Horizon Scanning Centre
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Cx601 (Alofisel®) for complex perianal fistula in adults with non-active or mildly-active luminal Crohn's disease – second line

SUMMARY **NIHR HSC ID: 4615**

Cx601 (Alofisel®) is intended to be used as a second line therapy for the treatment of complex perianal fistula in adult patients with non-active or mildly-active luminal Crohn's disease, where fistulas are refractory to conventional or biologic agents for Crohn's disease, or in patients intolerant to such treatments. If licensed, Cx601 will offer an additional novel, single administrative treatment option for such patients, a group that currently have few effective therapies available. Cx601 does not currently have Marketing Authorisation in the EU for any indication.

The prevalence of Crohn's disease in the UK is approximately 50-100 per 100,000. There are currently at least 115,000 people in the UK with Crohn's disease, and the cumulative risk of perianal fistulas in patients 20 years after diagnosis is 26%. Among patients with Crohn's disease who develop perianal fistulas, one-third develop recurring anal fistulas, and two-thirds develop multiple fistulas.

Crohn's disease is not curable, and the aim of therapy is to control manifestations of the disease, reduce symptoms, and to maintain or improve quality of life. Pharmaceutical options for the treatment of complex perianal fistula in patients with Crohn's disease include antibiotics accompanied by appropriate surgical drainage or in addition to immunosuppressant therapy. Biological agents are an option for second line treatment of fistulas. Surgical approaches such as advancement flap repair, fibrin glue, anal fistula plug, faecal diversion with fistula repair and various seton techniques are also options when treating complex fistula. Cx601 is currently in one clinical trial comparing its effect on fistula collections against treatment with placebo. The trial is expected to complete in April 2016.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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NHS National Institute for Health Research

TARGET GROUP

- Complex perianal fistula in adult patients with non-active or mildly-active luminal Crohn's disease – second line; where fistulas are refractory to conventional or biologic agents for Crohn's disease, or in patients intolerant to such treatments.

TECHNOLOGY

DESCRIPTION

Cx601 (Alofisel®; Cx-601) is a suspension of expanded human adipose-derived stem cells of allogeneic origin. Adult mesenchymal stem cells, including adipose-derived mesenchymal stem cells (ASCs) may have potential immunomodulatory capacity and paracrine effects through trophic factors with antifibrotic, anti-apoptotic, or pro-angiogenic properties. ASCs may regulate the function of a broad variety of immune cells including B lymphocytes, T lymphocytes, NK cells, monocyte-derived dendritic cells, and neutrophils[1]. Cx601 has demonstrated *in vitro* and *in vivo* anti-inflammatory and immune-modulatory capabilities relying on expression of IDO (indoleamine 2,3-dioxygenase) and generation of regulatory T cells.

Cx601 is administered by a single local (intralesional) injection at a dose of 120 million cells. Cx601 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, Cx601 will offer an additional novel, single administrative, treatment option for complex perianal fistula in adult patients with non-active or mildly-active luminal Crohn's disease, where fistulas are refractory to conventional or biologic agents, or in patients intolerant to such treatments, a group who currently have few effective therapies available.

DEVELOPER

TiGenix.

AVAILABILITY, LAUNCH OR MARKETING

Cx601 is a designated orphan drug in the EU, and is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Crohn's disease is a transmural, relapsing inflammatory condition that can involve any part of the gastrointestinal tract[2,3]. The causes of Crohn's disease are not fully understood, but it is thought to be caused by a cascade of immunologic reactions triggered by environmental factors in a genetically predisposed host[4]. Symptoms of Crohn's disease include chronic diarrhoea, abdominal pain, rectal bleeding and weight loss[5]. People with Crohn's disease have recurrent attacks, with acute exacerbations ('flares') in between periods of remission or less active disease[6].

Common complications of Crohn's are strictures (narrowing of the bowel), fistulas (development of abnormal passageways between the bowel and other structures) and perianal disease (comprising fissures, fistulas and abscesses)[5]. Fistulating Crohn's disease comprises fistulae arising in the perianal area, together with those occurring between the intestine and other organs or the abdominal wall[7]. An anal fistula is an abnormal tract between the anal canal and the skin around the anus, which usually arises from perianal abscesses[8]. Intersphincteric fistulae are the most common type and cross only the internal sphincter, while trans-sphincteric fistulae pass through both the internal and external sphincters[8]. Fistulae may be complex, with several openings onto the perianal skin; complex fistulas are more difficult to treat, have decreased healing rates, and are associated with less successful outcomes[8,9]. Symptoms arising from a perianal fistula include pain or discomfort in the anal area, and discharge of blood or pus[8].

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

- NHS England. 2013/14 NHS Standard Contract for Colorectal: Complex Inflammatory Bowel Disease (Adult) A08/S/c.
- Improving quality of life for people with long term conditions (2013).

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of Crohn's disease in the UK is approximately 50-100 per 100,000, and the annual incidence is 5-10 per 100,000 population[10]. There are currently at least 115,000 people in the UK with Crohn's disease[6]. Incidence is greatest in people aged between 15 and 30 years, however Crohn's disease may affect people of any age[11]; 15% of people with the disease are older than 60 years at diagnosis and 20-30% are younger than 20 years[11]. In 2013-14, there were 72,762 admissions for Crohn's disease (ICD-10 K50) in England, resulting in 94,084 bed-days and 81,318 finished consultant episodes[12]. In 2013 184 deaths from Crohn's disease were registered in England and Wales (ICD-10 K50)[13].

Perianal fistula is the most common fistula type, and it is estimated that the cumulative risk of perianal fistulas in patients with Crohn´s disease 20 years after diagnosis is 26%[14,15]. Within the patient population, the prevalence of perianal fistula varies according to disease location; with prevalence ranging from 12% in isolated ileal disease, to 92% in colonic disease involving the rectum[7]. Among patients with Crohn's disease who develop perianal fistulas, one-third of patients develop recurring anal fistulas, and two-thirds develop multiple fistulas[16]. The population likely to be eligible to receive Cx601 could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Crohn's disease (moderate to severe) - vedolizumab [ID690]. Expected date of issue to be confirmed.
- NICE technology appraisal. Infliximab (review) and adalimumab for the treatment of Crohn's disease (TA187). May 2010.
- NICE clinical guideline. Crohn's disease: management in adults, children and young people (CG152). October 2012.

- NICE clinical guideline. Colonoscopic surveillance for the prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (CG118). March 2011.
- NICE interventional procedure guideline. Closure of anal fistula using a suturable bioprosthetic plug (IPG14). November 2011.
- NICE interventional procedure guidance. Extracorporeal photopheresis for Crohn's disease. (IPG288). February 2009.

Other Guidance

- The European Crohn's and Colitis Organisation. Guidelines for the management of inflammatory bowel disease in adults. 2011[17].
- The European Crohn's and Colitis Organisation consensus on Crohn's disease. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. 2010[18].
- The European Crohn's and Colitis Organisation consensus on Crohn's disease. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. 2010[19].
- The European Crohn's and Colitis Organisation consensus on Crohn's disease. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. 2010[7].

CURRENT TREATMENT OPTIONS

Crohn's disease is not curable and hence the aim of therapy is to control manifestations of the disease, reduce symptoms, and to maintain or improve quality of life, while minimising short- and long-term adverse effects[6]. The treatment strategy used depends on disease activity, site, behaviour of disease (inflammatory, fistulising or stricturing), response to previous treatments, treatment side-effect profiles, and extra-intestinal manifestations (such as uveitis and arthritis)[6]. Treatment pathways generally include a wide range of drugs (corticosteroids, aminosalicylates, immunosuppressants, and antibiotics), nutritional therapy, and surgery[5]. Tumour necrosis factor (TNF) inhibitors (antiTNF-α agents) such as infliximab are also an option for patients with Crohn's disease[5].

Pharmaceutical options for the treatment of complex perianal fistula in patients with Crohn's disease include antibiotics (i.e. metronidazole and ciprofloxacin), accompanied by appropriate surgical drainage[7,9]. Antibiotics may also be used in addition to immunosuppressant therapy (azathioprine or 6-mercaptopurine)[9]. In patients where antibiotics and immunosuppressant agents are not sufficiently effective, biological agents including infliximab and adalimumab are an option for second line treatment of fistulas[9]. Treatment of perianal fistula in patients with Crohn's disease usually involves surgery and depends on the position of the fistula in relation to the sphincters[8]. Various surgical approaches may be utilised in treating complex fistula. These include advancement flap repair, fibrin glue, anal fistula plug, faecal diversion with fistula repair and various seton techniques[20]

EFFICACY and SAFETY

Trial	ADMIRE-CD, NCT01541579; Cx601 vs placebo; phase III.	NCT01372969; Cx601; phase I/IIa.
Sponsor	TiGenix SAU.	TiGenix SAU.
Status	Ongoing.	Published.
Source of information	Trial registry[21].	Publication[1], trial registry[22].

Location	EU (not UK), and Israel.	EU (not UK).
Design	Randomised, placebo-controlled.	Uncontrolled, single arm.
Participants	n=289; aged ≥18 years; non-active or mildly active luminal Crohn's Disease (CD) (Crohn's disease activity index [CDAI] ≤220); presence of complex perianal fistulas[a] with a maximum of 2 fistulas (internal openings) and a maximum of 3 external openings, assessed by clinical assessment and MRI; fistula draining for ≥6 weeks; no concomitant rectovaginal fistulas; previous specific treatment for perianal fistulising Crohn's disease, including antibiotics; no abscess or collections >2 cm, unless resolved in the preparation procedure (week -3 to day 0); no rectal and/or anal stenosis and/or active proctitis if this means a limitation to any surgical procedure; no previous surgery for the fistula other than drainage or seton placement; no diverting stomas; no ongoing steroid treatment or steroids in the last 4 weeks; no major surgery or severe trauma within the previous 6 months.	n=24; aged ≥18 years; non-active luminal CD (CDAI ≤200) diagnosed ≥12 months; persistent and active complex perianal fistula; presence of complex perianal fistula with ≤3 fistulous tracts assessed by MRI; no severe proctitis (prominent friability, spontaneous bleeding, multiple erosions, deep ulcers) or dominant active luminal disease requiring immediate therapy; no subjects with an abscess (unless a complete toilet of the area with drainage of the collections and the absence of abscess and other collections is confirmed prior to treatment start); no setons unless removed prior to treatment; no rectal and/or anal stenosis; no infliximab or any other anti-TNF agent in the 8 weeks before treatment; no tacrolimus or ciclosporin in the 4 weeks before treatment; no rectovaginal fistula, anal fistula(s), and/or non-perianal enterocutaneous fistula; no subjects in need of surgery in the perianal region for reasons other than fistulas, or where a need for such surgery is foreseen in the 26 weeks after treatment; no major surgery or severe trauma within the previous 6 months.
Schedule	Cx601, 120 million expanded ASCs (5 million cells/mL) as a single intralesional injection; or placebo 24mL as a single intralesional injection.	Cx601, 20 million expanded ASCs (5 million cells/mL) as a single intralesional injection, and where there is incomplete closure of the fistula at 12 weeks, administration of a further 40 million expanded ASCs as a single intralesional injection.
Follow-up	Active treatment consists of one administration of Cx601, follow-up 52 weeks.	Active treatment consists of one or two administrations of Cx601, follow-up for 24 weeks after initial administration.
Primary outcome/s	Absence of collections >2cm of the treated perianal fistulas at 24 weeks confirmed by MRI.	Incidence of treatment emergent adverse-events.
Secondary outcome/s	Response, defined as closure of at least 50% of all external openings that were draining at baseline; time to remission, (first visit with closure of all external openings that were draining at baseline, as clinically assessed); time to response; severity of perianal CD assessed with the Perianal Disease Activity Index (PDAI); quality of life (QoL) assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ); adverse events (AEs); CDAI score.	Reduction in the number of draining fistulas; increase in the number of closed fistulas; percentage of subjects in whom, the external openings of treated perianal fistula have closed; percentage of subjects with MRI fistula healing (absence of collections >2cm); percentage of subjects presenting luminal relapse. No QoL measurement included in trial outcomes.

[a] A complex perianal fistula is defined as a fistula that met ≥1 of the following criteria: high inter-sphincteric, trans-sphincteric, extra-sphincteric or supra-sphincteric; presence of ≥2 external openings (tracts); associated collections.

Key results		Results at 24 weeks[b]: reduction ≥1 draining fistula, 69.2%; reduction in 1 draining fistula, 61.5%; reduction in 2 draining fistula, 7.7%; closure of the external opening of the treated perianal fistula, 56.3 %.
Adverse effects (AEs)		Five treatment-related AEs were reported: anal abscess in three patients, pyrexia in one patient, and uterine leiomyoma in one patient. Two serious AEs were reported: pyrexia and perianal abscess (in the investigator's opinion, these events were considered to be possibly related to the study treatment).
Expected reporting date	Study completion date reported as April 2016.	-

ESTIMATED COST and IMPACT

COST

The cost of Cx601 is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☐ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☑ Other: *potential to be beneficial in an area which can be problematic to treat[c], and earlier return to normal activities, including employment.*
- ☐ No impact identified

Impact on Health and Social Care Services

- ☐ Increased use of existing services
- ☑ Decreased use of existing services: *if treatment is effective it may result in a reduced need for interventional procedures.*
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other.
- ☐ None identified

Impact on Costs and Other Resource Use

- ☐ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs:
- ☑ Other reduction in costs: *if treatment is effective it may result in a reduced need for interventional procedures.*
- ☑ Other: *uncertain unit cost compared to existing treatments*
- ☐ None identified

[b] All results refer to the full analysis population i.e. the intention-to-treat population (ITT): all subjects who received at least one dose of study treatment.

[c] Expert personal opinion.

Other Issues

☐ Clinical uncertainty or other research question identified: *approval of Cx601 would be dependent on safety and preliminary evidence for efficacy, which is currently rather limited. However this is an area of unmet need and research in this field is greatly to be encouraged since perianal disease impacts on patient quality of life and may potentially reduce the need for surgery*[d].

☐ None identified

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