



## Clinical trial results:

### A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Moxifloxacin IV/PO for Treating Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2013-004071-13                |
| Trial protocol           | SK HU CZ LV DE ES BE PL GR HR |
| Global end of trial date | 17 February 2017              |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 14 April 2018 |
| First version publication date | 14 April 2018 |

#### Trial information

##### Trial identification

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | PTK0796-CABP-1200 |
|-----------------------|-------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02531438 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Paratek Pharma LLC  |
| Sponsor organisation address | 75 Park Plaza, Boston, MA, 02116, United States,                    |
| Public contact               | Head of Clinical of Development, Paratek Pharma LLC, +1 6172750040, |
| Scientific contact           | Head of Clinical of Development, Paratek Pharma LLC, +1 6172750040, |

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                       | 30 January 2018  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 17 February 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 17 February 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate that omadacycline 100 mg intravenous (iv) once every 12 hours (q12h) for 2 doses, followed by 100 mg iv/300 mg per oral (po) once every 24 hours (q24h) is non-inferior to moxifloxacin 400 mg iv/po q24h in the treatment of adults with CABP with a Pneumonia Outcomes Research Team (PORT) Risk Class of III/IV.

Protection of trial subjects:

The switching from iv to po treatment, the first dose of po therapy should begin in the morning, 24 hours after the last iv dose, to ensure the subjects continued to receive uninterrupted daily therapy. To facilitate study enrollment infusion times were adjusted to iv q12h (first 2 doses), followed by iv q24h (starting 24 hours after first dose) and switch to po q24h after at least 3 days (4 doses) of iv treatment infusion interval to achieve desired administration schedule.

Background therapy: -

Evidence for comparator:

Moxifloxacin was selected as the optimal comparator, given its long history of efficacy and tolerability. Moxifloxacin has a similar spectrum of activity with coverage against the most common typical and atypical causes of CABP. Moxifloxacin can be administered iv and po and has regulatory approval for the treatment of CABP.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 06 November 2015 |
| 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 | Poland: 40             |
| Country: Number of subjects enrolled | Romania: 61            |
| Country: Number of subjects enrolled | Slovakia: 4            |
| Country: Number of subjects enrolled | Spain: 1               |
| Country: Number of subjects enrolled | Croatia: 81            |
| Country: Number of subjects enrolled | Bulgaria: 105          |
| Country: Number of subjects enrolled | Czech Republic: 27     |
| Country: Number of subjects enrolled | Greece: 30             |
| Country: Number of subjects enrolled | Hungary: 81            |
| Country: Number of subjects enrolled | Latvia: 37             |
| Country: Number of subjects enrolled | United States: 3       |
| Country: Number of subjects enrolled | Georgia: 26            |
| Country: Number of subjects enrolled | Russian Federation: 26 |

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Ukraine: 157     |
| Country: Number of subjects enrolled | Brazil: 4        |
| Country: Number of subjects enrolled | Israel: 19       |
| Country: Number of subjects enrolled | Peru: 8          |
| Country: Number of subjects enrolled | Philippines: 31  |
| Country: Number of subjects enrolled | Turkey: 2        |
| Country: Number of subjects enrolled | Taiwan: 1        |
| Country: Number of subjects enrolled | South Africa: 29 |
| Country: Number of subjects enrolled | Mexico: 1        |
| Worldwide total number of subjects   | 774              |
| EEA total number of subjects         | 467              |

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)                      | 450 |
| From 65 to 84 years                       | 285 |
| 85 years and over                         | 39  |

## Subject disposition

### Recruitment

#### Recruitment details:

The study is designed to enroll adults with CABP. Subject randomization was stratified by PORT Risk Class (II or III/IV), receipt of an allowed antibacterial therapy in the 72 hours prior to study treatment, and geographic region. All subjects were expected to present with CABP severe enough to require a minimum of at least 3 days of iv treatment.

