A phase III, randomised, double blind, parallel group, placebo controlled, multicentre study to assess efficacy and safety of expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of perianal fistulising Crohn*s disease over a period of 24 weeks and an extended follow-up period up to 104 weeks. ADMIRE-CD study.

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To evaluate the efficacy and safety of eASCs compared to placebo for the treatment of complex fistulas in Crohn*s disease over a 24- and 104-week period.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON41535

Source
ToetsingOnline

Brief title
ADMIRE-CD study

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammation of intestine

Research involving
Human

Sponsors and support

Primary sponsor: TIGENIX, S.A.U.
Source(s) of monetary or material Support: TiGenix S.A.U. (voorheen Cellerix S.A. geheten)

Intervention

Keyword: Adipose-derived stem cells, Crohn's disease, fistula

Outcome measures

Primary outcome

Remission of perianal fistulising Crohn*s disease at week 24 confirmed by MRI, defined as the clinical assessment of closure of all the external openings that were draining at baseline despite gentle finger compression, confirmed by MRI as absence of collections > 2 cm of the treated perianal fistulas (central blind assessment).

Secondary outcome

Efficacy analysis at week 24

• KEY: Clinical Remission defined as closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed by week 24

• KEY: Response defined as closure of at least 50% of all treated external openings that were draining at baseline, as clinically assessed by week 24

• Time to Clinical Remission by week 24 (defined as time from treatment start to first visit with closure of all treated external openings that were draining

at baseline, as clinically assessed)

• Time to Response by week 24 (defined as time from treatment start to first visit with closure of at least 50% of all treated external openings that were draining at baseline, as clinically assessed)

• Relapse by week 24 defined, in patients with Clinical Remission at previous visit, as reopening of any of the treated external openings with active drainage as clinically assessed, or the development of a perianal collection > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment by week 24)

• Time to Relapse by week 24 in patients with Clinical Remission (defined as time from Clinical Remission to first visit with reopening of any of the treated external openings with active drainage as clinically assessed, or the development of a perianal collection > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment by week 24)

• Severity of the perianal Crohn's disease up to week 24, assessed with the Perianal Disease Activity Index (PDAI)

• Quality of Life (QoL) up to week 24 assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ)

• CDAI score up to week 24

• Van Assche score up to week 24

Efficacy analysis at week 52:

• Combined Remission of perianal fistulising Crohn's disease defined as the clinical assessment of closure of all the treated external openings that were draining at baseline

despite gentle finger compression at week 52, and absence of collections > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment by week 52

• Clinical Remission defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed at week 52

• Response defined as closure of at least 50% of all treated external openings that were draining at baseline, as clinically assessed at week 52.

• Time to Combined Remission by week 52 (defined as time from treatment start to first visit with clinical assessment of closure of all the treated external openings that were draining at baseline despite gentle finger compression at week 52, and absence of collections > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment by week 52)

• Time to Clinical Remission by week 52 (defined as time from treatment start to first visit with closure of all treated external openings that were draining at baseline, as clinically assessed)

• Time to Response by week 52 (defined as time from treatment start to first visit with closure of at least 50% of all treated external openings that were draining at baseline,
as clinically assessed)

• Relapse by week 52 in patients with Combined Remission at week 24, defined as reopening of any of the treated external openings with active drainage as clinically assessed or the development of a perianal collection > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment by 52

weeks

• Time to Relapse by week 52 in patients with Combined Remission at week 24 (defined as time from Combined Remission to first visit with reopening of any of the treated external openings with active drainage as clinically assessed, or the development of a perianal collection > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment by week 52

• Severity of the perianal Crohn's disease up to week 52, assessed with PDAI

• Quality of Life (QoL) up to week 52 assessed by IBQD

• CDAI score up to week 52

• Van Assche score up to week 52

Efficacy analysis at week 104:

• Clinical Remission of perianal fistulising Crohn's disease defined as the clinical assessment of closure of all treated external openings that were draining at baseline despitegentle finger compression at week 104

• Relapse by week 104 in patients with Combined Remission at week 52, defined as reopening of any of the treated external openings with active drainage as clinically assessed

• Time to Relapse by week 104 in patients with Combined Remission at week 52 (defined as time from Combined Remission to first visit with reopening of any of the treated external openings with active drainage as clinically assessed)

• Severity of the perianal Crohn's disease, assessed with PDAI up to week 104

• Quality of Life (QoL) assessed by the IBQD up to week 104

• CDAI score up to week 104

Timepoints of evaluation of this endpoint at 24, 52 and 104 weeks after the

treatment

Study description

Background summary

Crohn's disease is an inflammatory bowel disease which causes inflammation of the lining of the digestive tract, which can lead to abdominal pain, severe diarrhea and even malnutrition. The inflammation caused by Crohn's disease often spreads deep into the layers of affected bowel tissue and sometimes may lead to life-threatening complications such as perianal fistulas. These are small tunnels, starting from the anus or rectum, and poured into either the tissue up to the outer skin or to other spaces that surround the anus, rectum and pelvic organs. This study is intended to assess the safety and efficacy of a new cell therapy for the perianal fistulas in Crohn*s disease. The cell therapy consists of lipoaspirates obtained from healthy donors. These lipoaspirates include a population of stem cells of mesenchymal origin with multilineage capacity: adipose derived mesenchymal stem cells. The previous phase II trial (Cx601-0101, EudraCT Number: 2008-007445-31) with expanded allogeneic adipose-derived stem cells (eASCs) administered locally for the treatment of complex perianal fistula showed promising efficacy results with 36.8% of closure of the external opening of the treated perianal fistula at week 12, and 53.3% at week 24 in the per protocol analysis, with similar results in the full analysis set.

Study objective

To evaluate the efficacy and safety of eASCs compared to placebo for the treatment of complex fistulas in Crohn*s disease over a 24- and 104-week period.

Study design

This will be a phase III, randomised, double blind, parallel group, placebo controlled, multicentre study to assess efficacy and safety of expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of perianal fistulising Crohn*s disease over a period of 24 and 104 weeks.

Intervention

The study will permit previous treatment continuation in an add-on design (i.e., anti-TNFs, immunosuppressants, etc.). Baseline homogeneity will be

guaranteed by means of an exploration under anesthesia, fistula curettage for all the patients and seton placement if clinically indicated, done 2 weeks before randomization. In case of seton placement, it will be withdrawn at the administration day, just before the administration of the study treatment. Cx601 is a cell suspension in aseptic buffered solution containing human eASCs of allogeneic origin in disposable vials with no preservative agents. The cells will be given at a dose of 120 million cells (5 million cells/ml) for intralesional injection. Placebo (saline solution) will be given as an intralesional injection in the same volume (24 ml) and following the same schedule.

Study burden and risks

Available preclinical and clinical results on cellular therapy with autologous and allogeneic eASCs have shown that this is a safe treatment for fistulas that would overcome most of the problems encountered with surgery and systemic anti-TNFs, currently used for the management of perianal fistulas. Possible risks and side effects of the eASCs administration include injection site nodules (small lumps) and fever. The rectosigmoidoscopy is a well tolerated outpatient procedure, and the curettage is also the standard procedure for cleaning the fistula and have little to no complications, but may associate some type of discomfort related to bleeding of the injury. During this study, blood will be drawn to perform a variety of tests. Drawing blood can be painful and sometimes causes bruising and infection in the area where the blood is taken. Dizziness and fainting can also occur when blood is being taken. No significant risk has been reported for magnetic resonance imaging because it uses no radiation (unlike X rays). A benefit of taking part in this study is that the patient*s fistulising Crohn*s disease will be checked regularly, and the treatment might improve or heal fistula during the study, but may also not provide any personal benefit. However, depending on the results of the study, participation may provide information that will help other people who have similar medical problem in the future.

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 Crohn*s Disease (CD) diagnosed at least 6 months earlier in accordance with accepted clinical, endoscopic, histological and/or radiologic criteria
(3)Presence of complex perianal fistulas with a maximum of 2 internal openings and a maximum of 3 external openings, assessed by clinical assessment and MRI. Fistula must have been draining for at least 6 weeks prior to the inclusion.
A complex perianal fistula is defined as a fistula that met one or more of the following criteria during its evolution:
•High inter-sphincteric, trans-sphincteric, extra-sphincteric or supra-sphincteric
•Presence of >= 2 external openings (tracts)
•Associated collections
(4)Non-active or mildly active luminal CD defined by a CDAI <= 220
(5)Patients of either sex aged 18 years or older
(6)Good general state of health according to clinical history and a physical examination
(7)For women of a childbearing age, they must have negative serum or urine pregnancy test (sensitive to 25 IU human chorionic gonadotropin [hCG]). Both men and women should use appropriate birth control methods defined by the investigator
*To participate in the extension follow-up period up to 52 and 104 weeks, it is required the previous participation in the Cx601-0302 study, having completed 24 and 52 weeks respectively. Patients should have signed the informed consent for the extension follow-up period up to 52 and 104 weeks.

Exclusion criteria

(1)Presence of dominant luminal active Crohn*s disease requiring immediate therapy
(2)CDAI >220
(3)Concomitant rectovaginal fistulas
(4)Patient naïve to specific treatment for perianal fistulising Crohn*s disease including antibiotics
(5)Presence of an abscess or collections > 2 cm, unless resolved in the preparation procedure (week -3 to day 0)
(6)Presence of > 2 internal openings
(7)Presence of > 3 external openings
(8)Rectal and/or anal stenosis and / or active proctitis, if this means a limitation for any surgical procedure
(9)Patient who underwent surgery for the fistula other than drainage or seton placement
(10)Patient with diverting stomas
(11)Patient with ongoing steroid treatment or treated with steroids in the last 4 weeks
(12)Renal impairment defined by creatinine clearance below 60 ml/min calculated using Cockcroft-Gault formula or by serum creatinine >= 1.5 x upper limit of normality (ULN)
(13)Hepatic impairment defined by both of the following laboratory ranges:
•Total bilirubin >= 1.5 x ULN
•AST and ALT >= 2.5 x ULN
(14)Known history of abuse of alcohol or other addictive substances in the 6 months prior to inclusion
(15)Malignant tumour or patients with a prior history of any malignant tumour, including any type of fistula carcinoma
(16)Current or recent history of abnormal, severe, progressive, uncontrolled hepatic, haematological, gastrointestinal (except CD), endocrine, pulmonary, cardiac, neurological, psychiatric, or cerebral disease
(17)Congenital or acquired immunodeficiencies
(18)Known allergies or hypersensivity to antibiotics including but not limited to penicillin, streptomycin, gentamicin, aminoglycosides; HSA (Human Serum Albumin); DMEM (Dulbecco Modified Eagle*s Medium); materials of bovin origin; local anaesthetics or gadolinium (MRI contrast)
(19)Contraindication to MRI scan, (e.g., due to the presence of pacemakers, hip replacements or severe claustrophobia)
(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 previously treated with eASCs can not be enrol into this clinical study
(25)Subjects who need surgery in the perianal region for reasons other than fistulas at the time of inclusion in the study, or for whom such surgery is foreseen in this region in the 24 weeks after treatment administration
(26)Contraindication to the anaesthetic procedure

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-09-2012
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic
Product type:	Medicine
Brand name:	Cx601
Generic name:	NA

Ethics review

Approved WMO Date:	09-03-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-07-2012

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-08-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-12-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-03-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	01-07-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-11-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-11-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-08-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-10-2016
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	EUCTR2011-006064-43-NL
CCMO	NL39170.000.12