Clinical trial results:
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.

Summary

EudraCT number	2011-006064-43
Trial protocol	DE BE ES IT AT NL
Global end of trial date	10 February 2017

Results information

Result version number	v1 (current)
This version publication date	21 April 2018
First version publication date	21 April 2018

Trial information

Trial identification

Sponsor protocol code	Cx601-0302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01541579
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TiGenix S.A.U.
Sponsor organisation address	C/ Marconi, 1, Parque Tecnológico de Madrid, Tres Cantos, Madrid, Spain, 28760
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objective was to evaluate the efficacy and safety of Cx601 compared to placebo for the treatment of perianal fistulising CD over 24, 52 and 104 weeks. Dates of Database Locks were 27 Jul 2015 (Week 24); 29 Feb 2016 (Week 52) and 10 Feb 2017 (Week 104)

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. No trial procedures were performed on trial participants until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the Ethics committee.
Routine monitoring was performed to verify that rights and well being of patients were protected. Also, any medication considered necessary for the patient's safety and well-being was given at the discretion of the Investigator.
Each patient was free to withdraw from the study at any time without giving a reason.

Background therapy:

The following treatments were permitted:
Antibiotics to treat the fistula during the study (including but not limited to ciprofloxacin and/or metronidazole) or antibiotics active against bacteria of the
perianal region, provided no more than 4 weeks of continued treatment was administered.
Azathioprine, 6-MP, or methotrexate, maintained at a stable dose, could be taken from IMP administration up to Week 52. No new treatment with azathioprine, 6-MP, or methotrexate was allowed up to Week 52. If there were complications derived from their use, a decrease in dose or suspension of the drug was allowed.
Anti-TNFs maintained at stable doses. No new treatment with anti-TNF agents was allowed up to Week 52.
Use of 5-ASA from time of treatment administration; thereafter only decreases in dose were allowed up to Week 52.
Medications taken by the patient for other disease(s) were allowed. In event of doubt about concomitant treatments, the trial monitor was to be contacted.
Patients were not allowed to receive investigational drugs or other local investigational treatments in the perianal region while participating in the study.
Prior to Week 52, in case of a flare of the luminal disease, it was permitted to use an oral steroid course starting with prednisone/prednisolone at 40 mg, or equivalent, and tapering over 12 weeks, following usual clinical practice at the site.
In this situation, the patient could continue in the study; but if the patient required a new immunosuppressant or new anti-TNF agent, or required higher doses of their existing immunosuppressant or anti-TNF medication compared to baseline, the patient was to be withdrawn and considered a treatment failure.

Evidence for comparator:

The use of a placebo comparator group is in accordance with the EMA guideline, "Guideline on the development of new medicinal products for the treatment of Crohn's Disease" CPMP/EWP/2284/99 Rev. 1, 2008 which states that "for an add-on indication, placebo is an acceptable comparator".

Actual start date of recruitment	06 July 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 31
Worldwide total number of subjects	212
EEA total number of subjects	194

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	205
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 212 patients were randomised in 8 countries (Austria, Belgium, France, Germany, Israel, Italy, the Netherlands and Spain) at 47 sites. Enrolment started on 06 July 2012. Last patient visit was on 10 Feb 2017 (week 104 follow-up).

Pre-assignment

Screening details:

A 5-week screening period was scheduled to determine a patient's eligibility for inclusion in the study. All patients underwent the same pre-study preparatory surgery, performed at least 2 weeks before the administration day.

Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

IMP administration was not masked, because the cell suspension is clearly identifiable compared to the saline solution. One Investigator (surgeon) administered the IMP + another Investigator evaluated the fistula(s) in a blinded fashion. Surgeons who administered the IMP were not allowed to participate in any patient clinical assessment. Investigators responsible for patient assessments + patients remained blinded to the patients' treatment allocation up to Week 52.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cx601 - ITT

Arm description:

The ITT Population included all patients randomised, irrespective of having received study medication.

Arm type	Experimental
Investigational medicinal product name	Allogenic eASCs 5 million cells/ml suspension for injection. CX601
Investigational medicinal product code	Cx601p
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralesional use

Dosage and administration details:

Cx601 is a cell suspension in sterile buffered solution containing eASC of allogeneic origin. Cx601 for clinical use was supplied as a sterile, off-white or slightly yellowish homogenous suspension for intralesional administration, provided in 4x6 mL disposable vials (suspension of 5 million eASC/mL of DMEM with 5% HSA). Patients received Cx601, at a dose of 120 million cells, i.e. a total volume of 24 mL (5 million cells/mL), by intralesional injection.

Arm title	Placebo - ITT

Arm description:

The ITT Population included all patients randomised, irrespective of having received study medication.

Arm type	Placebo
Investigational medicinal product name	Saline solution
Investigational medicinal product code	Saline solution
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:
Placebo (saline solution) by intralesional injection at a volume of 24 mL.

Number of subjects in period 1	Cx601 - ITT	Placebo - ITT
Started	107	105
Completed	23	14
Not completed	84	91
Consent withdrawn by subject	2	1
patient decision, clinical deterioration, other	-	25
clinical deterioration, patient decision, other	18	-
Adverse event, non-fatal	11	9
Lost to follow-up	49	49
Protocol deviation	4	7

Baseline characteristics

Reporting groups	
Reporting group title	Cx601 - ITT
Reporting group description:	
The ITT Population included all patients randomised, irrespective of having received study medication.	
Reporting group title	Placebo - ITT
Reporting group description:	
The ITT Population included all patients randomised, irrespective of having received study medication.	

Reporting group values	Cx601 - ITT	Placebo - ITT	Total
Number of subjects	107	105	212
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	104	101	205
From 65-84 years	3	4	7
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	39.0	37.6	
standard deviation	± 13.11	± 13.12	-
Gender categorical Units: Subjects			
Female	47	49	96
Male	60	56	116
Race Units: Subjects			
White	100	96	196
Black	4	1	5
Asian	0	0	0
Other	0	1	1
Missing	3	7	10
Weight Units: kg			
arithmetic mean	73.93	71.33	
standard deviation	± 15.006	± 14.922	-

End points

End points reporting groups

Reporting group title	Cx601 - ITT
Reporting group description:	
The ITT Population included all patients randomised, irrespective of having received study medication.	
Reporting group title	Placebo - ITT
Reporting group description:	
The ITT Population included all patients randomised, irrespective of having received study medication.	

Primary: Combined Remission of perianal fistulising CD - week 24

End point title	Combined Remission of perianal fistulising CD - week 24

End point description:

The primary efficacy variable for this study was Combined Remission of perianal fistulising CD (defined as the clinical closure of all treated EOs that were draining at baseline despite gentle finger compression) and absence of collections >2 cm of the treated perianal fistula confirmed by evaluation of MRI images by a central laboratory that was blinded to the individual patient's treatment and visit by Week 24.
The main analysis was based on ITT approach where any patient with a missing value was imputed as a non-response. However, in case of missing clinical assessment by Week 24, the last observation carried forward (LOCF) from the latest earlier post-baseline visit (including an Early Termination Visit, if applicable) applied. In case of missing MRI data by Week 24, if there was an MRI at an Early Termination Visit prior to Week 24 then LOCF applied to this MRI.

End point type	Primary

End point timeframe:

Fistula closure, used to assess the primary endpoints was clinically evaluated at Week 6, 12, 18, 24, 36, 52, 78, and 104 after initial administration of cells or placebo and evaluated via radiological assessment (MRI) at Week 24 and Week 52.

End point values	Cx601 - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	105		
Units: patients with Combined Remission (n)				
week 24 (n)	53	36		

Statistical analyses

Statistical analysis title	Primary endpoint statistics
Comparison groups	Cx601 - ITT v Placebo - ITT

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Remission Rate %
Point estimate	15.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.2
upper limit	30.3

Notes:

[1] - P-value determined by Cochran-Mantel-Haenszel test adjusted for randomisation strata (use of anti TNF agents or immunosuppressants at randomisation).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred from completion of ICF were recorded, regardless of the intensity, seriousness or relationship to study drug until the Week 52 assessment at each visit; from Week 52 to Week 104 only SAEs were collected.

Adverse event reporting additional description:

Treatment-Emergent Adverse Events up to Week 52 in ≥2 Patients in Either Treatment Group (Safety Population) are presented.
Serious Treatment-Emergent Adverse Events up to Week 104 in Either Treatment Group (Safety Population) are presented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cx601 - Safety
Reporting group description: -	
Reporting group title	Placebo - Safety

Reporting group description: -

Serious adverse events	Cx601 - Safety	Placebo - Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 103 (27.18%)	22 / 102 (21.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-Cell Lymphoma			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			

subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 103 (0.97%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Proctalgia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Inflammation			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal cyst			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's Disease			
subjects affected / exposed	0 / 103 (0.00%)	3 / 102 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	5 / 103 (4.85%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 103 (0.97%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female Genital Tract Fistula			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fistula Discharge			
subjects affected / exposed	1 / 103 (0.97%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal Abscess			
subjects affected / exposed	15 / 103 (14.56%)	8 / 102 (7.84%)	
occurrences causally related to treatment / all	7 / 15	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin Abscess			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar Abscess			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 103 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 103 (0.97%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.02 %

Non-serious adverse events	Cx601 - Safety	Placebo - Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 103 (76.70%)	74 / 102 (72.55%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 103 (1.94%)	4 / 102 (3.92%)	
occurrences (all)	2	4	
White blood cell count increased			
subjects affected / exposed	1 / 103 (0.97%)	2 / 102 (1.96%)	
occurrences (all)	1	2	
Injury, poisoning and procedural complications			
Post procedural inflammation			
subjects affected / exposed	2 / 103 (1.94%)	0 / 102 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 103 (3.88%)	0 / 102 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 103 (0.97%)	4 / 102 (3.92%)	
occurrences (all)	1	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 103 (1.94%)	2 / 102 (1.96%)	
occurrences (all)	2	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Proctalgia			
subjects affected / exposed	15 / 103 (14.56%)	12 / 102 (11.76%)	
occurrences (all)	20	17	
Anal fistula			
subjects affected / exposed	11 / 103 (10.68%)	8 / 102 (7.84%)	
occurrences (all)	12	8	
Diarrhoea			
subjects affected / exposed	9 / 103 (8.74%)	3 / 102 (2.94%)	
occurrences (all)	11	5	
Abdominal pain			
subjects affected / exposed	5 / 103 (4.85%)	7 / 102 (6.86%)	
occurrences (all)	5	8	
Crohn’s disease			
subjects affected / exposed	4 / 103 (3.88%)	8 / 102 (7.84%)	
occurrences (all)	4	8	
Perianal erythema			
subjects affected / exposed	3 / 103 (2.91%)	2 / 102 (1.96%)	
occurrences (all)	3	2	
Haemorrhoids			
subjects affected / exposed	3 / 103 (2.91%)	0 / 102 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	3 / 103 (2.91%)	0 / 102 (0.00%)	
occurrences (all)	3	0	
Vomiting			

subjects affected / exposed	3 / 103 (2.91%)	2 / 102 (1.96%)	
occurrences (all)	3	2	
Abdominal mass			
subjects affected / exposed	2 / 103 (1.94%)	0 / 102 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	2 / 103 (1.94%)	3 / 102 (2.94%)	
occurrences (all)	2	4	
Anal fissure			
subjects affected / exposed	0 / 103 (0.00%)	3 / 102 (2.94%)	
occurrences (all)	0	3	
Anal Inflammation			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Anal haemorrhage			
subjects affected / exposed	0 / 103 (0.00%)	3 / 102 (2.94%)	
occurrences (all)	0	3	
Proctitis			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 103 (1.94%)	2 / 102 (1.96%)	
occurrences (all)	2	2	
Erythema			
subjects affected / exposed	2 / 103 (1.94%)	0 / 102 (0.00%)	
occurrences (all)	2	0	
Psoriasis			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 103 (5.83%)	4 / 102 (3.92%)	
occurrences (all)	6	4	
Fistula discharge			