### Pre-assignment

#### Screening details:

Subjects who met inclusion criteria and did not meet exclusion criteria will be randomly assigned to a treatment group, and should receive their first dose of test article within 4 hours after randomization. All subjects were expected to present with CABP PORT Risk Class II, III, or IV to require a minimum of at least 3 days of iv treatment

### Period 1

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

#### Blinding implementation details:

Treatment phase (both iv and po) of the study was double-blind and double-dummy. In an effort to maintain blinding, each site employed shrouding of the iv bag and iv lines used for infusion of test article. To maintain double-blinding, subjects in each study arm will receive the same infusion volumes with the same blinded administration instructions and when switch to PO subjects will receive 2 tablets and 1 over-encapsulated tablet in the morning

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Omadacycline |

#### Arm description:

Omadacycline, 100 mg iv q12h (first 2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg (two 150 mg omadacycline tablets and 1 over-encapsulated placebo tablet matching moxifloxacin) po q24h after at least 3 days (4 doses) of iv treatment. The total duration of test article therapy (iv plus po) for all subjects was at least 7 days and no more than 14 days.

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Omadacycline                |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Powder for infusion, Tablet |
| Routes of administration               | Intravenous use, Oral use   |

#### Dosage and administration details:

2 doses of Omadacycline (100 mg) iv every 12 hours, followed by 100 mg iv every 24 hours, with the option to switch 300 mg po every 24 hours.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Moxifloxacin |
|------------------|--------------|

#### Arm description:

Moxifloxacin, 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1) with the option to switch to 400 mg (one 400 mg moxifloxacin over-encapsulated tablet and 2 placebo tablets matching omadacycline tablets) po q24h after at least 3 days (4 doses) of iv treatment. The total duration of test article therapy (iv plus po) for all subjects was at least 7 days and no more than 14 days.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |                               |
|--|-------------------------------|
| Investigational medicinal product name | Moxifloxacin                  |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Solution for infusion, Tablet |
| Routes of administration               | Intravenous use, Oral use     |

Dosage and administration details:

Moxifloxacin 400 mg iv q24h with the option to switch to 400 mg po q24h.

| <b>Number of subjects in period 1</b> | Omadacycline | Moxifloxacin |
|---------------------------------------|--------------|--------------|
| Started                               | 386          | 388          |
| Completed                             | 352          | 346          |
| Not completed                         | 34           | 42           |
| Consent withdrawn by subject          | 4            | 3            |
| Physician decision                    | 3            | 9            |
| Death                                 | 4            | 1            |
| Other                                 | 6            | -            |
| Adverse event                         | 17           | 28           |
| Lost to follow-up                     | -            | 1            |

## Baseline characteristics

### Reporting groups

|                                |                    |
|--------------------------------|--------------------|
| Reporting group title          | Treatment period 1 |
| Reporting group description: - |                    |

| Reporting group values                             | Treatment period 1 | Total |  |
|--|--------------------|-------|--|
| Number of subjects                                 | 774                | 774   |  |
| Age categorical                                    |                    |       |  |
| Units: Subjects                                    |                    |       |  |
| In utero   | 0                  | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0                  | 0     |  |
| Newborns (0-27 days)                               | 0                  | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0                  | 0     |  |
| Children (2-11 years)                              | 0                  | 0     |  |
| Adolescents (12-17 years)                          | 0                  | 0     |  |
| Adults (18-64 years)                               | 450                | 450   |  |
| From 65-84 years                                   | 324                | 324   |  |
| 85 years and over                                  | 0                  | 0     |  |
| Gender categorical                                 |                    |       |  |
| Units: Subjects                                    |                    |       |  |
| Female   | 347                | 347   |  |
| Male   | 427                | 427   |  |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT population     |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

The ITT population consisted of all randomized subjects regardless of whether or not the subject received test article. A subject was considered randomized when the Interactive Response System provided the test article assignment (ie, completed a randomization transaction).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Safety population |
| Subject analysis set type  | Safety analysis   |

Subject analysis set description:

The Safety population consisted of all randomized subjects who received test article (either active or placebo). All safety analyses were conducted in this population.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | CE - EOT population |
| Subject analysis set type  | Full analysis       |

Subject analysis set description:

Two CE analysis sets were defined, the CE-EOT and CE-PTE. The CE population consisted of all ITT subjects who received test article, have a qualifying CABP, an assessment of outcome, and met all other evaluability criteria.

