



## Clinical trial results:

### A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous CXA-201 and Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-023452-87    |
| Trial protocol           | DE HU SK LV EE RO |
| Global end of trial date | 04 September 2013 |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v2 (current)   |
| This version publication date     | 06 May 2016  |
| First version publication date    | 05 August 2015   |
| Version creation reason           | <ul style="list-style-type: none"><li>Changes to summary attachments</li></ul> Adding attachment which contains a clarifying statement regarding sister study results. |
| Summary attachment (see zip file) | statement regarding sister study results (7625A-005+6_2016-04-20_EudraCT_DualResultStatement.docx)   |

#### Trial information

##### Trial identification

|                       |                                   |
|-----------------------|-----------------------------------|
| Sponsor protocol code | CXA-cUTI-10-04 and CXA-cUTI-10-05 |
|-----------------------|-----------------------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01345929 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Cubist Pharmaceuticals, Inc.                                |
| Sponsor organisation address | 65 Hayden Avenue, Lexington, United States,                 |
| Public contact               | Study Director, Cubist Pharmaceuticals, Inc., 1 7818608660, |
| Scientific contact           | Study Director, Cubist Pharmaceuticals, Inc., 1 7818608660, |

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                       | 04 September 2013 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 04 September 2013 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 04 September 2013 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

This is a Phase 3, multicenter, prospective, randomized, double-blind, double dummy study of CXA-201 intravenous (IV) infusions (1500 milligrams [mg] total, including 1000 mg ceftolozane and 500 mg tazobactam, every 8 hours [q8h]) versus levofloxacin IV infusions (750 mg once a day [qd]) for the treatment of adults with a complicated urinary tract infection (cUTI; including pyelonephritis).

Two Phase 3 protocols were initiated (CXA-cUTI-10-04 and CXA-cUTI-10-05). Then, Cubist and the FDA agreed that integrated data from the 2 protocols could be analyzed and reported in a single Clinical Study Report. A total of 1083 subjects were enrolled: 558 to CXA-cUTI-10-04 and 525 to CXA-cUTI-10-05. Of these, 552 and 516 received treatment.

One subject's age was unknown after enrollment, so this subject is counted in the "Adults (18-64 years)" age category for the purpose of this report.

Protection of trial subjects:

This study was conducted in compliance with institutional review board (IRB)/independent ethics committee (IEC) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B R3), with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10), and with guidelines of local regulatory agencies. In addition, this study adhered to all local regulatory requirements, and requirements for data protection.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 01 June 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Brazil: 17   |
| Country: Number of subjects enrolled | Bulgaria: 15 |
| Country: Number of subjects enrolled | Chile: 1     |
| Country: Number of subjects enrolled | Colombia: 41 |
| Country: Number of subjects enrolled | Croatia: 12  |
| Country: Number of subjects enrolled | Estonia: 27  |
| Country: Number of subjects enrolled | Georgia: 60  |
| Country: Number of subjects enrolled | Hungary: 71  |
| Country: Number of subjects enrolled | India: 38    |
| Country: Number of subjects enrolled | Israel: 24   |
| Country: Number of subjects enrolled | Latvia: 53   |

|                                      |                          |
|--------------------------------------|--------------------------|
| Country: Number of subjects enrolled | Mexico: 27               |
| Country: Number of subjects enrolled | Moldova, Republic of: 17 |
| Country: Number of subjects enrolled | Peru: 32                 |
| Country: Number of subjects enrolled | Serbia: 5                |
| Country: Number of subjects enrolled | Poland: 77               |
| Country: Number of subjects enrolled | Romania: 115             |
| Country: Number of subjects enrolled | Russian Federation: 188  |
| Country: Number of subjects enrolled | Slovakia: 5              |
| Country: Number of subjects enrolled | Slovenia: 7              |
| Country: Number of subjects enrolled | South Africa: 13         |
| Country: Number of subjects enrolled | Korea, Republic of: 16   |
| Country: Number of subjects enrolled | Thailand: 39             |
| Country: Number of subjects enrolled | Ukraine: 160             |
| Country: Number of subjects enrolled | United States: 23        |
| Worldwide total number of subjects   | 1083                     |
| EEA total number of subjects         | 382                      |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 802 |
| From 65 to 84 years                       | 261 |
| 85 years and over                         | 20  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects enrolled in this study were at least 18 years of age with a complicated urinary tract infection. Subjects were eligible to participate in the study if they met all of the inclusion criteria and none of the exclusion criteria at the Screening visit.

### 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, Carer, Assessor |

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | CXA-201 as treatment for cUTI |

Arm description:

CXA-201 IV infusion (1000 mg of ceftolozane and 500 mg of tazobactam) every 8 hours for 7 days.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | CXA-201                |
| Investigational medicinal product code |                        |
| Other name                             | Ceftolozane/Tazobactam |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

1500 mg (1000 mg of ceftolozane and 500 mg of tazobactam) every 8 hours for 7 days

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Levofloxacin as treatment for cUTI |
|------------------|------------------------------------|

Arm description:

Levofloxacin IV infusion (750 mg qd) for 7 days.

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | levofloxacin           |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

750 mg once daily for 7 days

| <b>Number of subjects in period 1</b> | CXA-201 as treatment for cUTI | Levofloxacin as treatment for cUTI |
|---------------------------------------|-------------------------------|------------------------------------|
| Started                               | 543                           | 540                                |
| Completed                             | 513                           | 515                                |
| Not completed                         | 30                            | 25                                 |
| Consent withdrawn by subject          | 13                            | 10                                 |
| Adverse event, non-fatal              | -                             | 1                                  |
| Not specified                         | 7                             | 4                                  |
| Lost to follow-up                     | 9                             | 10                                 |
| Lack of Informed Consent              | 1                             | -                                  |

## Baseline characteristics

### Reporting groups

|   |                                    |
|---|------------------------------------|
| Reporting group title   | CXA-201 as treatment for cUTI      |
| Reporting group description:<br>CXA-201 IV infusion (1000 mg of ceftolozane and 500 mg of tazobactam) every 8 hours for 7 days. |                                    |
| Reporting group title   | Levofloxacin as treatment for cUTI |
| Reporting group description:<br>Levofloxacin IV infusion (750 mg qd) for 7 days.  |                                    |

| Reporting group values  | CXA-201 as treatment for cUTI | Levofloxacin as treatment for cUTI | Total |
|---|-------------------------------|------------------------------------|-------|
| Number of subjects  | 543                           | 540                                |       |
| Age categorical<br>Units: Subjects                                      |                               |                                    |       |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 49.8<br>± 19.6                | 48.7<br>± 20.1                     | -     |
| Gender, Male/Female<br>Units: participants                              |                               |                                    |       |
| Female  |                               |                                    | 0     |
| Male  |                               |                                    | 0     |

### Subject analysis sets

|  |  |
|--|--|
| Subject analysis set title   | CXA-201 as treatment for cUTI - Safety Population      |
| Subject analysis set type  | Safety analysis  |
| Subject analysis set description:<br>All subjects who received any amount of the study drug. Subjects in the Safety population were categorised based on the actual treatment that the subjects received, irrespective of the treatment to which they were randomised.   |  |
| Subject analysis set title   | Levofloxacin as treatment for cUTI - Safety Population |
| Subject analysis set type  | Safety analysis  |
| Subject analysis set description:<br>All subjects who received any amount of the study drug. Subjects in the Safety population were categorised based on the actual treatment that the subjects received, irrespective of the treatment to which they were randomised.   |  |
| Subject analysis set title   | CXA-201 as treatment for cUTI - ME Population          |
| Subject analysis set type  | Sub-group analysis                                     |
| Subject analysis set description:<br>The microbiologically evaluable (ME) population is a subset of the clinically evaluable (CE) population who adhered to study procedures and had an appropriately collected urine culture specimen and interpretable urine culture result at the TOC visit. The CE population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria. |  |
| Subject analysis set title   | Levofloxacin as treatment for cUTI - ME Population     |
| Subject analysis set type  | Sub-group analysis                                     |

Subject analysis set description:

The microbiologically evaluable (ME) population is a subset of the clinically evaluable (CE) population who adhered to study procedures and had an appropriately collected urine culture specimen and interpretable urine culture result at the TOC visit. The CE population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria.

|                            |  |
|----------------------------|--|
| Subject analysis set title | CXA-201 as treatment for cUTI - mMITT Population |
| Subject analysis set type  | Sub-group analysis                               |

Subject analysis set description:

The microbiological modified intent-to-treat (mMITT) population was a subset of the modified intent-to-treat (MITT) population that included subjects who had at least 1 qualified uropathogen from a study-qualifying pretreatment baseline urine specimen. The MITT population consisted of all randomised subjects who received any amount of study drug.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Levofloxacin as treatment for cUTI - mMITT Population |
| Subject analysis set type  | Sub-group analysis                                    |

Subject analysis set description:

The microbiological modified intent-to-treat (mMITT) population was a subset of the modified intent-to-treat (MITT) population that included subjects who had at least 1 qualified uropathogen from a study-qualifying pretreatment baseline urine specimen. The MITT population consisted of all randomised subjects who received any amount of study drug.

| Reporting group values             | CXA-201 as treatment for cUTI - Safety Population | Levofloxacin as treatment for cUTI - Safety Population | CXA-201 as treatment for cUTI - ME Population |
|------------------------------------|---|--|---|
| Number of subjects                 | 533   | 535  | 340   |
| Age categorical<br>Units: Subjects |   |  |   |

|   |     |     |   |
|---|-----|-----|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ±   | ±   | ± |
| Gender, Male/Female<br>Units: participants                              |     |     |   |
| Female  | 374 | 380 |   |
| Male  | 159 | 155 |   |

| Reporting group values             | Levofloxacin as treatment for cUTI - ME Population | CXA-201 as treatment for cUTI - mMITT Population | Levofloxacin as treatment for cUTI - mMITT Population |
|------------------------------------|--|--|---|
| Number of subjects                 | 353  | 398  | 402   |
| Age categorical<br>Units: Subjects |  |  |   |

|   |   |   |   |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ± | ± | ± |
| Gender, Male/Female<br>Units: participants                              |   |   |   |
| Female  |   |   |   |
| Male  |   |   |   |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | CXA-201 as treatment for cUTI                          |
| Reporting group description:<br>CXA-201 IV infusion (1000 mg of ceftolozane and 500 mg of tazobactam) every 8 hours for 7 days.  |  |
| Reporting group title  | Levofloxacin as treatment for cUTI                     |
| Reporting group description:<br>Levofloxacin IV infusion (750 mg qd) for 7 days.   |  |
| Subject analysis set title   | CXA-201 as treatment for cUTI - Safety Population      |
| Subject analysis set type  | Safety analysis  |
| Subject analysis set description:<br>All subjects who received any amount of the study drug. Subjects in the Safety population were categorised based on the actual treatment that the subjects received, irrespective of the treatment to which they were randomised.   |  |
| Subject analysis set title   | Levofloxacin as treatment for cUTI - Safety Population |
| Subject analysis set type  | Safety analysis  |
| Subject analysis set description:<br>All subjects who received any amount of the study drug. Subjects in the Safety population were categorised based on the actual treatment that the subjects received, irrespective of the treatment to which they were randomised.   |  |
| Subject analysis set title   | CXA-201 as treatment for cUTI - ME Population          |
| Subject analysis set type  | Sub-group analysis                                     |
| Subject analysis set description:<br>The microbiologically evaluable (ME) population is a subset of the clinically evaluable (CE) population who adhered to study procedures and had an appropriately collected urine culture specimen and interpretable urine culture result at the TOC visit. The CE population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria. |  |
| Subject analysis set title   | Levofloxacin as treatment for cUTI - ME Population     |
| Subject analysis set type  | Sub-group analysis                                     |
| Subject analysis set description:<br>The microbiologically evaluable (ME) population is a subset of the clinically evaluable (CE) population who adhered to study procedures and had an appropriately collected urine culture specimen and interpretable urine culture result at the TOC visit. The CE population was a subset of the intention-to-treat (ITT) population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a test-of-cure (TOC) visit within the specified visit window. Subjects in this population had no confounding factors that interfered with the assessment of outcome and met the key inclusion/exclusion criteria and additional protocol-defined criteria. |  |
| Subject analysis set title   | CXA-201 as treatment for cUTI - mMITT Population       |
| Subject analysis set type  | Sub-group analysis                                     |
| Subject analysis set description:<br>The microbiological modified intent-to-treat (mMITT) population was a subset of the modified intent-to-treat (MITT) population that included subjects who had at least 1 qualified uropathogen from a study-qualifying pretreatment baseline urine specimen. The MITT population consisted of all randomised subjects who received any amount of study drug.  |  |
| Subject analysis set title   | Levofloxacin as treatment for cUTI - mMITT Population  |
| Subject analysis set type  | Sub-group analysis                                     |
| Subject analysis set description:<br>The microbiological modified intent-to-treat (mMITT) population was a subset of the modified intent-to-treat (MITT) population that included subjects who had at least 1 qualified uropathogen from a study-qualifying pretreatment baseline urine specimen. The MITT population consisted of all randomised subjects who received any amount of study drug.  |  |



**Primary: The percentage of subjects who have both a per-subject microbiological outcome of eradication and a clinical outcome of cure at the Test of Cure (TOC) Visit in the Microbiologically Evaluable (ME) Population**

|   |   |
|---|---|
| End point title   | The percentage of subjects who have both a per-subject microbiological outcome of eradication and a clinical outcome of cure at the Test of Cure (TOC) Visit in the Microbiologically Evaluable (ME) Population |
| End point description:  |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| Test of Cure Visit (7 Days [ $\pm$ 2 days] after completion of study drug administration) |   |

| End point values              | CXA-201 as treatment for cUTI - ME Population | Levofloxacin as treatment for cUTI - ME Population |  |  |
|-------------------------------|---|--|--|--|
| Subject group type            | Subject analysis set                          | Subject analysis set                               |  |  |
| Number of subjects analysed   | 340   | 353  |  |  |
| Units: percentage of subjects |   |  |  |  |
| number (not applicable)       | 84.7  | 75.4   |  |  |

**Statistical analyses**

|   |  |
|---|--|
| Statistical analysis title              | STATISTICAL_ANALYSIS   |
| Comparison groups                       | CXA-201 as treatment for cUTI - ME Population v Levofloxacin as treatment for cUTI - ME Population |
| Number of subjects included in analysis | 693  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | non-inferiority <sup>[1]</sup>   |
| Parameter estimate                      | Risk difference (RD)   |
| Point estimate                          | 9.4  |
| Confidence interval                     |  |
| level                                   | Other: 99 %  |
| sides                                   | 2-sided  |
| lower limit                             | 1.54   |
| upper limit                             | 17.12  |

Notes:

[1] - Non-inferiority was concluded if the lower bound of the 2-sided 99% CI was greater than -10%.

**Secondary: The percentage of subjects who have both a per-subject microbiological outcome of eradication and a clinical outcome of cure at the TOC Visit in the microbiological modified intent to-treat (mMITT) population**

|                        |  |
|------------------------|--|
| End point title        | The percentage of subjects who have both a per-subject microbiological outcome of eradication and a clinical outcome of cure at the TOC Visit in the microbiological modified intent to-treat (mMITT) population |
| End point description: |  |

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Test of Cure Visit (7 Days [ $\pm$ 2 days] after completion of study drug administration) |           |

| End point values              | CXA-201 as treatment for cUTI - mMITT Population | Levofloxacin as treatment for cUTI - mMITT Population |  |  |
|-------------------------------|--|---|--|--|
| Subject group type            | Subject analysis set                             | Subject analysis set                                  |  |  |
| Number of subjects analysed   | 398  | 402   |  |  |
| Units: percentage of subjects |  |   |  |  |
| number (not applicable)       | 78.6   | 69.9  |  |  |

### Statistical analyses

| Statistical analysis title              | Statistical Analysis   |
|---|--|
| Comparison groups                       | CXA-201 as treatment for cUTI - mMITT Population v Levofloxacin as treatment for cUTI - mMITT Population |
| Number of subjects included in analysis | 800  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | non-inferiority <sup>[2]</sup>   |
| Parameter estimate                      | Risk difference (RD)   |
| Point estimate                          | 8.7  |
| Confidence interval                     |  |
| level                                   | Other: 99 %  |
| sides                                   | 2-sided  |
| lower limit                             | 0.77   |
| upper limit                             | 16.57  |

Notes:

[2] - Non-inferiority was concluded if the lower bound of the 2-sided 99% CI was greater than -10%.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded for all subjects from the start of study drug administration through the last follow up visit, which occurred 28 to 35 days after the last dose of study drug.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

### Reporting groups

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Levofloxacin as treatment for cUTI |
|-----------------------|------------------------------------|

Reporting group description:

Levofloxacin IV infusion (750 mg qd) for 7 days

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | CXA-201 as treatment for cUTI |
|-----------------------|-------------------------------|

Reporting group description:

CXA-201 IV infusion (1500 mg q8) for 7 days

| Serious adverse events  | Levofloxacin as treatment for cUTI | CXA-201 as treatment for cUTI |  |
|---|------------------------------------|-------------------------------|--|
| Total subjects affected by serious adverse events                   |                                    |                               |  |
| subjects affected / exposed   | 18 / 535 (3.36%)                   | 15 / 533 (2.81%)              |  |
| number of deaths (all causes)                                       | 0                                  | 1                             |  |
| number of deaths resulting from adverse events                      | 0                                  | 0                             |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                    |                               |  |
| Bladder cancer  |                                    |                               |  |
| subjects affected / exposed   | 0 / 535 (0.00%)                    | 2 / 533 (0.38%)               |  |
| occurrences causally related to treatment / all                     | 0 / 0                              | 0 / 2                         |  |
| deaths causally related to treatment / all                          | 0 / 0                              | 0 / 1                         |  |
| Injury, poisoning and procedural complications                      |                                    |                               |  |
| Pneumothorax traumatic  |                                    |                               |  |
| subjects affected / exposed   | 1 / 535 (0.19%)                    | 0 / 533 (0.00%)               |  |
| occurrences causally related to treatment / all                     | 0 / 1                              | 0 / 0                         |  |
| deaths causally related to treatment / all                          | 0 / 0                              | 0 / 0                         |  |
| Cardiac disorders   |                                    |                               |  |
| Cardiac failure congestive  |                                    |                               |  |
| subjects affected / exposed   | 1 / 535 (0.19%)                    | 0 / 533 (0.00%)               |  |
| occurrences causally related to treatment / all                     | 0 / 1                              | 0 / 0                         |  |
| deaths causally related to treatment / all                          | 0 / 0                              | 0 / 0                         |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Angina unstable<br>subjects affected / exposed  | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Nervous system disorders<br>Transient ischaemic attack<br>subjects affected / exposed   | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| General disorders and administration<br>site conditions<br>Hernia obstructive<br>subjects affected / exposed                  | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Immune system disorders<br>Contrast media allergy<br>subjects affected / exposed  | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Eye disorders<br>Diabetic retinopathy<br>subjects affected / exposed  | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders<br>Gastric ulcer<br>subjects affected / exposed  | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Chronic obstructive pulmonary<br>disease<br>subjects affected / exposed | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Renal and urinary disorders                     |                 |                 |  |
| Calculus urinary                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal colic                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular acidosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 535 (0.19%) | 0 / 533 (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                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal abscess                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Emphysematous pyelonephritis                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pseudomembranous colitis                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 2 / 533 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 1 / 533 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 6 / 535 (1.12%) | 0 / 533 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 535 (0.19%) | 0 / 533 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 535 (0.00%) | 2 / 533 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 535 (0.37%) | 3 / 533 (0.56%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Levofloxacin as treatment for cUTI | CXA-201 as treatment for cUTI |  |
|---|------------------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events |                                    |                               |  |
| subjects affected / exposed                           | 26 / 535 (4.86%)                   | 31 / 533 (5.82%)              |  |
| Nervous system disorders                              |                                    |                               |  |
| Headache  |                                    |                               |  |
| subjects affected / exposed                           | 26 / 535 (4.86%)                   | 31 / 533 (5.82%)              |  |
| occurrences (all)                                     | 26                                 | 35                            |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| Two identical protocols were initiated (CXA-cUTI-10-04 and CXA-cUTI-10-05). Then, Cubist and the FDA agreed that integrated data from the 2 protocols could be analyzed and reported in a single Clinical Study Report. These analyses are presented here. |
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Notes: