

**Clinical trial results:**

A Phase III, Randomized, Double Blind, Parallel Group, Placebo Controlled, International, Multicentre Study to Assess Efficacy and Safety of Cx601, Adult Allogeneic Expanded Adipose-Derived Stem Cells (eASC), for the Treatment of Complex Perianal Fistula(s) in Patients With Crohn's Disease Over a Period of 24 Weeks and a Follow-Up Period Up to 52 Weeks

Summary

EudraCT number	2017-000725-12
Trial protocol	CZ BE ES HU PL GB DE FR SE DK IT
Global end of trial date	26 July 2023

Results information

Result version number	v1 (current)
This version publication date	28 July 2024
First version publication date	28 July 2024

Trial information**Trial identification**

Sponsor protocol code	Cx601-0303
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03279081
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TiGenix, S.A.U.
Sponsor organisation address	Parque Tecnológico de Madrid, Tres Cantos, Madrid, Spain, 28760
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

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	26 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy of darvadstrocel compared with placebo in participants with complex Crohn's perianal fistulas (CPFs) to achieve combined remission at week 24.

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 34
Country: Number of subjects enrolled	Czechia: 38
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Spain: 68
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 231
Worldwide total number of subjects	568
EEA total number of subjects	281

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	557
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 113 investigative sites in Belgium, Czechia, Denmark, France, Germany, Hungary, Israel, Italy, Poland, Spain, United Kingdom, Canada, and United States from 15 September 2017 to 26 July 2023.

Pre-assignment

Screening details:

A total of 568 participants with a diagnosis of Crohn's disease were enrolled in a 1:1 ratio to receive either Cx601 or matching placebo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo (saline) 24 milliliters (mL) was administered once by local injection.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Placebo (saline) 24 milliliters (mL) was administered once by local injection.

Arm title	Cx601
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Arm description:

Cx601 expanded adipose-derived stem cells (eASCs) 120 million cells (5 million cells per mL) was administered once by local injection.

Arm type	Experimental
Investigational medicinal product name	Cx601
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Cx601 expanded adipose-derived stem cells (eASCs) 120 million cells (5 million cells per mL) was administered once by local injection.

Number of subjects in period 1	Placebo	Cx601
Started	285	283
Completed	246	249
Not completed	39	34
Adverse event, serious fatal	-	1
Consent withdrawn by subject	12	20
Physician decision	4	1
Adverse event, non-fatal	1	-
Lost to follow-up	8	8
Reason not Specified	14	4

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo (saline) 24 milliliters (mL) was administered once by local injection.	
Reporting group title	Cx601
Reporting group description: Cx601 expanded adipose-derived stem cells (eASCs) 120 million cells (5 million cells per mL) was administered once by local injection.	

Reporting group values	Placebo	Cx601	Total
Number of subjects	285	283	568
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	37.7 ± 10.78	38.4 ± 11.91	-
Gender categorical Units: Subjects			
Female	130	121	251
Male	155	162	317
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13	13	26
Not Hispanic or Latino	250	240	490
Unknown or Not Reported	22	30	52
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	5	8	13
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	8	15
White	254	243	497
More than one race	0	0	0
Unknown or Not Reported	18	24	42
Body Mass Index (BMI) Units: Subjects			
Less than 18.5 kilograms per square meter(kg/m ²)	4	9	13
18.5 to <25.0 kg/m ²	132	110	242
25.0 to <30.0 kg/m ²	81	92	173
30.0 kg/m ² or Higher	57	67	124
Not recorded	11	5	16

Height Units: centimeters (cm) arithmetic mean standard deviation			
	±	±	-
Weight Units: kilograms (kg) arithmetic mean standard deviation			
	±	±	-

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Placebo (saline) 24 milliliters (mL) was administered once by local injection.	
Subject analysis set title	Cx601
Subject analysis set type	Sub-group analysis
Subject analysis set description: Cx601 expanded adipose-derived stem cells (eASCs) 120 million cells (5 million cells per mL) was administered once by local injection.	