CE-EOT: The number and percentage of subjects in each treatment group with a clinical success, clinical failure, at EOT visit occurred on the day of, or within 2 days following the last dose of test article based on the investigator's assessment.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | microITT population |
|----------------------------|---------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The microITT population consisted of all subjects in the ITT population who had at least 1 causative bacterial pathogen identified from a culture of a respiratory specimen (eg, respiratory fluid obtained by BAL or bronchoscopy, pleural fluid obtained by thoracentesis, or expectorated or induced sputum meeting adequacy criteria as defined by the Gram stain results), culture of blood, or from a culture-independent method (eg, positive urinary antigen test [UAT] for *Streptococcus pneumoniae* or *Legionella pneumophila*, or positive serology for *Legionella pneumophila*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*) at Baseline.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | CE-PTE population |
|----------------------------|-------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Two CE analysis sets were defined, the CE-EOT and CE-PTE. The CE population consisted of all ITT subjects who received test article, have a qualifying CABP, an assessment of outcome, and met all other evaluability criteria.

CE-PTE: The number and percentage of subjects in each treatment group with a clinical success, clinical failure, and indeterminate for the overall assessment of clinical response at PTE visit. PTE visit occurred 5 to 10 days after the last dose of test article (based on the investigator's assessment) unless the subject was considered to be a clinical failure based on the investigator's assessment at the EOT visit or the subject died after EOT and before PTE.

| Reporting group values                                | ITT population | Safety population | CE - EOT population |
|---|----------------|-------------------|---------------------|
| Number of subjects                                    | 774            | 770               | 714                 |
| Age categorical<br>Units: Subjects                    |                |                   |                     |
| In utero  | 0              |                   |                     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 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)                                  | 450            |                   |                     |
| From 65-84 years                                      | 324            |                   |                     |
| 85 years and over                                     | 0              |                   |                     |
| Gender categorical<br>Units: Subjects                 |                |                   |                     |
| Female  | 347            |                   |                     |
| Male  | 427            |                   |                     |

| Reporting group values                                | microITT population | CE-PTE population |  |
|---|---------------------|-------------------|--|
| Number of subjects                                    | 386                 | 685               |  |
| Age categorical<br>Units: Subjects                    |                     |                   |  |
| In utero  |                     |                   |  |
| Preterm newborn infants<br>(gestational age < 37 wks) |                     |                   |  |
| Newborns (0-27 days)                                  |                     |                   |  |
| Infants and toddlers (28 days-23 months)              |                     |                   |  |
| Children (2-11 years)                                 |                     |                   |  |
| Adolescents (12-17 years)                             |                     |                   |  |
| Adults (18-64 years)                                  |                     |                   |  |
| From 65-84 years                                      |                     |                   |  |

|                   |  |  |  |
|-------------------|--|--|--|
| 85 years and over |  |  |  |
|-------------------|--|--|--|

|                    |  |  |  |
|--------------------|--|--|--|
| Gender categorical |  |  |  |
| Units: Subjects    |  |  |  |
| Female             |  |  |  |
| Male               |  |  |  |

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## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Omadacycline |
|-----------------------|--------------|

Reporting group description:

Omadacycline, 100 mg iv q12h (first 2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg (two 150 mg omadacycline tablets and 1 over-encapsulated placebo tablet matching moxifloxacin) po q24h after at least 3 days (4 doses) of iv treatment. The total duration of test article therapy (iv plus po) for all subjects was at least 7 days and no more than 14 days.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Moxifloxacin |
|-----------------------|--------------|

Reporting group description:

Moxifloxacin, 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1) with the option to switch to 400 mg (one 400 mg moxifloxacin over-encapsulated tablet and 2 placebo tablets matching omadacycline tablets) po q24h after at least 3 days (4 doses) of iv treatment. The total duration of test article therapy (iv plus po) for all subjects was at least 7 days and no more than 14 days.

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | ITT population |
|----------------------------|----------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The ITT population consisted of all randomized subjects regardless of whether or not the subject received test article. A subject was considered randomized when the Interactive Response System provided the test article assignment (ie, completed a randomization transaction).

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Safety population |
|----------------------------|-------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The Safety population consisted of all randomized subjects who received test article (either active or placebo). All safety analyses were conducted in this population.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | CE - EOT population |
|----------------------------|---------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Two CE analysis sets were defined, the CE-EOT and CE-PTE. The CE population consisted of all ITT subjects who received test article, have a qualifying CABP, an assessment of outcome, and met all other evaluability criteria.

CE-EOT: The number and percentage of subjects in each treatment group with a clinical success, clinical failure, at EOT visit occurred on the day of, or within 2 days following the last dose of test article based on the investigator's assessment.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | microITT population |
|----------------------------|---------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The microITT population consisted of all subjects in the ITT population who had at least 1 causative bacterial pathogen identified from a culture of a respiratory specimen (eg, respiratory fluid obtained by BAL or bronchoscopy, pleural fluid obtained by thoracentesis, or expectorated or induced sputum meeting adequacy criteria as defined by the Gram stain results), culture of blood, or from a culture-independent method (eg, positive urinary antigen test [UAT] for *Streptococcus pneumoniae* or *Legionella pneumophila*, or positive serology for *Legionella pneumophila*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*) at Baseline.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | CE-PTE population |
|----------------------------|-------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Two CE analysis sets were defined, the CE-EOT and CE-PTE. The CE population consisted of all ITT subjects who received test article, have a qualifying CABP, an assessment of outcome, and met all other evaluability criteria.

CE-PTE: The number and percentage of subjects in each treatment group with a clinical success, clinical failure, and indeterminate for the overall assessment of clinical response at PTE visit. PTE visit occurred

5 to 10 days after the last dose of test article (based on the investigator's assessment) unless the subject was considered to be a clinical failure based on the investigator's assessment at the EOT visit or the subject died after EOT and before PTE.

## Primary: Overall Clinical Response at the EOT and PTE Visit Based on Investigator Assessments

|                 |  |
|-----------------|--|
| End point title | Overall Clinical Response at the EOT and PTE Visit Based on Investigator Assessments |
|-----------------|--|

End point description:

At the EOT visit the investigator indicated the clinical status of the infection under study as follows: Clinical Success, Clinical Failure or Indeterminate (the clinical response to test article could not be adequately inferred).

At the PTE visit the investigator indicated 1 of the following outcomes relating to the primary infection under study: Clinical Success, Clinical Failure or Indeterminate (the clinical response to test article could not be adequately inferred). If the lower limit of the 97.5% CI for the difference in both the ITT and CE-PTE populations exceeded -10%, then the null hypothesis was rejected and the non-inferiority of omadacycline to moxifloxacin was declared.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

End of Trial (EOT visit) was on the calendar day of, or within 2 days following the last dose of test article. Post Treatment Evaluation (PTE) visit was 5 to 10 days after the subject's last day of study therapy.

| End point values                   | Omadacycline    | Moxifloxacin    | ITT population       | CE - EOT population  |
|------------------------------------|-----------------|-----------------|----------------------|----------------------|
| Subject group type                 | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed        | 329             | 331             | 660                  | 616                  |
| Units: Number of subjects analysed |                 |                 |                      |                      |
| Clinical success                   | 291             | 282             | 573                  | 574                  |
| Indeterminate                      | 11              | 14              | 25                   | 0                    |
| Clinical failure                   | 27              | 35              | 62                   | 42                   |

| End point values                   | CE-PTE population    |  |  |  |
|------------------------------------|----------------------|--|--|--|
| Subject group type                 | Subject analysis set |  |  |  |
| Number of subjects analysed        | 591                  |  |  |  |
| Units: Number of subjects analysed |                      |  |  |  |
| Clinical success                   | 541                  |  |  |  |
| Indeterminate                      | 0                    |  |  |  |
| Clinical failure                   | 50                   |  |  |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | SAP dated 24 March 2017/ ITT Population |
|----------------------------|---|

Statistical analysis description:

To test the null hypothesis, a 2-sided 97.5% CI for the observed difference in primary outcome rates (omadacycline treatment group minus moxifloxacin treatment group) was calculated for the ITT and CE-PTE populations. The 2-sided 97.5% CI for non-inferiority testing based on the difference of clinical

success rates, was computed using the method proposed with stratification.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Moxifloxacin v Omadacycline    |
| Number of subjects included in analysis | 660                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| Parameter estimate                      | Median difference (net)        |
| Point estimate                          | 3.3                            |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | -2.7                           |
| upper limit                             | 9.3                            |
| Variability estimate                    | Standard deviation             |

Notes:

[1] - The primary efficacy analyses were based on subjects with an eCRF PORT Risk Class of III/IV in the ITT and CE-PTE populations.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | SAP dated 24 March 2017/ CE-PTE Population |
|-----------------------------------|--|

Statistical analysis description:

To test the null hypothesis, a 2-sided 97.5% CI for the observed difference in primary outcome rates was calculated for the ITT and CE-PTE populations. If the lower limit of the 97.5% CI for the difference in both the ITT and CE-PTE populations exceeded -10%, then the null hypothesis was rejected and the non-inferiority of omadacycline to moxifloxacin was declared. Subjects in this analysis: Omadacycline arm - 295; Moxifloxacin arm - 296; all subjects - 591

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Omadacycline v Moxifloxacin    |
| Number of subjects included in analysis | 660                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[2]</sup> |
| Parameter estimate                      | Median difference (net)        |
| Point estimate                          | 2                              |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | -3.2                           |
| upper limit                             | 7.4                            |
| Variability estimate                    | Standard deviation             |

Notes:

[2] - Given that the lower limit of the 97.5% CI for the treatment difference (omadacycline – moxifloxacin) was greater than -10% in both the ITT and CE-PTE populations, omadacycline was considered non-inferior to moxifloxacin.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed from the signing of ICF to the time of the Final Follow-up assessment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Omadacycline |
|-----------------------|--------------|

Reporting group description:

Investigational therapy: omadacycline, 100 mg iv q12h (first 2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg (two 150 mg omadacycline tablets and 1 over-encapsulated placebo tablet matching moxifloxacin) po q24h after at least 3 days (4 doses) of iv treatment.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Moxifloxacin |
|-----------------------|--------------|

Reporting group description:

Reference therapy: moxifloxacin, 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1) with the option to switch to 400 mg (one 400 mg moxifloxacin over-encapsulated tablet and 2 placebo tablets matching omadacycline tablets) po q24h after at least 3 days (4 doses) of iv treatment.

