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INVITED EDITORIAL

# Editorial: Mesenchymal Stem Cell Therapy for Perianal Fistulising Crohn's Disease—Effective or Hype? Authors' Reply

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We appreciate the thoughtful comments by Drs. McCurdy and Wong regarding our study on the effectiveness and safety of mesenchymal stem cell treatment for fistulising Crohn's disease. We analysed 223 patients in an international, multicentre setting, who underwent darvadstrocel treatment [1, 2]. They clearly highlighted the unmet need for new therapeutic approaches for perianal fistulising Crohn's disease (PFCD) in their editorial. We agree that discrepancies between the effectiveness results of large clinical trials and observational studies need to be carefully reconsidered to support position statements on the use of mesenchymal stem cell treatment in PFCD.

First, in our real-world study, preparation—including curettage and seton placement—preceded the administration of darvadstrocel in all cases, in accordance with the protocols followed in pivotal clinical trials. Controlled, high-quality perianal surgery can achieve a high success rate, even in refractory cases, if performed in a highly experienced centre [3]. Due to the structural design of our real-world study, it is not possible to determine the exact contribution of darvadstrocel to the improvements observed in our patients, relative to the surgical intervention. However, the 62% closure rate is clearly higher than the closure rate seen in the placebo arm of the ADMIRE studies.

Second, we acknowledge that increased effectiveness rates are often observed in real-world settings compared with randomised trials, particularly in the field of pharmacological sciences. This discrepancy is probably due to differences in population characteristics, inclusion criteria, study design, data collection methods and statistical considerations (such as the handling of confounders). We reported clinical remission rates of 72.2% at Week 26 and 62.3% at Week 52, which align with the cumulative effectiveness of 68.1%–77.2% in a systematic review of observational trials with darvadstrocel, with negligible between-study heterogeneity [4]. It is also worth noting that combined remission (defined as the MRI endpoint of absence of collections > 2 cm) was observed in 60.6% of patients at Week 26 and 52.3% at Week 52.

Third, while evaluating combined remission can provide a robust end point, it has limitations. MRI assessment of PFCD requires expert interpretation, and the precise definitions of fistula healing remain inconclusive [5]. Furthermore, regular monitoring of fistula healing with MRI is not yet part of standard clinical practice, as evidenced by our real-world results. From a patients' perspective, the cessation of fistula drainage and the resolution of symptoms such as the feeling of uncleanliness are considered more important than MRI findings.

Furthermore, we found that approximately 80% of patients expressed satisfaction with the treatment after 1 year, highlighting its positive impact on quality of life, especially given the challenges of managing PFCD. However, this end point is inherently subjective and difficult to measure objectively.

In conclusion, while the effectiveness data remain debated, potential predictors of treatment success have been identified. Nevertheless, further research is necessary to definitively determine whether darvadstrocel treatment is truly effective or simply a treatment hype.

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### Author Contributions

**Péter Bacsur:** conceptualization, writing – original draft. **Klaudia Farkas:** conceptualization, writing – original draft. **Tamás Molnár:** conceptualization, writing – review and editing.


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### Data Availability Statement

The authors have nothing to report.

### Linked Content

This article is linked to Bacsur et al papers. To view these articles, visit https://doi.org/10.1111/apt.18359 and https://doi.org/10.1111/apt.18408.

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