Reporting group values	Placebo	Cx601	
Number of subjects	274	278	
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation			
	±	±	
Gender categorical Units: Subjects			
Female Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Body Mass Index (BMI) Units: Subjects			

Less than 18.5 kilograms per square meter(kg/m ²) 18.5 to <25.0 kg/m ² 25.0 to <30.0 kg/m ² 30.0 kg/m ² or Higher Not recorded			
Height Units: centimeters (cm) arithmetic mean standard deviation	171.78 ± 9.088	171.59 ± 9.429	
Weight Units: kilograms (kg) arithmetic mean standard deviation	77.69 ± 16.675	78.73 ± 19.620	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo (saline) 24 milliliters (mL) was administered once by local injection.	
Reporting group title	Cx601
Reporting group description: Cx601 expanded adipose-derived stem cells (eASCs) 120 million cells (5 million cells per mL) was administered once by local injection.	
Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Placebo (saline) 24 milliliters (mL) was administered once by local injection.	
Subject analysis set title	Cx601
Subject analysis set type	Sub-group analysis
Subject analysis set description: Cx601 expanded adipose-derived stem cells (eASCs) 120 million cells (5 million cells per mL) was administered once by local injection.	

Primary: Percentage of Participants with Combined Remission at Week 24

End point title	Percentage of Participants with Combined Remission at Week 24
End point description: Combined remission was defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression and absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by blinded central magnetic resonance imaging (MRI) assessment. Percentages are rounded off to whole number at the nearest decimal. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not.	
End point type	Primary
End point timeframe: Week 24	

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	283		
Units: percentage of participants				
number (confidence interval 95%)	46.32 (40.53 to 52.10)	48.76 (42.94 to 54.59)		

Statistical analyses

Statistical analysis title	Combined Remission at Week 24
Comparison groups	Placebo v Cx601

Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.571 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Combined Remission Rate
Point estimate	2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.82
upper limit	10.55

Notes:

[1] - P-value was based on stratified Cochran-Mantel-Haenszel (CMH) test adjusting for interactive web response system (IWRS) randomization stratification factors.

Secondary: Percentage of Participants with Clinical Remission at Week 24

End point title	Percentage of Participants with Clinical Remission at Week 24
End point description:	
Clinical remission was defined as closure of all treated external openings that were draining at baseline despite gentle finger compression. Percentages are rounded off to whole number at the nearest decimal. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	283		
Units: percentage of participants				
number (confidence interval 95%)	47.02 (41.22 to 52.81)	49.82 (44.00 to 55.65)		

Statistical analyses

Statistical analysis title	Clinical Remission at Week 24
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.515 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Clinical Remission Rate
Point estimate	2.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.47
upper limit	10.9

Notes:

[2] - P-value was based on stratified CMH test adjusting for IWRS randomization stratification factors.

Secondary: Percentage of Participants with Combined Remission at Week 52

End point title	Percentage of Participants with Combined Remission at Week 52
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End point description:

Combined remission was defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression, and absence of collections >2 cm (in at least 2 dimensions) confirmed by blinded central MRI assessment. Percentages are rounded off to whole number at the nearest decimal. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not.

End point type	Secondary
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End point timeframe:

Week 52

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	283		
Units: percentage of participants				
number (confidence interval 95%)	39.65 (33.97 to 45.33)	40.99 (35.26 to 46.72)		

Statistical analyses

Statistical analysis title	Combined Remission at Week 52
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.757 ^[3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Combined Remission Rate
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.77
upper limit	9.31

Notes:

[3] - P-value was based on stratified CMH test adjusting for IWRS randomization stratification factors.

Secondary: Percentage of Participants with Clinical Remission at Week 52

End point title	Percentage of Participants with Clinical Remission at Week 52
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End point description:

Clinical remission was defined as closure of all treated external openings that were draining at baseline despite gentle finger compression. Percentages are rounded off to whole number at the nearest decimal. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not.