| Serious adverse events  | Omadacycline     | Moxifloxacin     |  |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                  |                  |  |
| subjects affected / exposed   | 23 / 386 (5.96%) | 26 / 388 (6.70%) |  |
| number of deaths (all causes)                                       | 8                | 4                |  |
| number of deaths resulting from adverse events                      | 8                | 4                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |  |
| Lung neoplasm   |                  |                  |  |
| subjects affected / exposed   | 2 / 386 (0.52%)  | 2 / 388 (0.52%)  |  |
| occurrences causally related to treatment / all                     | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 1            |  |
| Chronic lymphocytic leukaemia                                       |                  |                  |  |
| subjects affected / exposed   | 0 / 386 (0.00%)  | 1 / 388 (0.26%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Adenocarcinoma  |                  |                  |  |
| subjects affected / exposed   | 0 / 386 (0.00%)  | 1 / 388 (0.26%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Pancreatic carcinoma                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Colon cancer metastatic                              |                 |                 |  |
| subjects affected / exposed                          | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Aortic aneurysm rupture                              |                 |                 |  |
| subjects affected / exposed                          | 1 / 386 (0.26%) | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Peripheral ischaemia                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Multi-organ failure                                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 386 (0.26%) | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Pleural effusion                                     |                 |                 |  |
| subjects affected / exposed                          | 3 / 386 (0.78%) | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Acute respiratory distress syndrome                  |                 |                 |  |
| subjects affected / exposed                          | 2 / 386 (0.52%) | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Acute respiratory failure                            |                 |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 2 / 386 (0.52%)  | 3 / 388 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 1           |  |
| Acute pulmonary oedema                          |  |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)  | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Psychiatric disorders                           |  |                 |  |
| Anxiety   |  |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)  | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Injury, poisoning and procedural complications  |  |                 |  |
| Bladder injury                                  | Additional description: Urinary bladder damage                 |                 |  |
| subjects affected / exposed                     | 0 / 386 (0.00%)  | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cardiac disorders                               |  |                 |  |
| Cardiac failure                                 |  |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)  | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 1           |  |
| Cardiac arrest                                  |  |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)  | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Tachycardia                                     |  |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)  | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Acute myocardial infarction                     | Additional description: Non ST elevation myocardial infarction |                 |  |
| subjects affected / exposed                     | 2 / 386 (0.52%)  | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0           |  |

|   |   |                 |  |
|---|---|-----------------|--|
| Cardiogenic shock                               |   |                 |  |
| subjects affected / exposed                     | 2 / 386 (0.52%)   | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Cardio-respiratory arrest                       |   |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)   | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Pericardial effusion                            |   |                 |  |
| subjects affected / exposed                     | 0 / 386 (0.00%)   | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Right ventricular failure                       |   |                 |  |
| subjects affected / exposed                     | 0 / 386 (0.00%)   | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Blood and lymphatic system disorders            |   |                 |  |
| Cerebrovascular accident                        | Additional description: Ischemic cerebrovascular accident |                 |  |
| subjects affected / exposed                     | 2 / 386 (0.52%)   | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| Gastrointestinal disorders                      |   |                 |  |
| Colitis   |   |                 |  |
| subjects affected / exposed                     | 0 / 386 (0.00%)   | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hepatobiliary disorders                         |   |                 |  |
| Cholecystitis acute                             |   |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)   | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hepatic failure                                 |   |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 386 (0.26%) | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic congestion                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 386 (0.00%) | 2 / 388 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Lumbago   |                 |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%) | 0 / 388 (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                     |                 |                 |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%) | 2 / 388 (0.52%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 386 (0.78%) | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 386 (0.52%) | 6 / 388 (1.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%) | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Atypical mycobacterial pneumonia<br>subjects affected / exposed            | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Lung abscess<br>subjects affected / exposed                                | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection<br>subjects affected / exposed             | 0 / 386 (0.00%) | 2 / 388 (0.52%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 1 / 2           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis<br>subjects affected / exposed               | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| HIV infection<br>subjects affected / exposed                               | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Infectious pleural effusion<br>subjects affected / exposed                 | 1 / 386 (0.26%) | 1 / 388 (0.26%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Infective exacerbation of<br>bronchiectasis<br>subjects affected / exposed | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Pneumonia viral<br>subjects affected / exposed                             | 0 / 386 (0.00%) | 1 / 388 (0.26%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders   |                 |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| Decreased appetite                              | Additional description: Worsening of anorexia |                 |  |
| subjects affected / exposed                     | 1 / 386 (0.26%)                               | 0 / 388 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Omadacycline       | Moxifloxacin       |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 157 / 386 (40.67%) | 188 / 388 (48.45%) |  |
| Cardiac disorders                                     |                    |                    |  |
| Cardiac disorders                                     |                    |                    |  |
| subjects affected / exposed                           | 15 / 386 (3.89%)   | 20 / 388 (5.15%)   |  |
| occurrences (all)                                     | 15                 | 20                 |  |
| Gastrointestinal disorders                            |                    |                    |  |
| Nausea  |                    |                    |  |
| subjects affected / exposed                           | 9 / 386 (2.33%)    | 21 / 388 (5.41%)   |  |
| occurrences (all)                                     | 9                  | 21                 |  |
| Diarrhea  |                    |                    |  |
| subjects affected / exposed                           | 4 / 386 (1.04%)    | 31 / 388 (7.99%)   |  |
| occurrences (all)                                     | 4                  | 31                 |  |
| Respiratory, thoracic and mediastinal disorders       |                    |                    |  |
| Respiratory, thoracic, and mediastinal disorders      |                    |                    |  |
| subjects affected / exposed                           | 22 / 386 (5.70%)   | 29 / 388 (7.47%)   |  |
| occurrences (all)                                     | 22                 | 29                 |  |
| Infections and infestations                           |                    |                    |  |
| Infections and infestations                           |                    |                    |  |
| subjects affected / exposed                           | 35 / 386 (9.07%)   | 41 / 388 (10.57%)  |  |
| occurrences (all)                                     | 35                 | 41                 |  |
| Metabolism and nutrition disorders                    |                    |                    |  |
| Metabolism and nutrition disorders                    |                    |                    |  |
| subjects affected / exposed                           | 15 / 386 (3.89%)   | 20 / 388 (5.15%)   |  |
| occurrences (all)                                     | 15                 | 20                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 27 October 2015 | <p>There was 1 amendment to the protocol (dated 27-OCT-2015 and labeled as Version 2). In addition to minor administrative changes and clarifications, the following key modifications were made:</p> <ul style="list-style-type: none"><li>- Inclusion criterion #5 was changed to "hypoxemia (PaO<sub>2</sub> &lt; 60 mm Hg by ABG or oxygen saturation &lt; 90% by pulse oximetry)"</li><li>- Inclusion Criterion #9 was changed from a "highly effective method" to "an acceptable method" because of the different regional definitions of highly effective methods of birth control; postmenopausal was added as a method of birth control</li><li>- In exclusion criterion #7, specific QT interval thresholds were added for clarification</li><li>- In exclusion criterion #10, regarding the receipt of corticosteroids equivalent to prednisone, a reference and hyperlink to Appendix 4 was added</li><li>- In exclusion criterion #10, known or suspected "active tuberculosis" was added</li><li>- The Safety population definition was updated to subjects who received any amount of test article, including less than 1 complete dose</li><li>- "Subjects should receive their first dose of test article within 4 hours after randomization" was added to ensure subjects received timely treatment of their infection</li><li>- Population PK sampling schedule was updated to reflect blood samples for the PK analysis collected on Days 1 to 7</li><li>- Language was added to indicate that at the PTE visit, a respiratory specimen culture, and Gram stain should be obtained only for subjects who were clinical failures and required alternative antibacterial treatment for the infection under study</li><li>- Urine antigen screening for Legionella pneumophila and Streptococcus pneumoniae was removed at the PTE visit</li><li>- The criteria for an adequate quality sputum specimen were changed to "1) &lt; 10 SECs/lpf (ie, 100 ×), 2) &gt; 25 PMN/lpf (ie, 100 ×)"</li><li>- The results of Cempira's solithromycin oral CABP study, the first completed study to use the ECR endpoint, reported following finalization of the original protocol and were added to the discussion</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported