# 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 |

**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 |

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 | 37.7 | 38.4 | |
| standard deviation | ± 10.78 | ± 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<br>Units: centimeters (cm)<br>arithmetic mean<br>standard deviation | ±<br> | ±<br> | -<br> |
| Weight<br>Units: kilograms (kg)<br>arithmetic mean<br>standard deviation | ±<br> | ±<br> | -<br> |

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

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

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 |

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 |
|---|---|

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 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cx601 |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Placebo |

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