



# Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial

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## Summary

**Background** Complex perianal fistulas in Crohn's disease are challenging to treat. Allogeneic, expanded, adipose-derived stem cells (Cx601) are a promising new therapeutic approach. We aimed to assess the safety and efficacy of Cx601 for treatment-refractory complex perianal fistulas in patients with Crohn's disease.

**Methods** We did this randomised, double-blind, parallel-group, placebo-controlled study at 49 hospitals in seven European countries and Israel from July 6, 2012, to July 27, 2015. Adult patients ( $\geq 18$  years) with Crohn's disease and treatment-refractory, draining complex perianal fistulas were randomly assigned (1:1) using a pre-established randomisation list to a single intralesional injection of 120 million Cx601 cells or 24 mL saline solution (placebo), with stratification according to concomitant baseline treatment. Treatment was administered by an unmasked surgeon, with a masked gastroenterologist and radiologist assessing the therapeutic effect. The primary endpoint was combined remission at week 24 (ie, clinical assessment of closure of all treated external openings that were draining at baseline, and absence of collections  $>2$  cm of the treated perianal fistulas confirmed by masked central MRI). Efficacy was assessed in the intention-to-treat (ITT) and modified ITT populations; safety was assessed in the safety population. This study is registered with ClinicalTrials.gov, number NCT01541579.

**Findings** 212 patients were randomly assigned: 107 to Cx601 and 105 to placebo. A significantly greater proportion of patients treated with Cx601 versus placebo achieved combined remission in the ITT (53 of 107 [50%] vs 36 of 105 [34%]; difference 15.2%, 97.5% CI 0.2–30.3;  $p=0.024$ ) and modified ITT populations (53 of 103 [51%] vs 36 of 101 [36%]; 15.8%, 0.5–31.2;  $p=0.021$ ). 18 (17%) of 103 patients in the Cx601 group versus 30 (29%) of 103 in the placebo group experienced treatment-related adverse events, the most common of which were anal abscess (six in the Cx601 group vs nine in the placebo group) and proctalgia (five vs nine).

**Interpretation** Cx601 is an effective and safe treatment for complex perianal fistulas in patients with Crohn's disease who did not respond to conventional or biological treatments, or both.

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## Introduction

Crohn's disease is a chronic inflammatory bowel disease characterised by transmural inflammation and fistula formation.<sup>1</sup> The prevalence of Crohn's disease varies geographically, with the highest figures reported in the USA, Canada, and Europe, where prevalence rates above 300 per 100 000 people have been described.<sup>2</sup>

Perianal fistulas are a common complication of Crohn's disease and are estimated to affect up to 28% of patients in the first two decades after diagnosis,<sup>3,4</sup> particularly those with colonic disease and rectal involvement.<sup>5</sup> They severely impair patients' quality of life and cause substantial morbidity.<sup>6</sup> About 70–80% of perianal fistulas are complex,<sup>4,7</sup> and these are challenging to treat since they are particularly refractory to conventional medical treatment strategies (ie, antibiotics and immunomodulators) and anti-tumour necrosis factor (anti-TNF) treatments.<sup>8–12</sup> Furthermore, 60–70% of patients relapse after stopping treatment,<sup>13–17</sup> and only a few patients

achieve long-term remission.<sup>18</sup> So far, the only approved drug that has shown efficacy in a randomised clinical trial setting is the anti-TNF drug infliximab.<sup>8,12</sup> Failure of or intolerance to medical treatment can ultimately result in debilitating surgical approaches, such as diverting stoma or proctectomy.<sup>19</sup> Therefore, there remains an unmet need for alternative treatments for perianal fistulising Crohn's disease.

Although the exact pathogenesis of perianal fistulas is largely unknown, they are thought to arise from an epithelial defect that might be caused by ongoing inflammation.<sup>6</sup> Adipose-derived mesenchymal stem cells are a promising new approach for the treatment of such fistulas because of their anti-inflammatory and immunomodulatory potential.<sup>20–22</sup> Initial proof of concept was achieved in an open-label phase 1/2a clinical study<sup>23</sup> of allogeneic, expanded adipose-derived stem cells (Cx601) in 24 patients with Crohn's disease and complex perianal fistulas,<sup>23</sup> with 56% of patients showing complete closure

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