subjects affected / exposed	3 / 103 (2.91%)	2 / 102 (1.96%)	
occurrences (all)	3	3	
Neck pain			
subjects affected / exposed	2 / 103 (1.94%)	1 / 102 (0.98%)	
occurrences (all)	2	2	
Fistula			
subjects affected / exposed	2 / 103 (1.94%)	5 / 102 (4.90%)	
occurrences (all)	2	5	
Myalgia			
subjects affected / exposed	1 / 103 (0.97%)	2 / 102 (1.96%)	
occurrences (all)	1	2	
Infections and infestations			
Anal abscess			
subjects affected / exposed	20 / 103 (19.42%)	14 / 102 (13.73%)	
occurrences (all)	21	19	
Nasopharyngitis			
subjects affected / exposed	11 / 103 (10.68%)	5 / 102 (4.90%)	
occurrences (all)	14	5	
Infected fistula			
subjects affected / exposed	4 / 103 (3.88%)	4 / 102 (3.92%)	
occurrences (all)	4	4	
Bronchitis			
subjects affected / exposed	3 / 103 (2.91%)	4 / 102 (3.92%)	
occurrences (all)	3	4	
Urinary tract infection			
subjects affected / exposed	3 / 103 (2.91%)	3 / 102 (2.94%)	
occurrences (all)	3	3	
Gastroenteritis			
subjects affected / exposed	1 / 103 (0.97%)	3 / 102 (2.94%)	
occurrences (all)	1	3	
Folliculitis			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	3	

Influenza			
subjects affected / exposed	0 / 103 (0.00%)	3 / 102 (2.94%)	
occurrences (all)	0	3	
Acute tonsillitis			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	0 / 103 (0.00%)	3 / 102 (2.94%)	
occurrences (all)	0	4	
Tonsilitis			
subjects affected / exposed	0 / 103 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2012	Protocol amendment 1, version 2.0, included the following changes: - Addition of an extra 28-week follow-up period to allow assessment of long-term safety and efficacy; therefore, the overall study length was increased from 24 to 52 weeks. - Clarification of study procedures for fistula preparation, exclusion criteria, allowed rescue medication, placebo packaging and labelling, and cell product descriptions.
17 May 2013	Protocol amendment 2, version 3.0, included the following change: - Addition of immunological analysis of blood samples taken at Visit 0, Visit 2 and Visit 6 and Early Termination Visit (where appropriate) to allow assessment of alloreactivity in study patients. Update includes changes to visit procedures and update of informed consent process.
08 December 2014	Protocol amendment 5, version 6.0, included the following changes: - Addition of an extended follow-up period of up to 104 weeks to evaluate the long-term efficacy and clinical safety of Cx601 treatment, including additional assessments at Weeks 78 and 104. - Clarification of statistical analyses including definition of blinding procedures, primary and secondary efficacy and overall safety endpoints and definitions of datasets and analysis subsets. - Only SAEs will be reported and summarised in the 2nd follow-up period between Week 52 and Week 104.
12 May 2016	Protocol amendment 6, version 7.0, addressed the following changes: - After implementation of Amendment No. 5 it was noted that some points of the protocol might lead to potential misunderstandings and needed to be further clarified. Additionally, there were in the protocol some omissions that needed to be corrected for a correct understanding and compliance. - All analyses on other non-key secondary endpoints by Week 24, Week 52, and Week 104 will be only descriptive. - Urine analysis was removed from SAE laboratory parameters. - Only SAEs will be reported and summarised in the 2nd follow-up period between Week 52 and Week 104. The reference is added to some protocol sections which were inadvertently not updated when Amendment 5 was generated. - Percentages and difference between treatments will be expressed with their 95% CI calculated with a binomial exact method stratified asymptotic Wald's CIs. Time to Clinical Remission and time to Response will be analysed with KM estimates. The estimate of the Hazard ratio of eASCs relative to placebo from stratified Cox regression, adjusting for the randomisation strata, will be presented together with 95% CI. - Immunological Analysis results will be reported independently of the Clinical Study Report.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported