2. CLINICAL STUDY SYNOPSIS

Name of Company: CELLERIX, S.A.	**Volume:**	(For national authority use only)
Name of Finished Product: CX-401	**Page:**	
Name of Active Ingredient: CX-401 (adult expanded autologous adipose-derived stem cells)		

Title of Study: 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. FATT 2: Fistula Advanced Therapy Trial (II)

Protocol Number: CX-401/FATT2

Study Period: **Phase of Development:** Phase III

Date of first screening visit: 18 Dec 2008

Date of last patient visit: 25 Apr 2010

Date of premature study termination: 24 Feb 2010

Reason for Premature Study Termination:

The study was prematurely terminated for further inclusion of patients on 24 Feb 2010. The decision, following a strategic review, to early terminate the FATT-2 study and put the future development of CX-401 on hold was based on the following recently acquired knowledge: Following investigators' input through completion of the FATT-2 site survey and discussions with experts in the field, it had become apparent that the protocol was not reflective of clinical reality. The result of this was a lower patient recruitment rate, higher screening failure rate and higher patient withdrawal rate than expected, making it impossible to complete the trial as defined. In addition, preliminary results of previous studies based on similar experimental design suggested that the expected recruitment rate would not be feasible at all. The probability of screening failures and withdrawals would have been even much higher than in previous studies due to the factual features of the patient profile at the involved sites. Moreover, amending the protocol and adapting the study methods to the factual clinical needs would delay the performance of FATT-2 to dates that would not be acceptable. However, data of previous or current studies do not reveal any particular issue or concern on the patients' safety associated with CX-401.

Study Centers: 22 study centers in 5 countries in Europe.

Publication(s): Not applicable.

Objectives:

The primary objective of the study was 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).

The secondary objectives were:

- To evaluate the safety of intralesional administration of eASCs (CX-401) when given at baseline with a possible repeat dose at Week 12, and a follow-up period of 12 weeks.
- To evaluate the effect of intrafistular administration of eASCs (CX-401) on the incidence of complications of complex fistulas in patients with CD (such as abscesses or fluid collections) using magnetic resonance imaging (MRI).
- To compare the use of eASCs (CX-401) with placebo with regard to the fistular relapse rate.
- To obtain data regarding prevention of invasive surgical procedures and use of additional therapies.
- To obtain quality of life (QoL) data.

Study Design: This was a randomized, single-blind, placebo-controlled multicenter phase III study in patients with complex perianal fistulas in CD.

Number of Patients (planned and analyzed): 156 anti-tumor necrosis factor (TNF) exposed patients and about 40 anti-TNF naïve patients were planned to be randomized. Assuming 20% anti-TNF naïve patients and equal screening failure rates for anti-TNF naïve and anti-TNF exposed patients, a total of about 250 patients were planned to be screened.

Actually, 56 patients were screened (last patient on 12 Feb 2010).

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Diagnosis and Main Criteria for Inclusion:

A patient could be included in the study if he/she met ALL the criteria listed below:

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. Treatment failure meant persistence or recurrence of fistula-related discharge despite correctly conducted induction treatment with anti-TNF antibodies with at least 3 infusions/injections. It was, however, possible to authorize inclusion of patients who did not tolerate anti-TNF antibodies (allergy) and, in consequence, had not received a complete course of anti-TNF antibody treatment. Patients to whom treatment with anti-TNF agent was contraindicated may also have been included if they fulfilled other eligibility criteria.
3. Presence of complex perianal fistula with up to 3 external openings, assessed by MRI. The blinded fistulae branches visible through MRI were not considered fistula tracts but branches of the main tract. A complex perianal fistula was defined as a fistula that met 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 human chorionic gonadotropin [hCG]). Both men and women should have used appropriate birth control methods defined by the investigator.

Test Product, Dose and Mode of Administration, and Lot Number(s): CX-401. Suspension of adult eASCs at doses of 20 and 40 million cells (10 million cells/vial) administrated by intralesional injection.

Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Normal saline (5 mL) administrated by intralesional injection.

Duration of Treatment: The planned study treatment period per patient was 26 weeks.

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Criteria for Evaluation:

The primary endpoint was the percentage of anti-TNF exposed patients with complete closure of their treated complex perianal fistula at Week 24. Complete closure of the fistula was 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 had to be confirmed at both the Week 24 and the Week 26 visits.

Secondary endpoints were:

- Changes over time in the Perianal Disease Activity Index (PDAI) and the CD Activity Index (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 had to be confirmed at the Week 24 and the Week 26 visits.
- Percentage of patients with complete closure of the treated complex perianal fistula after 12 weeks of eASCs exposure. Clinically, complete closure had to be confirmed at the Week 10 and the Week 12 visits.
- 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 was 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.
- Quality of life (QoL) as measured by Short-Form-36 (SF-36) questionnaire.
- Percentage of patients for whom surgeries of the treated fistula could be avoided.

Safety endpoints were:

- 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.

Statistical Methods:

The planned statistical analyses were not performed. Selected data listings were produced.

Date of Report: 17 Nov 2010