# Randomized, single-blind, placebo controlled multicenter phase III study to assess the efficacy and safety of expanded autologous adipose-derived stem cells (eASCs) (CX-401), for treatment of complex perianal fistulas in Crohn*s disease.

Published: 23-09-2008
Last updated: 06-05-2024

The primary objective of the study is to evaluate the efficacy of intralesional administration of eASCs (CX-401) when added to standard surgical care and drainage for the treatment of complex perianal fistulas in patients with Crohn*s disease (CD...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Gastrointestinal stenosis and obstruction |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON35164

**Source**
ToetsingOnline

**Brief title**
FATT II: Fistula Advanced Therapy Trial (II)

### Condition

- Gastrointestinal stenosis and obstruction

**Synonym**
inflammation of intestine

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Cellerix S.A.
**Source(s) of monetary or material Support:** Cellerix

## Intervention

**Keyword:** adipose-derived stem cells, Crohn□s disease, placebo controlled

## Outcome measures

### Primary outcome

The primary endpoint is the percentage of anti-TNF previous exposed patients

with complete closure of their treated complex perianal fistula at Week 24.

Complete closure of the fistula is defined as:

•Absence of drainage/suppuration of the fistula through the external orifice,

either spontaneously or when applying pressure, and

•Complete re-epithelization of the external orifice (clinical evaluation), and

•Absence of fluid collections >2 cm directly related to the treated fistula

tract, as measured by MRI, in the longest diameter.

Clinically, complete closure must be confirmed at both, the Week 24 and the

Week 26 visit.

### Secondary outcome

Secondary:

•Changes over time in the PDAI and CDAI between baseline, Week 12 and Week 24

•Percentage of the complete set of patients with complete closure of their

treated complex perianal fistula at week 24. Clinically, complete closure must be confirmed at the week 24 and the week 26 visit.

•Percentage of patients with complete closure of the treated complex perianal fistula after 12 weeks of eASCs exposure. Clinically, complete closure must be confirmed at the Week 10 and the Week 12 visit.

•Percentage of patients with MRI confirmed absence of collections >2 cm of the treated perianal fistula at Weeks 12 and 24.

•Percentage of patients with exacerbation or relapse of CD at Weeks 12 and 24. This is herewith defined any deterioration in the CDAI total score.

•Changes over time in the MRI Score of Severity (MSS) between baseline, Week 12 and Week 24.

•QoL as measured by SF-36 questionnaire.

•Percentage of patients for whom surgeries of the treated fistula could be avoided.

Safety variables:

•Adverse events (AEs), serious adverse events (SAEs), signs, symptoms and clinical diagnosis, surgeries.

•Clinically relevant variations in physical examination findings during the study.

•Clinically relevant variations in vital signs during the study.

•Clinically relevant variations in laboratory data during the study.

# Study description

### Background summary

Crohn*s disease is a chronic inflammatory disease of the intestine of unknown etiology. It is characterized by focal or segmental transmural inflammation that can occur in any part of the digestive tract with occasional granuloma formation.

The cumulative incidence of perianal fistulas in Crohn*s disease varies between 20% and 50% perianal disease is associated with high morbidity and, typically, with local pain and discharge; it therefore has a very negative impact on the quality of life of the affected Subjects.

Cell therapy based on stem cell technologies is rapidly being introduced in a variety of areas of medicine, particularly since the introduction of adult stem cells. This allows for autologous transplantation, thus avoiding rejection-related issues and ethical concerns, such as those relative to embryonic stem cells.

The purpose of this study is to examine the efficacy and safety of a new therapy with expanded adipose derived stem cells (eASCs), in order to see if subjects experience improvement in their disease symptoms and quality of life. eASCs are thought to selectively affect the immune system to decrease inflammation, typically increased in fistulizing disease and in doing so, initiating tissue repair process, due to the natural repair properties of live cells.

### Study objective

The primary objective of the study is to evaluate the efficacy of intralesional administration of eASCs (CX-401) when added to standard surgical care and drainage for the treatment of complex perianal fistulas in patients with Crohn*s disease (CD).