End point type	Secondary
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End point timeframe:

Week 52

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	283		
Units: percentage of participants				
number (confidence interval 95%)	41.40 (35.69 to 47.12)	43.11 (37.34 to 48.88)		

Statistical analyses

Statistical analysis title	Clinical Remission at Week 52
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.697 ^[4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Clinical Remission Rate
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.46
upper limit	9.66

Notes:

[4] - P-value was based on stratified CMH test adjusting for IWRS randomization stratification factors.

Secondary: Percentage of Participants with Clinical Response at Week 24

End point title	Percentage of Participants with Clinical Response at Week 24
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End point description:

Clinical response was defined as closure of at least 50 percent (%) of all treated external openings that were draining at baseline despite gentle finger compression. Percentages are rounded off to whole number at the nearest decimal. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not.

End point type	Secondary
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End point timeframe:

Week 24

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	283		
Units: percentage of participants				
number (confidence interval 95%)	58.60 (52.88 to 64.31)	61.84 (56.18 to 67.50)		

Statistical analyses

Statistical analysis title	Clinical Response at Week 24
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428 ^[5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Clinical Response Rate
Point estimate	3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.76
upper limit	11.21

Notes:

[5] - P-value was based on stratified CMH test adjusting for IWRS randomization stratification factors.

Secondary: Percentage of Participants with Clinical Response at Week 52

End point title	Percentage of Participants with Clinical Response at Week 52
End point description:	Clinical response was defined as closure of at least 50% of all treated external openings that were draining at baseline, despite gentle finger compression. Percentages are rounded off to whole number at the nearest decimal. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not.
End point type	Secondary
End point timeframe:	Week 52

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	283		
Units: percentage of participants				
number (confidence interval 95%)	50.88 (45.07 to 56.68)	53.71 (47.90 to 59.52)		

Statistical analyses

Statistical analysis title	Clinical Response at Week 52
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.497 ^[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Clinical Response Rate
Point estimate	2.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.35
upper limit	11.03

Notes:

[6] - P-value was based on stratified CMH test adjusting for IWRS randomization stratification factors.

Secondary: Time to Clinical Remission at Week 24

End point title	Time to Clinical Remission at Week 24
End point description:	Time to clinical remission was defined as the time from treatment start to first visit with closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not. Overall number analyzed is the number of participants who had clinical remission at Week 24.
End point type	Secondary
End point timeframe:	Week 24

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	211		
Units: weeks				
median (confidence interval 95%)	7.14 (7.00 to 11.29)	7.00 (6.71 to 7.29)		

Statistical analyses

Statistical analysis title	Time to Clinical Remission at Week 24
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.374 ^[7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.32

Notes:

[7] - P-value was based on a stratified log-rank test adjusting for IWRS randomization stratification factors.

Secondary: Percentage of Participants with Relapse by Week 52 After Achieving Combined Remission at Week 24

End point title	Percentage of Participants with Relapse by Week 52 After Achieving Combined Remission at Week 24
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End point description:

Relapse was defined as reopening of any of the treated fistulas external openings with active drainage as clinically assessed, or the development of a perianal fluid collection >2 cm of the treated perianal fistula confirmed by centrally read MRI assessment in participants who were in combined remission at week 24. Percentages are rounded off to whole number at the nearest decimal. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not. Overall number analyzed is the number of participants who were responders (achieved combined remission) at Week 24.

End point type	Secondary
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End point timeframe:

From Week 24 to Week 52

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	138		
Units: percentage of participants				
number (confidence interval 95%)	31.06 (23.17 to 38.95)	34.06 (26.15 to 41.96)		

Statistical analyses

Statistical analysis title	Relapse by Week 52
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.599 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Relapse Rate
Point estimate	3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.28
upper limit	14.34

Notes:

[8] - P-value was based on stratified CMH test adjusting for IWRS randomization stratification factors.

Secondary: Time to Clinical Response at Week 52

End point title	Time to Clinical Response at Week 52
End point description:	
Time to clinical response was 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 despite gentle finger compression, as clinically assessed. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not. Overall number analyzed is the number of participants with clinical response at Week 52.	
End point type	Secondary
End point timeframe:	
Week 52	

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	241		
Units: weeks				
median (confidence interval 95%)	6.71 (6.29 to 6.86)	6.71 (6.43 to 7.00)		

Statistical analyses

Statistical analysis title	Time to Clinical Response at Week 52
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.717 ^[9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.16

Notes:

[9] - P-value was based on a stratified log-rank test adjusting for IWRS randomization stratification factors.

Secondary: Time to Clinical Response at Week 24

End point title	Time to Clinical Response at Week 24
End point description:	
Time to clinical response was defined as the time from treatment start to first visit with closure of at least 50% of all treated external openings that were draining at baseline, despite gentle finger compression, as clinically assessed. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not. Overall number analyzed is the number of participants with clinical response at Week 24.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232	236		
Units: weeks				
median (confidence interval 95%)	6.71 (6.29 to 6.86)	6.71 (6.43 to 7.00)		

Statistical analyses

Statistical analysis title	Time to Clinical Response at Week 24
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.833 ^[10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.18

Notes:

[10] - P-value was based on a stratified log-rank test adjusting for IWRS randomization stratification factors.

Secondary: Time to Clinical Remission at Week 52

End point title	Time to Clinical Remission at Week 52
End point description:	
Time to clinical remission was defined as the time from treatment start to first visit with closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed. The ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not. Overall number analyzed is the number of participants with clinical remission at Week 52.	
End point type	Secondary
End point timeframe:	
Week 52	

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	221		
Units: weeks				
median (confidence interval 95%)	7.14 (7.00 to 11.29)	7.00 (6.71 to 7.29)		

Statistical analyses

Statistical analysis title	Time to Clinical Remission at Week 52
Comparison groups	Placebo v Cx601
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363 ^[11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.32

Notes:

[11] - P-value was based on a stratified log-rank test adjusting for IWRS randomization stratification factors.

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), and Treatment-emergent Adverse Events of Special Interest (TEAESIs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), and Treatment-emergent Adverse Events of Special Interest (TEAESIs)
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End point description:

An adverse event(AE)=any untoward medical occurrence in a clinical investigation participant receiving a medicinal product; it did not necessarily have to have a causal relationship with this treatment. Serious adverse event(SAE)=any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization/prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital abnormality/birth defect, or was a medically significant event or required intervention to prevent at least one of the outcomes listed above, or was a suspected transmission of an infectious agent. AESIs included tumorigenicity, ectopic tissue formation, hypersensitivity reactions, transmission of infectious agents, immunogenicity/alloimmune reactions, and medication errors, as reported by the investigator. TEAE=AE whose onset occurred, severity worsened, or intensity increased after receiving the study treatment.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of follow up period (up to Week 52)

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	278		
Units: participants				
TEAEs	201	203		
TESAEs	35	41		
TEAESIs	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes in Vital Sign Parameters

End point title	Number of Participants With Clinically Significant Changes in Vital Sign Parameters
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End point description:

Vital signs included measurement of pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Clinically significant vital signs assessment was based on investigator interpretation. Number of participants with clinically significant changes in vital signs were reported. The Safety (SAF) Analysis Set included all randomized participants who received the actual study treatment.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of follow up period (up to Week 52)

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	278		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes in Laboratory Parameters

End point title	Number of Participants With Clinically Significant Changes in Laboratory Parameters
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End point description:

Laboratory parameters included blood chemistry and hematology. Clinically significant laboratory parameters assessment was based on investigator interpretation. Number of participants with clinically significant changes in laboratory parameters (hematology and blood chemistry) were reported. The SAF Analysis Set included all randomized participants who received the actual study treatment.

End point type	Secondary
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End point timeframe:

From first dose of study drug to end of follow up period (up to Week 52)

End point values	Placebo	Cx601		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	278		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to end of follow up period (up to Week 52)

Adverse event reporting additional description:

All-cause Mortality: ITT Analysis Set included all randomized participants regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not. Serious and Other Adverse Events: SAF Analysis Set included all randomized participants who received the actual study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26
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Reporting groups

Reporting group title	Cx601
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Reporting group description:

Cx601 eASCs 120 million cells (5 million cells/mL) was administered once by local injection.

Reporting group title	Placebo
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Reporting group description:

Placebo (saline) 24 mL was administered once by local injection.

Serious adverse events	Cx601	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 278 (14.75%)	35 / 274 (12.77%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fallopian tube cancer	Additional description: Number of participants at risk in each arm is based on the female population in this study.		
subjects affected / exposed ^[1]	0 / 121 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian cancer	Additional description: Number of participants at risk in each arm is based on the female population in this study.		
subjects affected / exposed ^[2]	0 / 121 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 278 (0.36%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			

subjects affected / exposed	4 / 278 (1.44%)	4 / 274 (1.46%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal discomfort			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal disorder			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	2 / 278 (0.72%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 278 (0.00%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 278 (0.00%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	5 / 278 (1.80%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	3 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 278 (0.72%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 278 (0.00%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula	Additional description: Number of participants at risk in each arm is based on the female population in this study.		

subjects affected / exposed ^[3]	1 / 121 (0.83%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	12 / 278 (4.32%)	12 / 274 (4.38%)	
occurrences causally related to treatment / all	3 / 14	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abscess limb			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 278 (1.08%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histoplasmosis disseminated			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 278 (0.36%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 278 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 278 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Number of participants at risk in each arm is based on the female population in this study.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Number of participants at risk in each arm is based on the female population in this study.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Number of participants at risk in each arm is based on the female population in this study.

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cx601	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 278 (23.74%)	67 / 274 (24.45%)	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	13 / 278 (4.68%)	16 / 274 (5.84%)	
occurrences (all)	16	18	
Proctalgia			
subjects affected / exposed	40 / 278 (14.39%)	40 / 274 (14.60%)	
occurrences (all)	43	52	
Infections and infestations			
COVID-19			
subjects affected / exposed	21 / 278 (7.55%)	22 / 274 (8.03%)	
occurrences (all)	22	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2018	The following changes were made as per Amendment 1: 1. Updated the number of study sites from approximately 100 to approximately 150. 2. Increased the screening period to a maximum of 5 weeks between signing of the ICF to the preparation visit and specified a minimum of 2 weeks and a maximum of 3 weeks between the preparation visit and Visit 0 (treatment administration visit). 3. Added a definition of severe anal and/or rectal stenosis to exclusion criterion. 4. Added major surgery within 6 months of screening to exclusion criterion. 5. Specified variables to assess safety throughout the study. 6. Added guidelines on rescheduling Visit 0 if needed. 7. Added classifications of possible causal relationships between AEs and the investigational medicinal product (IMP) administration procedure.
27 October 2019	The following changes were made as per Amendment 3: 1. Added an exploratory objective related to microbiome diversity. 2. Increased the study sample size 326 participants to 554 participants. 3. Added assessments to the screening visit. 4. Changed one of the key secondary endpoints from "clinical response" to "time to clinical remission." 5. Consistency update to treatment administration. 6. Removed text specifying a shelf life of 48 hours for darvadstrocel. 7. Added text regarding steps to maintain study blind. 8. Added a new section defining AESIs to reflect editorial changes to safety endpoints. 9. Added AESI reporting requirements. 10. Updated pregnancy reporting requirements. 11. Added the per-protocol (PP) analysis set and removed the SAF analysis set. 12. Changed analysis population for exploratory efficacy variables from mITT to ITT. 13. Updated to the subgroup analysis section to include subgroup analysis for each of the 2 stratification factors, concomitant treatment (4 levels), and region with United States (US) and non-US as the subgroups of interest. 14. Updated the schedule of assessments table to include optional samples of fistula curettage, fistula exudate, fistula swab for microbiome analysis, and fecal sample for microbiome analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported