Long-term effectiveness of darvadstrocel in patients with complex perianal fistulas in Crohn's disease: Results from INSPECT, a retrospective chart review study in Europe

[redacted]

Spain; France; United States; United Kingdom; Spain; Austria; the Netherlands; Canada; the Netherlands; Italy; Belgium; Italy; Israel; Austria; Canada; Switzerland; Germany;

Background/study aims

- Perianal fistulas are a complication of Crohn's disease (CD), with 23–38% of patients with CD developing one or more during their disease course[1,2]
- It has previously been demonstrated that darvadstrocel (DVS), a suspension of expanded allogeneic adipose-derived mesenchymal stem cells, is an effective and safe treatment for complex perianal fistulas in patients with CD who are unresponsive to conventional/biological treatments.[1,3] However, long-term results outside of a clinical trial setting are needed
- This study (INSPECT), aimed to collect 104 weeks of data outside the setting of a clinical trial to evaluate the longer-term effectiveness of DVS in patients who completed at least 52 weeks of the ADMIRE-CD trial; medication treatment patterns, health resources utilisation, and safety were investigated

Methods and study design

- INSPECT was a multi-centre, retrospective chart review study across seven countries in Europe (Austria, Belgium, France, Germany, Italy, the Netherlands, Spain) and Israel
- Patients were enrolled from both DVS and control arms from the ADMIRE-CD study in which they completed at least 52 weeks follow-up (Figure 1). Patients were excluded if they did not provide informed consent or if there was no information on patient care within the 104 weeks INSPECT study period (Figure 2)
- The outcomes evaluated included clinical remission, sustained remission and time to relapse (among those in remission at 52 weeks), and adverse events of special interest (AESIs; tumourigenicity and ectopic tissue formation)
- The index date was defined as treatment administration (DVS or placebo) at ADMIRE-CD initiation
- Continuous data were described by mean, standard deviation (SD), median, interquartile range and categorical variables by frequency and percentages (n, %); t-tests or Mann–Whitney tests were conducted to test for significant differences. Time-to-event data were analysed using survival analysis methods and were illustrated using Kaplan–Meier curves

Key definitions

Clinical remission: Closure of all external fistula openings that are draining at ADMIRE-CD baseline based on clinical assessment. In absence of draining status documentation, medical record documentation that the patient is in remission and/or had a complete response is used to define clinical remission

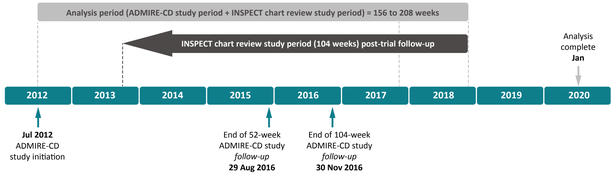
Sustained clinical remission: Patients are assumed to have sustained clinical remission if they meet the above definition at all subsequent follow-up assessments and/or did not have documentation of relapse of perianal fistula

Relapse: Reopening of any external fistula openings with active drainage – as assessed clinically; development of a perianal fluid collection >2 cm in anatomic proximity to a previously treated fistula as confirmed by magnetic resonance imaging (if conducted); development of a perianal abscess in anatomic proximity to a previously treated fistula; a new surgical intervention for a fistula; need for rescue medication documented as specifically for treatment of perianal disease; medical record documentation of fistula relapse and/or loss of remission

Need for rescue medication for perianal fistulising disease: Antibiotic treatment for more than 4 weeks, new anti-tumour necrosis factor alpha (TNFα) or other biologic treatment for at least 8 weeks, or a new immunomodulator for at least 12 weeks

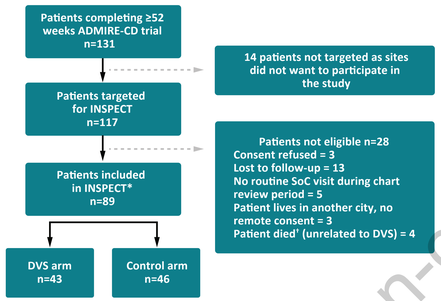
Study design

Figure 1: Study design



Results: Patient disposition

Figure 2: Patient disposition



*n=62 patients completed 52 weeks of ADMIRE-CD and n=27 patients completed 104 weeks of ADMIRE-CD; follow-up data, up to 104 weeks, was examined in both groups post trial completion; †no additional details on these patients were captured in compliance with the study protocol. SoC, standard of care.

Results: Patient demographics

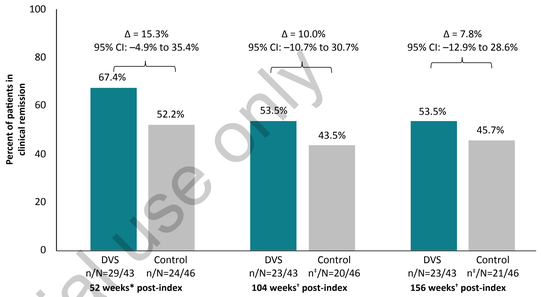
Table 1: Demographics and clinical characteristics for patients at index

Characteristics	DVS n=43	Control n=46	Unadjusted p-value
Age [years], mean (SD)	42.1 (13.7)	37.7 (13.5)	0.13
Sex [male], n (%)	24 (55.8)	25 (54.3)	1.00
Duration of CD at index [years], mean (SD)	12.7 (11.1)	11.0 (8.4)	0.42
Duration of perianal fistulising disease at index [years], mean (SD)	4.7 (5.9)	3.0 (3.6)	0.11
Number of fistula tracts, n (%)			
Single-tract fistula	20 (46.5)	29 (63.0)	0.14
Multiple-tract fistula	23 (53.5)	17 (37.0)	
Concomitant medications at index, n (%)			
Immunosuppressants only	3 (7.0)	7 (15.2)	0.57
Anti-TNF only	18 (41.9)	14 (30.4)	
Anti-TNF and immunosuppressant	15 (34.9)	17 (37.0)	
None	7 (16.3)	8 (17.4)	

Results: Clinical remission

- Numerically, more patients who received DVS versus control were in clinical remission at each time point assessed over the chart review period

Figure 3: Clinical remission in DVS and control groups at different timepoints

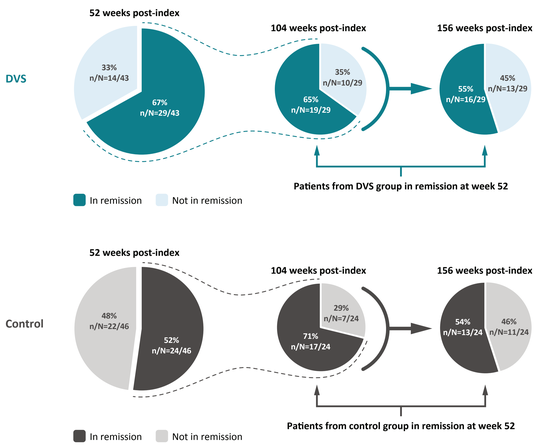


*Data from ADMIRE-CD trial; †includes data from INSPECT and ADMIRE-CD trial (for those who were in the trial for 104 weeks); ‡n in the control group varies between time points 104 and 156 weeks as the visit window for one specific patient did not fall within the 104-week time point as pre-specified in the study protocol. Index is defined as treatment administration (DVS or placebo) at ADMIRE-CD initiation. CI, confidence interval.

Results: Sustained clinical remission in remitters at week 52

- Sixty seven percent of the patients in DVS group were in clinical remission at 52 weeks
- Of those, 65% of patients were able to sustain the remission at 104 weeks and 55% at 156 weeks, demonstrating that patients who achieve clinical remission by 52 weeks are more likely to sustain the remission status for up to an additional 104 weeks

Figure 4: Sustained clinical remission



In the DVS group, 65% sustained the remission status up to 104 weeks and 55% up to 156 weeks, despite the more complex clinical characteristics at index in this group

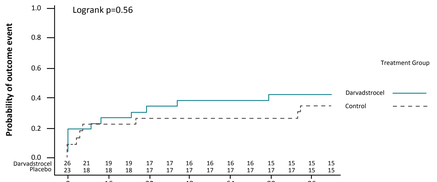
Results: Relapse and surgical requirements

- In patients who were in clinical remission at the end of ADMIRE-CD, the percentage of patients who experienced a relapse was comparable between the two groups at 156 weeks
- However, there were numerical differences between the number of patients requiring ≥1 surgical intervention (Table 2) with less patients in the DVS arm requiring intervention
- No significant differences were observed between the groups for time to first relapse* of ADMIRE-CD treated fistula at 2 years post-trial (Figure 5)

Table 2: Relapse of ADMIRE-CD treated fistula

Time point assessed post-trial	Relapse of ADMIRE-CD treated fistula		Relapsed patients requiring ≥1 surgical intervention	
	DVS, n=26	Control, n=23	DVS, n=26	Control, n=23
104 weeks	10 (38%)	6 (26%)	1/10 (10.0%)	2/6 (33.3%)
156 weeks	11 (42%)	8 (35%)	2/11 (18.2%)	3/8 (37.5%)

Figure 5: Time to first relapse of ADMIRE-CD treated fistula for patients who completed at least 52 weeks in ADMIRE-CD



*Time to first documented endpoint event is computed as the difference in weeks between the date of first documented remission and the date of the first documented incidence of the endpoint event. Censoring rules are that patients are counted as an event at first documentation of the outcome or as a right-censored value at the end of follow-up (e.g. earliest of 104 weeks post-ADMIRE-CD, death, or last contact with site).

Safety – AESIs

- One patient in each group experienced a tumourigenicity event during the chart review period; a benign event not product related (recorded as resolved) occurred in one patient in the DVS group and a malignant tumour (epidermoid carcinoma; recorded as non-resolved) occurred in one patient in the control group (DVS: n/N=1/43, control: n/N=1/46)
- There were no reports of events related to ectopic tissue formation

Strengths and limitations

- Study strengths: First study to report the long-term effectiveness and safety of DVS, which is a minimally invasive one time administration for perianal fistula in CD
- Study limitations: Inherent limitations related to chart review study design; data collected was limited to the data availability on the charts at the original trial site. Additional unknown confounders were not investigated

Conclusion

- This is the first study examining the longer-term effectiveness and safety (up to 104 weeks after the end of the trial) of DVS for the treatment of complex perianal fistula in patients with CD versus control, in a non-clinical trial setting
- One AESI within the DVS group was reported (benign tumour not product related, resolved) over 104 weeks of post-trial follow-up
- This study demonstrated that ≥55% of DVS patients were able to sustain the clinical remission up to 3 years post-DVS
- Based on the higher remission rate in the DVS group versus the control group at week 52, and as the following remission rates were kept for both groups on a comparable level, the long-term effectiveness seems to be more favourable for the treatment with DVS

References: **1.** Panés J, et al. Gastroenterology 2018;154(5):1334–42; **2.** Marco M, et al. World J Gastroenterol 2015;21(5):1394–1403; **3.** Panés J, et al. Lancet 2016;388(10051):1281–90. **Acknowledgments:** This study was sponsored and funded by Takeda Pharmaceuticals. PPD/Evidera received funding from Takeda to conduct the operations and analysis of the study. Syneos Health Communications, funded by Takeda, developed the poster. **Disclosures:** [redacted]

Date of preparation: September 2020