month follow-up period after darvadstrocel administration by February 2025, as they were not considered evaluable.

Data collection and outcome evaluation

The registration of patients treated with darvadstrocel in VALTERMED, together with the variables defined in the *Pharmacoclinical Protocol for the Use of Darvadstrocel in the Treatment of Complex Perianal Fistulas in Crohn's Disease in the SNS* [11], is carried out by the prescribing physicians and/or hospital pharmacists responsible for patient care. VALTERMED is designed so that only these designated users—those with "Physician" or "Hospital Pharmacy Manager" roles—can access the identifiable patient data within their own institution.

Users with the "Autonomous Community Manager" profile may analyze anonymized data from their region in order to verify adherence to the relevant pharmacoclinical protocol.

As this study is based on anonymized data and does not involve any patient intervention, approval from a Research Ethics Committee was not required.

The collected data included the following: (a) demographic data: age, sex, reference hospital; (b) clinical criteria for darvadstrocel use: presence and characteristics of complex fistulas, number of internal and external openings; (c) disease characteristics at diagnosis: date of CD diagnosis, Crohn's Disease Activity Index, prior pharmacologic treatments and previous surgeries for fistulas; and (d) clinical outcomes at 6 and 12 months, and any treatment-related adverse events.

The clinical outcomes at 6 months after administration of darvadstrocel were evaluated by classifying patients into 2 categories: responders and non-responders, according to the definitions established in the pharmacoclinical protocol [11]. A responder was defined as a patient who achieved combined remission, characterized by the clinical closure of all external draining fistulas and the absence of abscesses larger than 2 cm, confirmed by MRI. Patients not meeting both criteria were classified as non-responders. The same definitions were used to assess clinical outcomes at 12 months.

A subgroup analysis was conducted to evaluate treatment response at 6 months, based on categories including sex, time from CD diagnosis to darvadstrocel administration, and history of prior surgeries.

Economic impact was assessed through a review of the official records of the Monitoring Committee meetings, which specified whether the second installment payment was applicable, based on patients' achievement of combined remission at 6 months. This review enabled the quantification of the amount disbursed by SERGAS per treatment, distinguishing between responder and non-responder patients.

Statistical analysis

Data were analyzed using descriptive statistics. Quantitative variables were expressed as median and interquartile range (IQR), while qualitative variables were presented as absolute and relative frequencies. The proportion of responder patients at 6 and 12 months was reported as a percentage, along with the 95% confidence interval (CI) for proportions. For subgroup comparisons, Fisher's exact test was used. A P-value <0.05 was considered statistically significant. All analyses were performed using R statistical software (version 4.4.2).

Results

Patient characteristics

A total of 26 patients were included in the study, all of whom were treated at 3 hospitals within the autonomous community of Galicia, although they were referred from 5 different healthcare centers. These patients had a median age of 38.4 years (IQR 30.1-45.7) and 50.0% (n=13) were women (Table 1).

A total of 96.1% (n=25) had received at least 1 anti-TNF-α treatment, and 44.0% of these patients (n=11) had received 2 anti-TNF-α agents (adalimumab and infliximab).

Effectiveness, safety, and outcome-based payment results

At month 6, 69.2% (n=18; 95%CI 51.5-87.0) of patients treated with darvadstrocel achieved combined remission and were considered responders. The combined remission rate at month 12 was 57.7% in the overall study population (n=15; 95%CI 38.7-76.7). Follow-up data at 12 months were not available for 9 patients: for 6 of them, no data were recorded, and 3 had not yet reached that time point. These results are depicted in Fig. 1, which graphically displays the proportion of patients in remission at both time points, and allows for visualization of the evolution of treatment response over time.

Of those who had responded by month 6, 66.6% (n=12) maintained remission, while 37.5% (n=3) of the initial non-responders achieved remission by month 12. Fig. 2 illustrates patient status at both time points, including maintained remission, loss of response, and cases with incomplete follow up. No treatment-related adverse events were recorded in the VALTERMED platform.

Thirteen follow-up meetings were held with the MAH to analyze the clinical outcomes of the patients included in this study. In 8 patients (33.3%), the therapeutic objective set in the reimbursement agreement was not achieved by month 6; therefore, the second installment was not paid by SERGAS. Consequently, the OBPM allowed the cost to be covered at 81.5% by SERGAS for the total cost of the treatments administered, with the second installment being paid only for responder patients. Based on this outcome, and using the notified ex-factory price as published in the Spanish Ministry of Health's official pricing database, the estimated average cost per treated patient was approximately €48,900.

Subgroup analysis

In the subgroup analysis, no statistically significant differences were observed (P<0.05) among the groups analyzed (Table 2).

Discussion

The results of this study suggest that darvadstrocel may be effective in the treatment of patients with complex perianal fistulas associated with CD in real-world clinical practice, with a combined remission rate of 69.2% at 6 months. This proportion is higher than that reported in the pivotal ADMIRE-CD trial [3] and in other subsequent clinical trials, where rates ranged between 41.0% and 59.1% [14,15]. Nevertheless, in view of the

Table 1 Demographic characteristics of the study population

Variable	Study population
Age in years, median (IQR) (n=26)	38.4 (30.1-45.7)
Sex (n=26)	
Male, n (%)	13 (50.0)
Female, n (%)	13 (50.0)
Crohn's Disease Activity Index at diagnosis (n=26)	
<150, n (%)	23 (88.5)
150-220, n (%)	3 (11.5)
Fistula characteristics (n=26)	
Transsphincteric, n (%)	17 (65.4)
High intersphincteric, n (%)	7 (26.9)
Not recorded, n (%)	2 (7.7)
Time since diagnosis in years, median (IQR) (n=26)	14.4 (7.5-21.4)
<14.4 years, n (%)	12 (46.2)
≥14.4 years, n (%)	14 (53.8)
Number of internal openings (n=26)	
One opening, n (%)	21 (80.8)
Two openings, n (%)	5 (19.2)
Number of external openings (n=26)	
One opening, n (%)	16 (61.5)
Two openings, n (%)	10 (48.5)
Previous surgeries (n=26)	
Yes, n (%)	6 (23.1)
No, n (%)	16 (61.5)
Not recorded, n (%)	4 (15.4)
Number of treatment lines received (n=26)	
One line, n (%)	2 (7.7)
Two lines, n (%)	12 (46.2)
Three lines, n (%)	7 (26.9)
More than 3 lines, n (%)	4 (15.4)
Not recorded, n (%)	1 (3.8)
Treatments received (n=26)	
Infliximab, n (%)	22 (84.6)
Thiopurines, n (%)	20 (76.9)
Adalimumab, n (%)	14 (53.8)
Ustekinumab, n (%)	6 (23.1)
Methotrexate, n (%)	2 (7.7)
Vedolizumab, n (%)	2 (7.7)
Tacrolimus, n (%)	1 (3.8)
Mycophenolate mofetil, n (%)	1 (3.8)

IQR, interquartile range

Table 2 Subgroup response analysis at month 6

Subgroups	Combined remission	P-value
Sex (n=26)		
Male, n (%)	10 (76.9)	0.428
Female, n (%)	8 (61.5)	
Previous surgeries (n=22)*		
Yes, n (%)	3 (50.0)	0.611
No, n (%)	11 (68.8)	
Time since diagnosis (n=26)		
≥14.4 years, n (%)	7 (58.3)	0.401
>14.4 years, n (%)	11 (78.6)	

* Three patients were excluded because of a lack of data

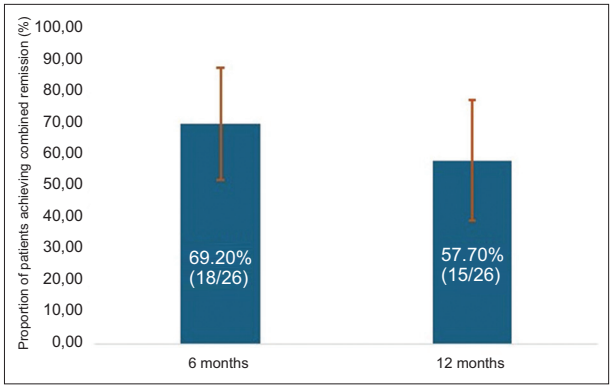

Figure 1 Proportion of patients achieving combined remission at months 6 and 12

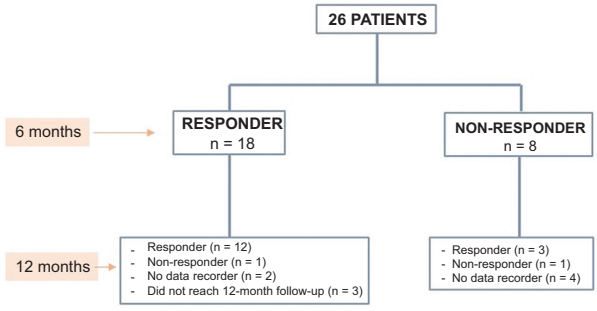

Figure 2 Combined remission diagram at 6 and 12 months

observational design of this study and the differences in patient populations, these results should be interpreted with caution.

Similarly, the findings of this study are slightly superior to those reported in other European observational studies conducted in real-world clinical settings, in which the combined remission rate at 24 weeks ranged between 41.6% and 63.1% [16,17]. Moderately higher remission rates have also been published (61.0-72.2%); however, these evaluations were based solely on clinical remission, without considering radiological remission, which may explain the observed differences [18,19]. Furthermore, in Spain, an analysis based on data recorded in the VALTERMED platform was published in 2022, documenting a combined remission rate at 6 months of 67% (n=32), a figure nearly identical to that observed in this study [20].

In the present study, the combined remission rate at month 12 was relatively high (57.7%, n=15) compared with other real-world clinical practice studies, in which this figure did not exceed 50% [16,21]. This value lies within the mid-range of clinical trials, where reported rates vary widely, ranging from 41.0-68.2% [14,15]. Additionally, the percentage of patients who experienced relapse at 12 months after achieving complete remission at month 6 (5.5%) was slightly lower than values described in the literature, which range from 13.3-15.4% [15,16]. On the other hand, it is important to note that data for 9 patients were unavailable at the time of analysis.

Although no predictors of response were identified, patient selection is a critical factor in achieving clinical outcomes [16,18]. In this study, all patients met the

clinical criteria for darvadstrocel use, as outlined in the *Pharmacoclinical Protocol for the Use of Darvadstrocel in the Treatment of Complex Perianal Fistulas in Crohn's Disease in the SNS* [11], which may have contributed to the high combined remission rate observed at 6 months post-administration.

The subgroup analysis at month 6 is consistent with findings reported in the literature [15,17], where no significant differences were observed in combined remission based on sex, the number of internal and external fistula openings during this period, time since CD diagnosis, or the number of prior surgeries. However, although no subgroup analysis was conducted at 12 months in this study, published evidence has identified significant differences according to disease duration. Specifically, patients with ≤9.7 years since diagnosis achieved a combined remission rate of 90.9%, while only 9.1% of patients with >9.7 years reached the same outcome [15]. However, the small sample size limits the statistical power of the subgroup analysis, and the possibility of undetected associations cannot be excluded.

From an economic perspective, OBPMs are reimbursement mechanisms that facilitate the introduction of innovative medicines that have sufficient scientific evidence and/or significant economic impact, by reducing uncertainty about their effectiveness through payments conditional on health outcomes [10]. In the case of darvadstrocel, SERGAS ultimately covered 81.5% of the total treatment cost under the applied OBPM. This model not only mitigates the uncertainty associated with the high cost of advanced therapies, but also optimizes the use of healthcare resources. Along these lines, the Andalusian Health Service has produced a detailed report on darvadstrocel, including a cost-effectiveness analysis based on evidence from both the SNS and other international health systems, such as the UK's National Health Service [22]. These evaluations suggest that, although the initial cost of these therapies may be high, their clinical benefits and the reduction in long-term complications may justify the investment. In our study, the real-world application of the OBPM resulted in an average cost per treated patient of approximately €48,900, calculated using the notified ex-factory price. While not directly comparable, this figure complements prior economic models and provides an objective benchmark aligned with actual reimbursement outcomes [22].

In our study, no adverse events related to darvadstrocel were reported, which aligns with existing data in the literature. Several studies have highlighted the favorable safety profile of this treatment, with a low incidence of serious adverse events [3,15,16]. According to national reports, 2 adverse reactions have been recorded in the FEDRA (Spanish Pharmacovigilance System for Adverse Reactions) database: one related to infection and another to general disorders or injection site reactions [23].

This study had several limitations. The most notable is the small sample size, which may constrain the external validity of the findings and limit their applicability to broader or more heterogeneous populations. Additionally, the retrospective design may have introduced selection and information biases, as it does not allow for prospective control over follow-up or data quality. Data availability beyond the 6-month mark was also limited, since the outcome-based payment model did not mandate further clinical assessments. Of the 26 patients registered in VALTERMED, 9 had no recorded follow-up data at 12 months (3 of them had not yet reached that milestone), and thus their subsequent clinical status is unknown. This absence of systematic follow-up beyond the first year represents an additional limitation, as it precludes evaluation of the long-term durability of clinical remission—an essential consideration in chronic diseases such as CD. Additionally, a multivariate analysis could not be performed because of the small sample size, which limited the ability to adjust for potential confounding factors and to identify independent predictors of treatment response.

In conclusion, despite its withdrawal from the market after failing to demonstrate superiority in combined remission at 24 weeks versus placebo in the ADMIRE-CD-II study [14], the use of darvadstrocel in real-world clinical practice among patients treated within the SERGAS proved to be an effective option for the treatment of complex perianal fistulas in CD patients. These findings highlight the importance of implementing OBPMs as an efficient reimbursement mechanism to enable access to advanced therapies, optimize resource allocation, and contribute to the economic sustainability of the healthcare system.

Summary Box

What is already known:

- Complex perianal fistulas in Crohn's disease are a difficult-to-treat complication with limited therapeutic options
- Darvadstrocel had demonstrated efficacy and safety in controlled clinical trials, leading to its approval for clinical use
- Real-world data on the use of darvadstrocel are limited, and evidence regarding its long-term effectiveness and economic implications in clinical practice is scarce
- Outcome-based payment models are increasingly being explored for high-cost therapies, but are rarely implemented or evaluated in inflammatory bowel disease

What the new findings are:

- Darvadstrocel showed consistent clinical effectiveness and safety in routine practice, confirming its utility outside trial settings
- No treatment-related adverse events were observed, reinforcing its favorable safety profile
- The use of an outcome-based payment model proved feasible in a real-world setting, reducing costs by linking reimbursement to therapeutic response.
- The model demonstrated potential as a sustainable financing strategy for advanced therapies in inflammatory bowel disease

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