### Study design

This is a phase III, multicenter, randomized, comparative, single-blind, placebo-controlled study to evaluate the efficacy and safety of a new therapy with eASCs for the treatment of complex perianal fistulas in patients with CD.

Both anti-TNF exposed patients (i.e. patients with previous anti-TNF therapy) and anti-TNF naive patients (i.e. patients without previous anti-TNF therapy) can be included. The recruitment will stop at the latest, when 156 anti-TNF exposed patients have been randomized, i.e. no further patients (neither

anti-TNF exposed nor anti-TNF naive) will be enrolled into the screening period after this time point, but patients already enrolled to the screening period at this time point are allowed to continue and can be randomized, if they meet the corresponding criteria. The recruitment might be stopped earlier, if a sufficient number of anti-TNF exposed patients is in the screening period to ensure a number of 156 randomized anti-TNF exposed patients.

Assuming a screening failure rate of 20%, about 198 anti-TNF exposed patients will be screened. The screening failure rate will be monitored during the study and the number of screened patients will be adapted as necessary to achieve a number of 156 randomized anti-TNF exposed patients.

The number of screened anti-TNF naive patients will be restricted to at most 50. The percentage of anti-TNF naive patients is roughly estimated to be around 20%, which would result in about 40 randomized anti-TNF naive patients, assuming the same screening failure rate of 20% as for the anti-TNF exposed patients.

Each eligible patient will be randomized in a 1:1 ratio to receive either a local intra-lesional injection eASCs in the fistula at a dose of 20 million cells, or placebo. Patients must have had CD for a minimum of 12 months* duration with a CD Activity Index (CDAI) score <220 scored over the 14 days prior to the first treatment with CX-401.

All patients will undergo a baseline magnetic resonance imaging (MRI) to assess the presence/absence of collections >2 cm associated to the fistula tract. All study patients will undergo a liposuction to isolate autologuous stem cells from the patients adipose tissue, in order to have an ASC bank available to be used for treatment during the study.

Complete fistula closure will be clinically evaluated twice at two consecutive visits (Weeks 10-12 as well as Weeks 24-26) by a blinded and unblinded physician/surgeon. In addition, presence/absence of collections >2 cm associated to the fistula tract will be radiologically evaluated by a blinded radiologist at Weeks 12 and 24.

In case of incomplete/partial closure of the treated fistula at Week 12, patients from the eASC group will receive a second dose of eASCs (40 million cells). Patients in both treatment groups will be followed until Week 26.

Patients from both groups may be treated with standard of care (SOC) for CD during the entire study period.

Patients from the placebo group with incomplete/partial fistula closure at Week 26 will be offered to participate in a separate open-label, single arm eASCs protocol, as long as cells have been obtained from the patient within the scope

of this protocol.

### Intervention

liposuction during visit -3. Administration of study treatment during visits 0 and 4b.

### Study burden and risks

No side effects attributable to application of stem cells have been reported in any patients so far. As this is a new treatment, the potential long term effects of this cell therapy are unknown. There are potential complications that may occur during surgery and on the days immediately following surgery (such as bleeding, occurrence of perianal abscesses or wound infection).
During this study your blood will be drawn to perform a variety of tests. The risk of drawing blood includes temporary discomfort, bruising, swelling and redness in the area where the blood is taken.
No significant risks have been reported for magnetic resonance imaging because it uses no radiation (unlike X rays). Some cases of mild dizziness have been reported in people experiencing a certain feeling of claustrophobia in the room where the scan is performed. However, this is uncommon and the test usually takes approximately 30 minutes.

## Contacts

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## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Signed informed consent.
2. Patients with CD diagnosed at least 12 months earlier in accordance with accepted clinical, endoscopic, anatomical/topographical and/or radiologic criteria. France and Italy only: Patients with CD diagnosed at least 12 months earlier in accordance with accepted clinical, endoscopic, anatomical/topographical and/or radiological criteria, unresponsive (treatment failure and/or intolerance and/or contraindication) to conventional treatment, including anti-TNF.
3. Presence of complex perianal fistula with up to 3 external openings, assessed by MRI. The blinded fistulae branches visible though MRI are not considered fistula tracts but branches of the main tract. A complex perianal fistula is defined as a fistula that meets one or more of the following criteria:
- High fistulas (high inter-sphincteric, high trans-sphincteric, extra-sphincteric or supra sphincteric)
- Presence of 3 or fewer external openings associated to a complex perianal fistula.
4. Non-active or mildly active luminal CD defined by a CDAI <=220.
5. Patients of either sex aged 18 years or older. Good general state of health according to clinical history and a physical examination.
6. Women of a childbearing age with negative serum or urine pregnancy test (sensitive to 25 IU hCG). Both men and women should use appropriate birth control methods defined by the investigator.

## Exclusion criteria

1. Presence of severe proctitis (prominent friability, spontaneous bleeding, multiple erosions, deep ulcers) or dominant active Crohns disease requiring immediate therapy, assessed by rectosigmoidoscopy
2. CDAI >220.
3. Presence of an abscess or collections >2 cm, unless a complete surgical debridement of the area has been performed, including drainage of the collection(s) and an MRI scan confirms absence of (residual) abscess before randomization.
4. Presence of setons. If present at screening they should be removed prior to treatment

administration.
5. Presence of >3 external openings.
6. Rectal and/or anal stenosis.
7. Treatment with infliximab or any other anti-TNF agent in the 8 weeks before the cell treatment administration.
8. Patients having received adalimumab in the 4 weeks before the cell treatment adminsitration.
9. Treatment with tracrolimus or cyclosporine in the 4 weeks before the cell treatment administration.
10. HIV, HBV, HCV or treponema infection.
11. Persistent chronic bacterial infections of temporary nature as well as local infections unless succesfully treated prior liposuction, such as syphilis, brucellosis, typhus, melioidosis, q-fever, meningitis, or other.
12. Renal impairment defined by creatinine clearance below 60 ml/min calculated using Cockcroft-Gault formula (see appendix I) or the following laboratory ranges:
Total bilirubin > 1.5 x upper limit of normal (ULN)
AST and ALT > 2.5 X ULN
Serum creatinine > 1.5 ULN
13. Known history of abuse of alcohol or other addictive substances in the 6 months prior to inclusion.
14. Malignant tumor or patients with a prior history of malignant tumors.
15. Current or recent history of abnormal, severe, progressive, uncontrolled liver function, anemia, hepatic, hematological, gastrointestinal (except CD), endocrine, pulmonary, cardiac, neurological, psychiatric ,or cerebral disease.
16. Congenital or acquired immunodeficiencies.
17. Known allergies or hypersensivity to antibiotics including but not limited to penicillin, streptomycin, gentamicin, aminoglycosides; HSA; DMEM; materials of bovin origin; local anesthetics or gadolinium (MRI contrast).
18. Contraindication to MRI scan, (e.g., due to the presence of pacemakers, hip replacements or severe claustrophobia).
19. Liposuction with extraction of at least 100 cm3 of fat from the abdominal wall is technically unfeasible or the patient does not consent to the procedure.
20. Major surgery or severe trauma within the previous 6 months.
21. Pregnant or breastfeeding women.
22. Patients who do not wish to or cannot comply with study procedures.
23. Patients currently receiving, or having received within 3 months prior to enrolment into this clinical study, any investigational drug.
24. Patients unlikely to comply with study procedures.

## Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Single blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 27-02-2009 |
| Enrollment: | 18 |
| Type: | Actual |

## Medical products/devices used

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| Product type: | Medicine |
| Generic name: | Somatic cells autologous |
| Product type: | Medicine |
| Brand name: | Cx401 |
| Generic name: | NAP |

# Ethics review

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| Approved WMO Date: | 23-09-2008 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 19-12-2008 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

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| Approved WMO Date: | 24-03-2009 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 07-04-2009 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 28-05-2009 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 23-06-2009 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 25-08-2009 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 07-09-2009 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 19-11-2009 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 21-01-2010 |
| Application type: | Amendment |

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|---|---|
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 03-03-2010 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 09-03-2010 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2008-004286-25-NL |
| CCMO | NL24602.000.08 |