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Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease

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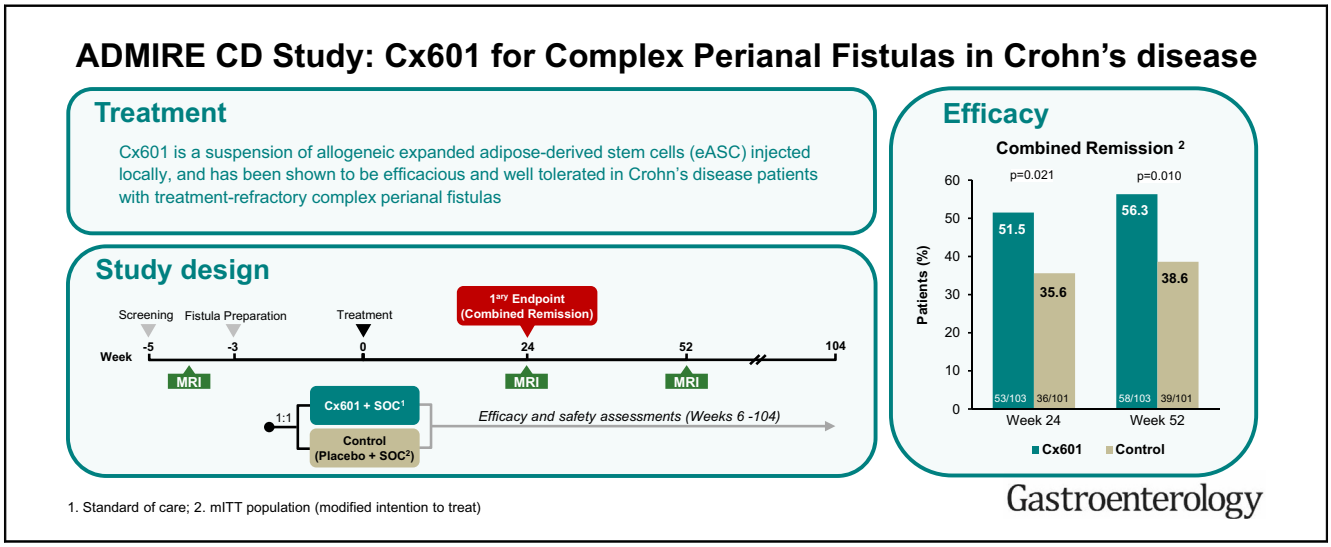

BACKGROUND & AIMS: Therapies for perianal fistulas in patients with Crohn's disease are often ineffective in producing long-term healing. We performed a randomized placebo-controlled trial to determine the long-term efficacy and safety of a single local administration of allogeneic expanded adipose-derived stem cells (Cx601) in patients with Crohn's disease and perianal fistulas. **METHODS:** We performed a double-blind study at 49 hospitals in Europe and Israel, comprising 212 patients with Crohn's disease and treatment-refractory, draining, complex perianal fistulas. Patients were randomly assigned (1:1) to groups given a single local injection of 120 million Cx601 cells or placebo (control), in addition to the standard of care. Efficacy endpoints evaluated in the modified intention-to-treat population (randomly assigned, treated, and with 1 or more post-baseline efficacy assessment) at week 52 included combined remission (closure of all treated external openings draining at baseline with absence of collections >2 cm, confirmed by magnetic resonance imaging) and clinical remission (absence of draining fistulas). **RESULTS:** The study's primary endpoint, at week 24, was previously reported (combined remission in 51.5% of patients given Cx601 vs 35.6% of controls, for a difference of 15.8 percentage points; 97.5% confidence interval [CI] 0.5–31.2; $P = .021$). At week 52, a significantly greater proportion of patients given Cx601 achieved combined remission (56.3%) vs controls (38.6%) (a difference of 17.7 percentage points; 95% CI 4.2–31.2; $P = .010$), and clinical remission (59.2% vs 41.6% of controls, for a difference of 17.6 percentage points; 95% CI 4.1–31.1;

EDITOR'S NOTES

BACKGROUND AND CONTEXT

Given the lack of durable perianal fistula healing with existing therapies, this study assessed long-term healing results obtained with allogeneic expanded adipose-derived stem cells (Cx601) in Crohn's disease patients.

NEW FINDINGS

The efficacy and safety of Cx601 vs control was maintained for up to 1 year in Crohn's disease patients with treatment-refractory complex perianal fistulas.

LIMITATIONS

35%–40% of patients in each group withdrew before the end of the study (1 year); however, nonresponse imputation after last observation carried forward confirmed the results.

IMPACT

Cx601 represents a novel and minimally invasive alternative for complex perianal fistulas, which may reduce the need for systemic immunosuppression and surgery.

$P = .013$). Safety was maintained throughout week 52; adverse events occurred in 76.7% of patients in the Cx601 group and 72.5% of patients in the control group. **CONCLUSION:** In a phase 3 trial of patients with Crohn's disease and treatment-refractory complex perianal fistulas, we found Cx601 to be safe and effective in closing external openings, compared with placebo, after 1 year. ClinicalTrials.gov no: NCT01541579.

Keywords: Combined Remission; Clinical Remission; Anal Fistula; Cell Therapy.

Crohn's disease is complicated by perianal fistulas in 30% to 40% of patients, with most being classified as complex.[1–3] The symptoms and complications of perianal fistulas can be debilitating, and lead to a substantial impairment of patients' quality of life.[4] Medical treatments for perianal fistulas aim to promote long-term fistula healing, while preserving continence and avoiding diverting stomas.[5] However, these goals are often unmet with currently available therapies, particularly when considering complex perianal fistulas, which are the most challenging to treat.[6] The rate of durable fistula closure reported in randomized clinical studies of the anti-tumor necrosis factor (anti-TNF) antibody, infliximab, so far the only approved treatment for this indication, was low, with only 23% of patients (36% of 64% of patients who responded to induction and, therefore, received maintenance treatment) having a complete closure of draining fistulas after approximately 1 year of therapy.[7,8] Long-term closure of fistulas in Crohn's disease has not been demonstrated with antibiotics or immunomodulators, and approximately 70% of patients relapse on treatment discontinuation.[9–12]

Perianal fistulas are considered to originate from an epithelial defect resulting from inflammation.[13] Allogeneic expanded adipose-derived mesenchymal stem cells (Cx601), which have anti-inflammatory and immunomodulatory properties,[14–16] were recently shown to be effective and safe for the treatment of complex perianal fistulas in patients with Crohn's disease who did not respond to conventional and/or biological treatments.[17] A significantly greater proportion of patients treated with Cx601 vs placebo, both added to standard of care, achieved the primary endpoint of combined remission assessed clinically and radiologically with magnetic resonance imaging (MRI) 24 weeks after treatment administration (51% vs 36%, $P = .021$).[17] Safety data have shown that Cx601 is well tolerated over 24 weeks of follow-up.[17,18]

Given the lack of durable fistula closing with existing therapies, it was important to determine whether the short-term efficacy results obtained with Cx601 were maintained over a longer duration of follow-up. Consequently, here we report efficacy and safety results up to 52 weeks after treatment administration to evaluate whether the initial responses observed with Cx601 were maintained over the long-term.

Methods

Study Design and Participants

This is a phase 3, randomized, double-blind, parallel-group, placebo-controlled study (NCT01541579) conducted in 49 hospitals in 7 European countries and Israel from July 6, 2012, to December 13, 2015 (ie, to the end of the 52-week follow-up). The study protocol was approved by the local ethics committee of participating centers and was conducted in accordance with the 2008 Declaration of Helsinki, as well as all relevant international, national, and local rules and regulations. Here, we report data up to 52 weeks after treatment administration. Full details of the study design, the patient eligibility criteria, and the primary outcome of the study after 24 weeks of follow-up have been published previously.[17] All authors had access to the study data and reviewed and approved the final manuscript.

In brief, adults with non- or mildly active luminal Crohn's disease were included in this study if they had complex perianal fistulas with a maximum of 2 internal and 3 external openings that had been draining for at least 6 weeks. Patients were refractory to antibiotics, immunosuppressants, and/or anti-TNF therapies. Patients were excluded if they had rectovaginal fistulas; rectal and/or anal stenosis; and/or active proctitis, diverting stomas, an abscess (collection >2 cm) that was not properly drained at the fistula preparation visit; or if they had previous surgery for the active fistula other than

Abbreviations used in this paper: **CDAI, Crohn's Disease Activity Index; CI, confidence interval; Cx601, allogeneic; expanded, adipose-derived stem cells; IBDQ, inflammatory bowel disease questionnaire; LOCF, last observation carried forward; mITT, modified intention-to-treat; MRI, magnetic resonance imaging; PDAI, Perianal Disease Activity Index; PP, per protocol; TEAE, treatment-emergent adverse event; TNF, tumor necrosis factor.**

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drainage or seton placement. All patients provided written informed consent before study participation.

Randomization, Blinding, and Study Procedures

Patients were randomized by a centrally located computer-generated randomization list to Cx601 added on to standard of care (active group) or placebo added on to standard of care (control group) in a 1:1 ratio, with stratification based on concomitant medication (anti-TNF and/or immunosuppressant or neither) at randomization, after the fistula preparation visit (see later in this article), at least 2 weeks before investigational product administration. The double-blind design of the study was maintained by a blinded gastroenterologist and blinded radiologist independently evaluating the clinical and radiological responses, respectively.

At least 2 weeks before investigational product was administered, a pelvic MRI scan was performed, and patients' fistulas were examined under anesthesia, curetted and a seton was placed, if clinically indicated, at the preparation visit.

Treatment administration and cell preparation procedures have been published.[17,18] Briefly, seton(s) were initially removed if present, and the internal fistula opening was closed with stitches. Patients in the Cx601 group received a single injection of 120 million cells suspended in 24 mL of a suitable excipient distributed throughout the fistula tracts. Half of the dose was injected along the tract walls, and the other half around the internal opening, whereas patients in the control group received an identical volume of saline (24 mL) similarly distributed throughout the fistulas. Therefore, the control group was treated with standard of care with a sham treatment administration.

Following study treatment administration, patients who were previously under treatment with immunosuppressants and anti-TNFs were to be maintained on stable doses of these medications during the study after Cx601 administration, and a maximum of 4 weeks of antibiotics was allowed during the study. Luminal disease flares occurring during follow-up could be treated with a 40-mg steroid dose tapered over a maximum of 12 weeks.

Fistula closure was clinically assessed at weeks 6, 12, 18, 24, 36, and 52. The blinded investigator examined the patient for the presence of spontaneous drainage and drainage after gentle finger compression at the treated external opening(s). Fistula-associated collections also were radiologically assessed at weeks 24 and 52 by blinded, centrally read pelvic MRI scans. Treatment-emergent adverse events (TEAEs) were recorded up to week 52 and coded according to the Medical Dictionary for Regulatory Activities version 18.0. The Perianal Disease Activity Index (PDAI) was completed at all the previously mentioned study visits by blinded investigators.[19] The Inflammatory Bowel Disease Questionnaire (IBDQ)[20] and the Crohn's Disease Activity Index (CDAI)[21] were completed at baseline and weeks 24 and 52.

Outcomes

The primary endpoint of the study was established at week 24 and has been previously reported.[17] Predefined secondary efficacy endpoints at week 52 reported here include combined remission, defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections >2 cm, confirmed by blinded MRI centrally read (BioClinica, Munich, Germany). The proportion of patients who had combined remission at week 24 and who did not relapse by week 52 was also evaluated. Relapse was defined as the reopening of any of the treated external openings with active drainage as clinically assessed or the development of a perianal collection >2 cm confirmed by blinded MRI assessment centrally read by 52 weeks. Other secondary endpoints assessed at week 52 included clinical remission (ie, closure of all treated external openings that were draining at baseline despite gentle finger compression) and response (ie, closure of at least 50% of all treated external openings that were draining at baseline). At this time point, we also assessed the secondary endpoints of changes in PDAI, IBDQ, and CDAI. Safety endpoints were TEAEs, serious TEAEs, TEAEs and serious TEAEs related to study treatment, TEAEs leading to discontinuation, and deaths.

Statistical Analysis

The rationale for the sample size and details of the statistical analyses conducted up to week 24 have been published.[17] For the week 52 results, we report efficacy analyses for the modified intention-to-treat (mITT) population, and the primary and key secondary endpoints, defined for the week 24 analyses,[17] also are reported in the per protocol (PP) population. The former included all randomized patients who received study treatment and had at least 1 post-baseline efficacy assessment. The latter included all randomized and treated patients who had both a post-baseline MRI and clinical fistula assessment, with no major protocol deviations that affected the primary endpoint. TEAEs were analyzed in the safety population (ie, all patients who received study treatment).

Treatment differences for combined remission, clinical remission, and response at week 52 were expressed with 95% confidence intervals (CIs) calculated with a Wald's asymptotic method. Statistical analysis compared secondary efficacy endpoints in the 2 treatment groups at week 52 using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization strata (ie, Crohn's disease treatments at randomization). Statistical significance was assessed by a 2-sided type I error level of 0.05, with the exception of the primary endpoint of combined remission at week 24, which was analyzed with a 2-sided type I error level of 0.025 due to regulatory requirements (consequently 97.5% CI are presented for the primary endpoint and 95% CI for the secondary endpoints). The last observation carried forward (LOCF) approach was applied in the case of missing data; treatment failure was imputed after rescue therapy even though rescue was for luminal disease (treatments considered as rescue medications were antibiotics for more than 4 weeks; corticosteroids at a maximum dose of 40 mg prednisone equivalent at treatment interval of more than 12 weeks; new anti-TNF or new immunomodulator compared with baseline therapy for at least 8 or 12 weeks, respectively; or a surgical intervention for the treated fistula). LOCF was not applied to the analysis of the proportion of patients who had combined remission at week 24 and who did not relapse by week 52 (missing values were considered to be no-remission). This was because an LOCF strategy applied to the analysis of relapse would have favored Cx601, whereas the chosen strategy of no LOCF was considered the most conservative approach (ie, the worst-case scenario). Additional post hoc sensitivity analyses explored the effects of

rescue events and missing data conventions on combined remission at week 52, including nonresponse imputation for all missing data and after rescue therapy (no LOCF) (Supplementary Table 1). A post hoc analysis was also done to evaluate the percentage of patients who achieved clinical remission at any time during the 52-week follow-up period. Safety outcomes were presented with descriptive statistics. All statistical analyses were done in SAS (version 9.1.3 or later; SAS Institute, Cary, NC).

Results

Patients

In total, 212 patients were randomized to Cx601 (n = 107) or control (n = 105) (Supplementary Figure 1). The baseline demographic and clinical characteristics of patients in the Cx601 and control groups were similar, as previously described.[17] In the mITT population (n = 204), the mean age of the patients was 38.3 years, 53.9% were male and 92.2% were white. Patients had Crohn's disease for a mean of 11.6 years and more than 70% of patients had received antibiotics, immunosuppressants, or anti-TNF therapy in the past 6 months. The proportion of patients with multiple tract fistulas was numerically higher in the Cx601 vs the control group (46.6% and 30.7%, respectively). A total of 171 patients (80.7% of those randomized) completed the 24-week follow-up, and 131 patients (61.8%) completed the 52-week follow-up (Supplementary Figure 1).

Efficacy Outcomes

The beneficial effect of Cx601 on combined remission previously reported at week 24[17] was maintained at week 52 when a significantly greater proportion of patients in the Cx601 vs the control group achieved combined remission in the mITT (58/103 [56.3%] and 39/101 [38.6%], respectively; difference [95% CI]: 17.7 percentage points [4.2–31.2]; $P = .010$]) and PP populations (49/86 [57.0%] and 33/84 [39.3%], respectively; difference 17.7 percentage points [2.9–32.5]; $P = .021$]; Figure 1). These results were confirmed in additional sensitivity analyses of combined remission at week 52 (Supplementary Table 1). Of the patients in the mITT population who achieved combined remission at week 24, a numerically greater proportion of those in the Cx601 vs control group did not relapse by week 52 (39/52 [75.0%] and 19/34 [55.9%]; difference 19.1 percentage points [−1.3 to 39.5]; $P = .052$). As LOCF was not applied to this calculation, 3 patients with combined remission at week 24 (1 in Cx601 and 2 in the control group) were excluded from this analysis. No evident trend was identified for changes in combined remission at week 52 according to the number of patients treated per site (Supplementary Figure 2), and no statistically significant

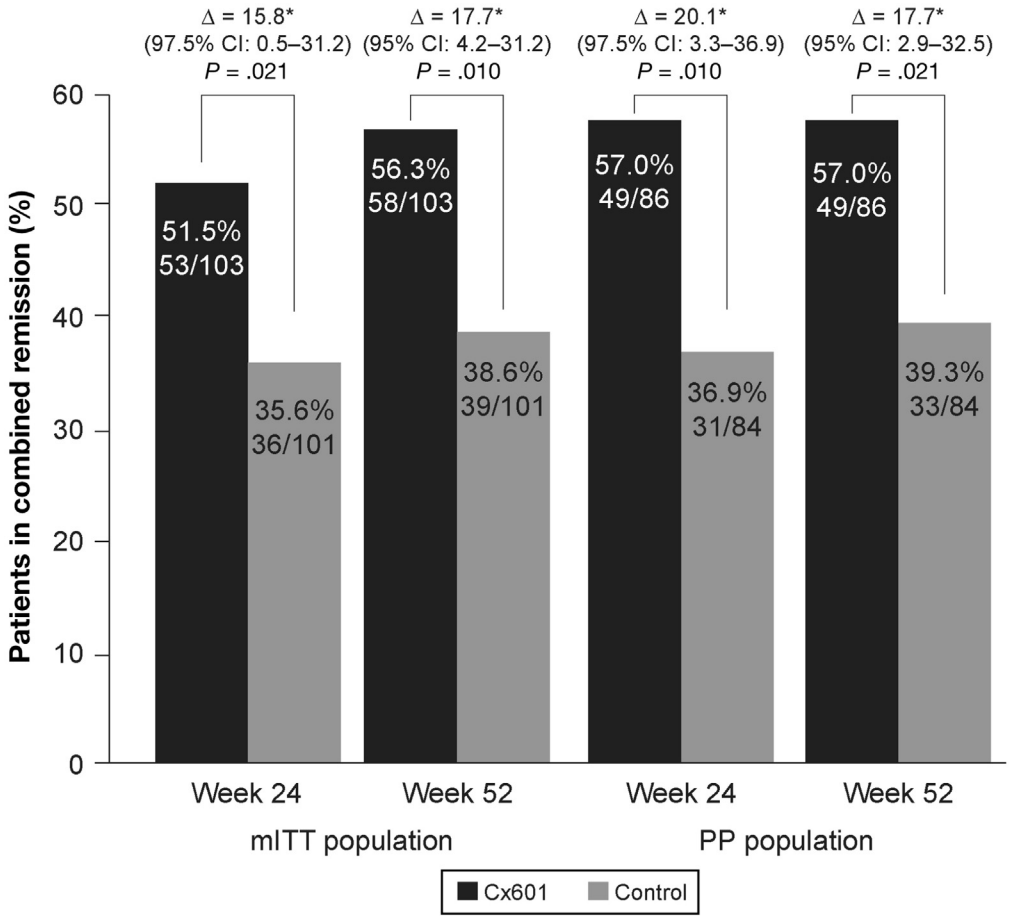

Figure 1. Combined remission in mITT and PP populations at weeks 24 and 52. *Difference in percentage points. Data at 24 weeks published in Panés et al.[17]

Table 1. Clinical Remission and Response at Weeks 24 and 52

Endpoint	mITT population				PP population			
	Cx601 (n = 103), *n (%)*	Control (n = 101), *n (%)*	Treatment difference[a] (95% CI)	*P*	Cx601 (n = 99), *n (%)*	Control (n = 95), *n (%)*	Treatment difference[a] (95% CI)	*P*
Clinical remission by week 24	57 (55.3)	43 (42.6)	12.8 (−0.8 to 26.4)	.057	56 (56.6)	41 (43.2)	13.4 (−0.5 to 27.4)	.052
Clinical remission by week 52	61 (59.2)	42 (41.6)	17.6 (4.1 to 31.1)	.013	59 (59.6)	40 (42.1)	17.5 (3.6 to 31.3)	.015
Response by week 24	71 (68.9)	56 (55.4)	13.5 (0.3 to 26.7)	.045	69 (69.7)	53 (55.8)	13.9 (0.4 to 27.4)	.041
Response by week 52	68 (66.0)	56 (55.4)	10.6 (−2.8 to 23.9)	.128	66 (66.7)	53 (55.8)	10.9 (−2.8 to 24.5)	.120

Data at 24 weeks published in Panés et al.[17]
[a]Difference in percentage points.

differences existed across concomitant treatment strata ($P = .34$), as occurred at week 24.[7]

A significantly greater proportion of patients achieved clinical remission in the Cx601 vs control group at week 52 in both the mITT (61/103 [59.2%] and 42/101 [41.6%], respectively; difference [95% CI]: 17.6 percentage points [4.1–31.1]; $P = .013$) and PP populations (59/99 [59.6%] and 40/95 [42.1%], respectively; difference 17.5 percentage points [3.6–31.3]; $P = .015$; Table 1). As shown in Figure 2, the treatment difference for Cx601 vs control for clinical remission was similar over the duration of the study in both the mITT and PP populations. In the mITT population, a significantly greater proportion of patients in the Cx601 vs control group achieved clinical remission at any time point during the 52-week follow-up period (67/103 [65.0%] and 49/101 [48.5%], respectively; difference [95% CI]: 16.5 percentage points [3.1–29.9]; $P = .019$).

At week 52, a numerically greater proportion of patients in the Cx601 vs control group had a response in the mITT (68/103 [66.0%] and 56/101 [55.4%], respectively; difference [95% CI]: 10.6 percentage points [−2.8 to 23.9]; $P = .128$) and PP populations (66/99 [66.7%] and 53/95 [55.8%], respectively; 10.9 percentage points [−2.8 to 24.5]; $P = .120$; Table 1).

The improvement in PDAI with Cx601 at weeks 24 and 52 was greater than that with control in the mITT population, although the differences between treatments did not reach statistical significance (Supplementary Table 2). There were no significant differences between the groups at weeks 24 or 52 for total and subdomain IBDQ and CDAI scores (Supplementary Table 2).

Safety

Over the 52-week study period, the percentage of patients who experienced TEAEs in the Cx601 and control groups was similar (79/103 [76.7%] and 74/102 [72.5%], respectively), although a numerically higher percentage of patients in the Cx601 group experienced serious TEAEs (24.3% [25/103] and 20.6% [21/102], respectively), the most common of which was anal abscess/fistula (Table 2). A low proportion of patients in both groups withdrew from the 52-week study period due to TEAEs (Cx601: 9/103 [8.7%]; control: 9/102 [8.8%]). No deaths occurred during the study.

The percentage of patients who experienced treatment-related TEAEs was numerically lower in the Cx601 vs control group (21/103 [20.4%] and 27/102 [26.5%], respectively), whereas a similar percentage of patients in the 2 groups experienced serious treatment-related TEAEs over 52 weeks of follow-up (7/103 [6.8%] and 7/102 [6.9%], respectively). In both treatment groups, the most common treatment-related TEAEs were anal abscess/fistula and proctalgia (Table 2).

Discussion

Complex perianal fistulas are debilitating for patients and challenging for physicians to treat. The ultimate goal of therapy is to provide long-term fistula healing. Using a robust efficacy endpoint combining remission evaluated both clinically and radiologically with MRI, the results of the current study demonstrate that the efficacy of Cx601 observed at 24 weeks was maintained for up to 1 year after administration in patients with Crohn's disease with treatment-refractory complex perianal fistulas when added on to current standard of care. In the mITT population, the treatment difference for Cx601 vs control for combined remission increased slightly from 15.8 percentage points at week 24 to 17.7 percentage points at week 52, which implies that at week 52, the number of patients with combined remission in the Cx601 group was 45.9% higher than in the control group. Seventy-five percent of the patients in the Cx601 who achieved combined remission at week 24 did not relapse by week 52, compared with 55.9% of patients in the control group. Long-term efficacy was confirmed in different statistical populations and across different efficacy endpoints.

No clear trend was identified for changes in efficacy according to the number of patients treated, which suggests that the administration of the product does not appear to be associated with relevant difficulties for surgeons.

It is important to carefully discuss and position the observed results, in an area with a significant level of unmet medical need. To date, long-term efficacy has been rarely documented in studies of medical or surgical therapies for perianal fistulas, and long-term remission is achieved in only a relatively small proportion of the overall population.[22] A 1-year randomized, placebo-controlled study of

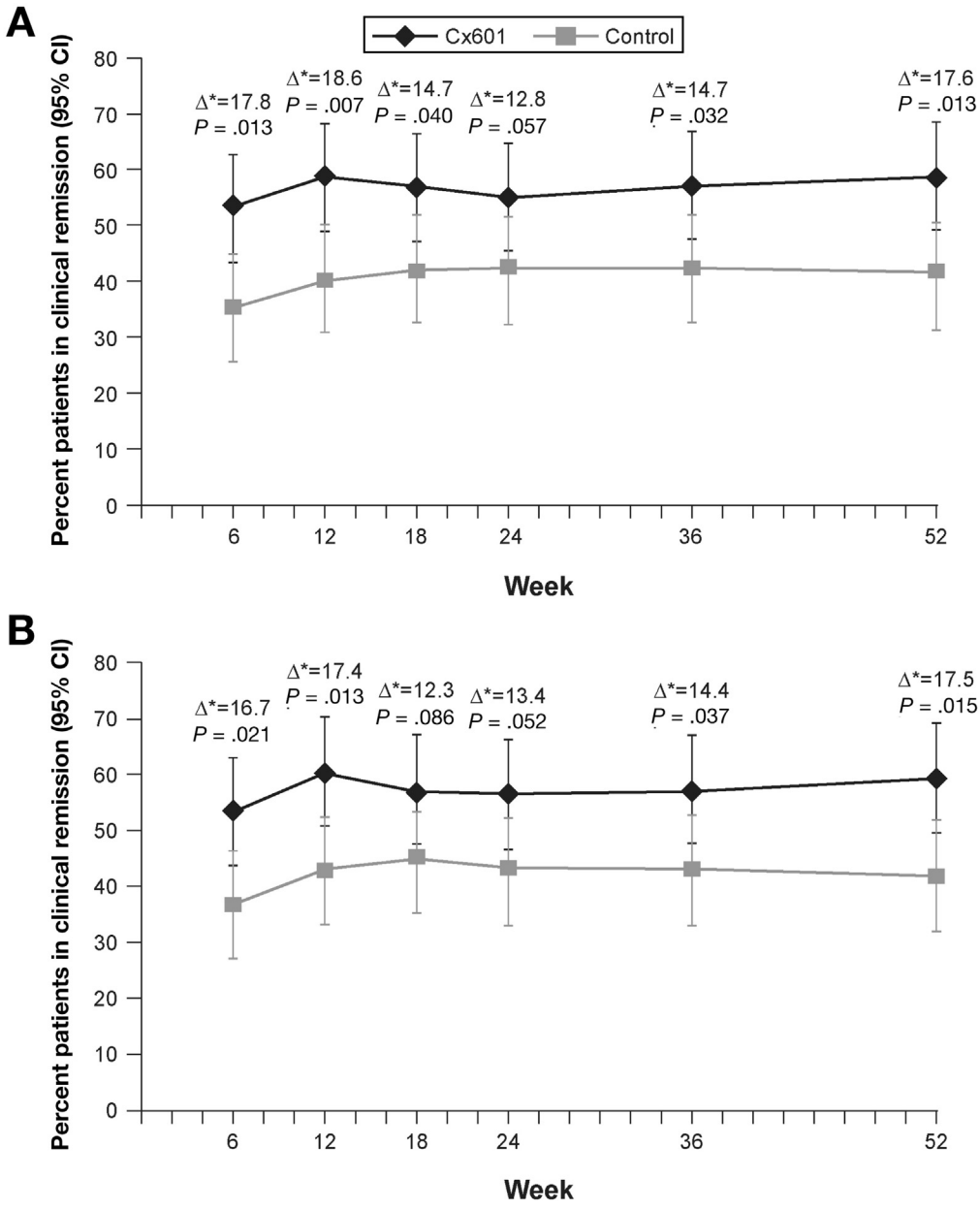

Figure 2. Clinical remission over time: (*A*) mITT population; (*B*) PP population. *Difference in percentage points.

infliximab induction followed by maintenance therapy given every 8 weeks to patients who responded to induction therapy showed that only a minority of patients (23%; ie, 36% of patients who responded to induction [64%]) had long-term fistula healing (defined as the absence of draining fistulas assessed clinically at week 54).[8] After the injection of Cx601, absence of draining fistulas assessed clinically (ie, clinical remission) at an equivalent long-term time point, 52 weeks, was observed in 59.2% of patients, even though, in contrast to infliximab trial, all patients treated with Cx601 had perianal fistulas classified as complex and were treatment-refractory (two-thirds of them to infliximab). In the 1-year clinical trial of infliximab, the absolute difference in absence of drainage between infliximab and the control group at week 54 was 11 percentage points (absence of drainage in the control group occurred in 12% of patients; ie, in 19% of patients who responded to induction [64%]). In the case of Cx601, the absolute difference in absence of drainage compared with the control group was 17.6 percentage points.

Furthermore, retrospective studies based on the review of hospital records have shown that discontinuation of infliximab after successful fistula healing is associated with an increased likelihood of relapse,[23,24] with a reported relapse rate of 66% 1 year after treatment withdrawal.[23] Additional uncontrolled long-term studies of small groups of patients with Crohn's disease with perianal fistulas who were treated with infliximab given alone or in combination with other treatments (eg, thiopurines or surgery) as intravenous infusions or as intralesional injections have shown that long-term fistula closure is rarely achieved.[25–27]

Table 2. Patients with TEAEs Up to Week 52 (Safety Population)

TEAE	Cx601 (n = 103), *n (%)*	Control (n = 102), *n (%)*
Overall	79 (76.7)	74 (72.5)
TEAEs leading to study withdrawal	9 (8.7)	9 (8.8)
TEAEs in ≥5.0% patients[a]		
Anal abscess/fistula[b]	34 (33.0)	30 (29.4)
Proctalgia	15 (14.6)	12 (11.8)
Nasopharyngitis	11 (10.7)	5 (4.9)
Diarrhea	9 (8.7)	3 (2.9)
Pyrexia	6 (5.8)	5 (4.9)
Arthralgia	6 (5.8)	4 (3.9)
Abdominal pain	5 (4.9)	7 (6.9)
Crohn's disease[c]	4 (3.9)	8 (7.8)
Treatment-related TEAEs	21 (20.4)	27 (26.5)
Treatment-related TEAEs in ≥2.0% patients[a]		
Anal abscess/fistula[b]	13 (12.6)	16 (15.7)
Proctalgia	5 (4.9)	8 (7.8)
Procedural pain	1 (1.0)	2 (2.0)
Induration	0	2 (2.0)
Serious TEAEs[d]	25 (24.3)	21 (20.6)
Serious TEAEs in ≥2.0% patients[a]		
Anal abscess/fistula[b]	16 (15.5)	10 (9.8)
Crohn's disease[c]	0	3 (2.9)
Serious-treatment related TEAEs	7 (6.8)	7 (6.9)
Anal abscess/fistula[b]	7 (6.8)	5 (4.9)
Proctalgia	0	1 (1.0)
Anal inflammation	0	1 (1.0)
Liver abscess	0	1 (1.0)

[a]In either treatment group.
[b]Includes the following preferred terms: anal abscess, anal fistula, fistula, fistula discharge, and infected fistula.
[c]Flare of Crohn's disease.
[d]Defined as any adverse event that at any dose resulted in death, was life-threatening, caused permanent incapacity or disability, resulted in hospital admission or prolonged a hospital stay, was a medically significant event, or was a suspected transmission of an infectious agent.

In addition to medical therapy, the management of perianal fistulas currently requires repeated surgeries over many years,[3,28] and despite this, healing is achieved in only a fraction of patients. For example, Molendijk et al[22] reported that, after a median follow-up of 10 years, complex perianal fistulas were still present in 78% of patients, even though potent drugs and surgical techniques were used. This has important implications for patients and health providers, as surgical approaches also can lead to distressing complications, such as sepsis, anal stenosis, and incontinence.[29] Incontinence of solid and liquid stools has been reported to affect 30% and 54% of patients with Crohn's disease, respectively, following surgical treatment for anal fistulas other than the creation of a permanent stoma.[30] The actual rate of incontinence following surgery for anal fistulas may be even higher, because permanent stoma-related interventions are conducted precisely to solve incontinence problems. Of note, no cases of incontinence were reported in this study.

The durable response that was observed with Cx601 over 1 year of follow-up suggests that the need for major surgical interventions may be reduced. Currently, up to 38% of patients with complex perianal fistulas require defunctioning stoma or proctectomy, procedures that are undesirable for patients and substantially impair their quality of life.[29]

Assessments of the PDAI, CDAI, and IBDQ in this study did not show any significant differences between treatment groups at weeks 24 or 52. However, at both weeks 24 and 52, the mean total PDAI score in the Cx601 group was near to the commonly assumed threshold for inactive perianal disease (PDAI <4).[31] Although the PDAI provides an assessment of the severity of perianal Crohn's disease, it does not specifically evaluate the severity of perianal fistulas. This was clearly evidenced by a study that showed that patients with Crohn's disease with perianal fistulas had a mean PDAI score of 2.9 (ie, below the threshold for active perianal disease) compared with a mean score of 9.5 in patients with a mixed phenotype of anal ulcerations plus fistulas.[32] Furthermore, a limitation of the PDAI is that it can be strongly influenced by luminal symptoms because 2 of its 5 domains are not specifically perianal (ie, pain/restriction of activities and restriction of sexual activity). Consequently, the score is likely influenced by interventions targeted to luminal symptoms. Differences in CDAI and IBDQ were not anticipated in our study, because these instruments are not sensitive to the type of morbidity experienced specifically by patients with perianal fistulas. The CDAI mainly evaluates the overall severity of Crohn's disease and the IBDQ is focused on the impact of luminal and systemic symptoms on quality of life. The lack of differences in CDAI and IBDQ also may be related to the relatively low CDAI and high IBDQ scores at baseline.[20,21] These results also highlight the need for new specific measures to assess the response of a perianal fistula to a medical or surgical therapy and the quality of life of patients with Crohn's disease with perianal fistulas.

The safety data at week 52 confirm the favorable tolerability profile for Cx601 that was reported at week 24,[17] and of particular importance, no new safety concerns were identified during extended follow-up. Overall, a similar percentage of patients in both groups experienced TEAEs, and a slightly higher percentage of patients in the control group experienced TEAEs that were considered to be treatment-related. This favorable tolerability may be due to the local application of the treatment and contrasts with other systemic medical therapies used to manage Crohn's disease symptoms and perianal fistulas. For example, infliximab use is associated with several serious safety concerns, such as infusion reactions, an increased rate of infections such as tuberculosis, delayed hypersensitivity, or skin lesions.[6]

General limitations of our study have been reported previously.[17] Limitations of the follow-up to week 52 are that approximately 35% to 40% of patients in each treatment group withdrew before the end of the study. Future

studies could evaluate Cx601 in patients with other types of Crohn's-related fistulas (eg, abdominal or rectovaginal) and in patients with fistulas of other etiologies, as well as the effects of repeated doses in patients with partial responses or additional doses in patients with a loss of response over prolonged time following initial therapy (ie, secondary loss of response).

In conclusion, the efficacy of Cx601 was maintained for up to 1 year after a single administration in treatment-refractory patients with Crohn's disease with complex perianal fistulas. The short-term favorable tolerability of Cx601 also was maintained over the long-term. Cx601 represents a novel and minimally invasive alternative for complex perianal fistulas, which may reduce the need for systemic immunosuppression or surgery. Until additional data are available in other subsets of patients, we believe that the product should be preferentially used in patients in whom perianal disease is the main complication of active Crohn's disease and who do not have severe proctitis. Patients who failed other medical treatments, or those in whom systemic immunosuppression is to be avoided, may benefit from this local cell therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.12.020.

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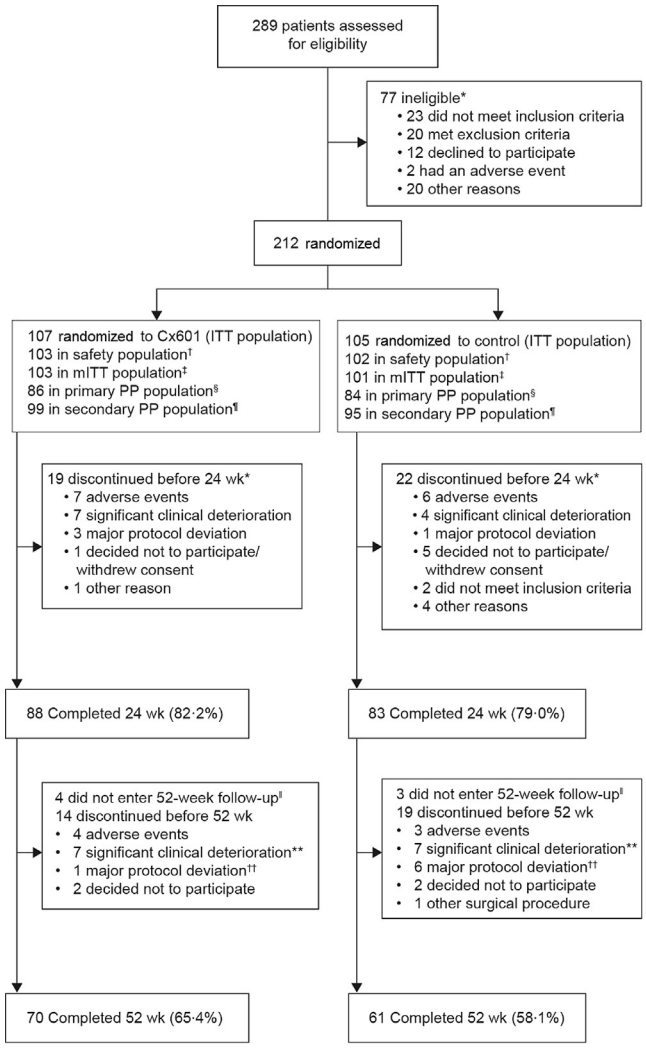
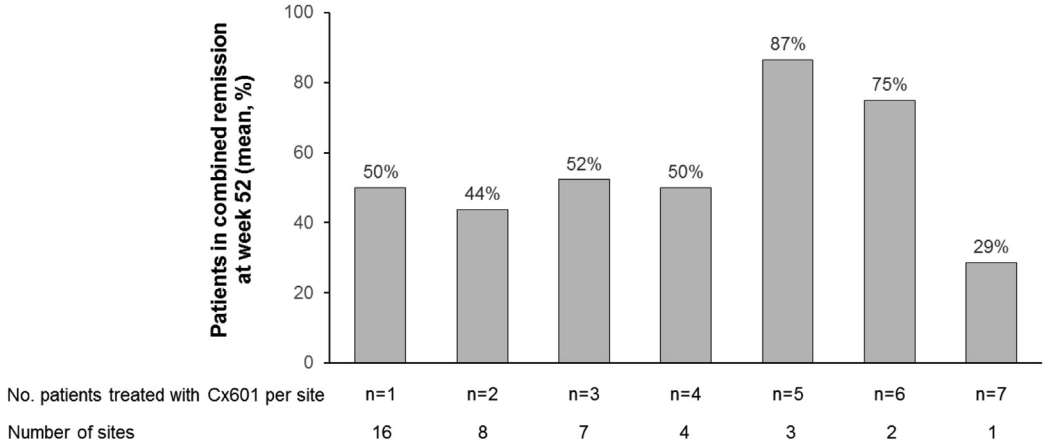


Supplementary Figure 1. Patient disposition. *Full details in Panes et al.[17] †Safety population = randomized and treated patients. ‡mITT population = randomized, treated, and ≥1 post-baseline efficacy assessment. §Primary PP population = randomized, treated, post-baseline MRI and clinical fistula assessment and no major deviations that affect combined remission. ¶Secondary PP population = randomized, treated, clinical fistula assessment and no major deviations that affect clinical remission or response. ‖Did not enter 52-week follow-up, as the protocol amendment for the extended follow-up was not in place. **No healing or worsening of symptoms; new course of antibiotics; new surgery in perianal region. ††Worsening of Crohn's disease requiring change in therapy.



Supplementary Figure 2. Cx601 combined remission rates at week 52 per number of patients treated with Cx601 per site.

Supplementary Table 1. Sensitivity Analyses for Combined Remission at Week 52[a]

Analysis set	Details of handling missing data	Cx601 n/N (%)	Placebo n/N (%)	Difference, % *points* (95% CI)	*P*
mITT	NRI for all missing data and after rescue therapy	50/103 (48.5)	31/101 (30.7)	17.9 (4.7–31.0)	.009
mITT	NRI after LOCF applied Logistic analysis including stratification factor and number of baseline external openings as factors	58/103 (56.3)	39/101 (38.6)	NA	.012
PP	NRI for all missing data and after rescue therapy	45/86 (52.3)	27/84 (32.1)	20.2 (5.7–34.7)	.008
PP	NRI after LOCF applied Logistic analysis including stratification factor and number of baseline external openings as factors	49/86 (57.0)	33/84 (39.3)	NA	.018

NOTE. Rescue therapy is defined as corticosteroids at 40 mg prednisone equivalent for ≥12 weeks; new anti-TNF compared with baseline therapy for ≥8 weeks; new immunosuppressant compared with baseline therapy for ≥12 weeks; or surgical intervention for the treated fistula.
NA, not applicable; NRI, nonresponse imputation.
[a]Clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections >2 cm of the treated perianal fistulas in at least 2 of 3 dimensions on centrally blinded MRI assessment. Clinical assessment of closure was defined as absence of draining despite gentle finger compression.

Supplementary Table 2. Patient-reported Outcomes From the PDAI,[a] CDAI,[b] and IBDQ[c] Scores Up to Week 52 (mITT Population)

PDAI	Cx601 (n = 103)	Placebo (n = 101)	Treatment difference (95% CI)	*P*
Total				
Baseline	6.7 (2.5)	6.5 (2.8)		
Total				
Week 24	4.4 (3.6)	5.1 (3.9)		
Change from baseline	−2.3 (3.8)	−1.3 (3.5)	−0.8 (−1.8 to 0.2)	.101
Total				
Week 52	4.4 (3.8)	5.0 (4.0)		
Change from baseline	−2.3 (4.1)	−1.4 (3.7)	−0.7 (−1.7 to 0.3)	.186
CDAI	**Cx601 (n = 103)**	**Placebo (n = 101)**	**Treatment difference (95% CI)**	***P***
Total				
Baseline	87.8 (48.3)	93.3 (55.0)		
Week 24	92.5 (66.5)	94.1 (76.1)		
Change from baseline	5.7 (62.2)	2.2 (65.5)	1.8 (−16.0 to 19.7)	.839
Week 52	97.4 (82.7)	99.2 (77.8)		
Change from baseline	11.1 (80.5)	7.6 (67.3)	1.3 (−19.6 to 22.1)	.906
No. of liquid stools				
Baseline	9.8 (12.3)	9.3 (9.4)		
Week 24	9.5 (12.6)	10.0 (12.6)		
Change from baseline	−0.0 (9.5)	0.9 (10.7)	−0.7 (−3.4 to 2.1)	.637
Week 52	11.0 (14.7)	10.9 (13.0)		
Change from baseline	1.4 (12.8)	1.9 (11.8)	−0.2 (−3.6 to 3.1)	.889
Abdominal pain				
Baseline	1.6 (2.9)	2.0 (3.1)		
Week 24	2.7 (4.5)	3.0 (4.1)		
Change from baseline	1.1 (4.4)	0.9 (4.0)	−0.1 (−1.2 to 1.1)	.878
Week 52	2.6 (4.4)	3.1 (4.4)		
Change from baseline	1.1 (4.4)	1.0 (4.2)	−0.2 (−1.3 to 1.0)	.795
General well-being				
Baseline	2.7 (3.7)	3.2 (4.1)		
Week 24	3.1 (4.6)	3.3 (4.7)		
Change from baseline	0.6 (4.5)	0.3 (4.5)	0.1 (−1.1 to 1.3)	.927
Week 52	3.4 (5.3)	3.7 (4.9)		
Change from baseline	0.8 (5.3)	0.7 (4.9)	−0.1 (−1.5 to 1.3)	.883
IBDQ	**Cx601 (n = 103)**	**Placebo (n = 101)**	**Treatment difference (95% CI)**	***P***
Total				
Baseline	173.5 (31.6)	169.4 (36.1)		
Week 24	178.3 (34.6)	174.7 (36.2)		
Change from baseline	3.8 (25.5)	4.0 (25.6)	0.3 (−6.6 to 7.3)	.923
Week 52	176.1 (38.1)	172.7 (40.6)		
Change from baseline	2.1 (27.4)	1.7 (25.0)	0.7 (−6.7 to 8.2)	.849
Bowel function				
Baseline	57.1 (9.2)	56.8 (9.8)		
Week 24	57.2 (10.2)	56.4 (9.8)		
Change from baseline	−0.0 (7.6)	−0.8 (7.9)	0.6 (−1.5 to 2.7)	.552
Week 52	56.3 (11.3)	55.7 (11.4)		
Change from baseline	−1.0 (9.3)	−1.6 (7.5)	0.5 (−1.9 to 2.9)	.666
Emotional status				
Baseline	63.2 (14.5)	61.5 (15.2)		
Week 24	64.7 (15.6)	63.9 (15.3)		
Change from baseline	1.4 (11.3)	2.0 (11.1)	−0.5 (−3.5 to 2.5)	.729
Week 52	64.4 (15.5)	63.1 (17.1)		
Change from baseline	1.0 (11.3)	1.1 (11.5)	0.1 (−3.0 to 3.3)	.932

Supplementary Table 2. Continued

IBDQ	Cx601 (n = 103)	Placebo (n = 101)	Treatment difference (95% CI)	*P*
Systemic symptoms				
Baseline	25.9 (5.2)	25.0 (6.4)		
Week 24	26.2 (5.9)	25.6 (6.3)		
Change from baseline	0.2 (4.7)	0.4 (4.9)	−0.0 (−1.3 to 1.2)	.959
Week 52	25.9 (6.3)	25.3 (6.7)		
Change from baseline	−0.0 (5.4)	0.1 (4.9)	0.1 (−1.3 to 1.5)	.927
Social function				
Baseline	27.7 (6.9)	26.5 (8.4)		
Week 24	29.5 (7.3)	28.4 (8.0)		
Change from baseline	1.6 (6.4)	1.7 (6.0)	0.3 (−1.3 to 2.0)	.673
Week 52	29.1 (7.7)	28.4 (8.4)		
Change from baseline	1.3 (7.1)	1.5 (5.8)	0.1 (−1.6 to 1.8)	.934

Data are means (standard deviation).
[a]Scores for PDAI can range from 0 to 20; higher scores indicate more severe disease.
[b]Scores for CDAI can range from 0 to 600; higher scores indicate more severe disease.
[c]Scores for IBDQ can range from 32 to 224; higher scores indicate better quality of life.