2. SYNOPSIS

Name of Sponsor: Cellerix (currently TiGenix)	**Individual Study Table Referring to Part of the Dossier** **Volume:** TBD	(For National Authority Use only)
Name of finished product: Cx601 – Cell suspension of adult expanded adipose-derived stem cells for allogeneic use.		
Name of active ingredient: Expanded allogeneic adipose-derived stem cells (eASCs)	**Page:** 487	

Title of study:	Multicenter phase I/IIa study to assess the safety and efficacy of expanded allogeneic adipose-derived stem cells (eASCs) (Cx601), for treatment of complex perianal fistulas in perianal Crohn's disease.
Investigators:	There were a total of 6 principal investigators with no study coordinator: Dr. Damián García Olmo, Dr. José Manuel Herrerías, Dr. Antonio Galindo Galindo, Dr. Francisco Alba Mesa, Dr. Fernando de la Portilla, Dr. Xavier González.
Study centre(s):	There were a total of 6 active centres in Spain where patients were recruited and no principal coordinator.
Publication (reference):	De la Portilla et al. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial. Int J Colorectal Dis, 2013;28(3):313-23
Studied period (years): **(date of first enrolment):** 27 Aug 2009 **(date of last completed):** 24 Sep 2010	**Phase of development:** I/IIa
Objectives:	**Primary:** The primary objective of this clinical trial was to assess the safety of eASCs. **Secondary:** The secondary objectives were to get a preliminary evaluation of the efficacy of eASC for the treatment of complex perianal fistulas in perianal Crohn's disease patients, and to assess its effect in certain paremeters of the disease.
Methodology:	Phase I/IIa, multicenter, open-label pilot study, aimed to assess the safety of a new therapy based on allogeneic adult expanded adipose-derived stem cells (eASCs) (Cx601) intended for the treatment of complex perianal fistulas in subjects with perianal Crohn's disease, with a preliminary evaluation of the efficacy.
No. of patients planned:	A total of 24 evaluable subjects was considered to be sufficient to fulfill the aim of the study.
No. of patients included:	24

Populations	**eASCs**
Safety population /Full analysis population	24 (100.0%)
Per protocol population	22 (91.7%)

Percentages calculated using included patients as base

Diagnosis and main criteria for inclusion	The study population eligible for inclusion were Crohn's disease patients over 18 years with with perianal complex fistulas.
Test product:	Cx601 – Suspension of adult allogeneic expanded adipose-derived stem cells (eASCs).
Dose:	20 or 40 million cells
Mode of admin.:	Intralesional injection
Batch no.:	

Batches no.:	
DONOR 8	**DONOR 10**
DON-8-001-A	DON-10-001-A
DON-8-004-A	DON-10-001-B
DON-8-003-A	DON-10-002-A
DON-8-005-A	DON-10-004-A
DON-8-006-A	DON-10-005-A
DON-8-007-A	DON-10-006-A
DON-8-010-A	DON-10-006-B
DON-8-010-B	DON-10-007-A
DON-8-010-C	DON-10-009-A
DON-8-011-A	DON-10-011-A
DON-8-012-B	DON-10-012-A
	DON-10-013-A
	DON-10-014-A
	DON-10-016-A

Duration of treatment:	24 weeks
Reference therapy:	N/A.
Dose:	N/A.
Mode of admin.:	N/A.
Batch no.:	N/A.
Criteria for evaluation:	.
Safety:	• Treatment-related treatment emergent adverse events (TEAEs) - Primary outcome. • Subjects exposed. • TEAEs. • Serious TEAEs. • Treatment-related serious TEAEs. • TEAEs leading to withdrawal from study. • Variations in laboratory parameters and in vital signs. • Physical examinations.

Efficacy:	• Reduction in the number of draining fistulas at weeks 12 and 24. • Increase in the number of closed fistulas at weeks 12 and 24. Fistula closure was defined as absence of suppuration of the fistula through the external orifice, spontaneously and by pressure, complete re-epithelization of the external orifice in the clinical evaluation and absence of collections > 2 cm, in three axis, directly related to the fistula tract treated. • Closure of the external openings of the treated perianal fistula at weeks 12 and 24. • MRI fistula healing (absence of collections > 2 cm) at weeks 12 and 24. • Luminal relapse at weeks 12 and 24. • Changes over time in the Perianal Disease Activity Index (PDAI), in the Crohn's Disease Activity Index (CDAI), and in the MRI Score of Severity (MSS).
Statistical methods:	The population for the safety analysis was the Safety/Full analysis population. Efficacy variables were analyzed for both Per protocol population and the Safety/Full analysis population (safety population) and the. For quantitative variables, standard descriptive summary statistics (for absolute values and absolute changes from baseline) were displayed. Likewise, the Wilcoxon Signed-rank test was performed for each visit change in order to determine response changes. Frequency tables were performed for categorical data. Likewise, baseline to post-baseline shift tables were also performed, which showed the frequencies of patients shifting among the analyzed categories. The Stuart-Maxwell test was used to analyzed the mentioned shifts.

Summary of results and conclusions:

<u>Safety</u>(safety population):

- Treatment-related TEAEs were reported in 5 (20.8%) patients: Anal abscess was reported in 3 (12.5%) patients, whereas Pyrexia and Uterine leiomyoma were reported in 1 (4.2%) patient each.
- Approximately half of patients reported at least one TEAE during the study.
- The most frequently reported TEAEs were Pyrexia and Anal abscess (16.7% of patients each) and C-Reactive protein increased and Anxiety (12.5% of patients each).
- There were 2 patients (8.3%) who presented treatment-related serious TEAEs, Pyrexia and Anal abscess, respectively.

<u>Efficacy</u> (full analysis population):

- A reduction in the number of draining fistulas was shown in 60.0% of patients at 12 weeks, and in 69.2% at 24 weeks.
- The number of closed fistulas increased in 28.6% of patients at 12 weeks, and in 40.0% at 24 weeks.
- Closure of the external opening of the treated perianal fistula was observed in 38.1% of patients at 12 weeks, and in 56.3% at 24 weeks.
- No patients reported luminal relapse at 12 weeks, while 5 patients presented it at 24 weeks.
- A statistically significant improvement in the PDAI score was shown at visits 7 and 8 (22 and 24 weeks).
- MRI Score of Severity showed a statistically significant reduction at 12 weeks. At 24 weeks, there also was a similar reduction, although not statistically significant.

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Conclusions

	Six months after the initial administration of Cx601 for the treatment of complex perianal fistulas in Crohn's disease patients, there was no evidence of relevant safety concerns. Cx601 showed a favourable safety profile, with low numbers of treatment-related TEAEs (5 patients; 20.8%) and of treatment-related serious TEAEs (2 patients; 8.3%). Although this study was not powered to assess efficacy, it included a number of secondary efficacy outcomes that have provided preliminary evidence of the effectiveness of Cx601 in the treatment of complex perianal fistulas in Crohn's disease patients. In particular, after 24 weeks, it has been shown a reduction in the number of draining fistulas in 69.2% of patients, an increase in the number of closed fistulas in 40.0% of patients, and closure of the external openings of the treated perianal fistula in 56.3% of patients (full analysis population).
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